

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-second report



World Health
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This report contains the views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the World Health Organization



**World Health
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WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report
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Geneva, 16–20 October 2017

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Declarations of interest

Members of the WHO Expert Committee on Specifications for Pharmaceutical Preparations and temporary advisers reported the following:

Dr I. Aljuffali, Dr J. Gordon, Dr J. Gouws, Professor J. Hoogmartens, Professor Jin S., Mrs K. Kikule, Dr F.-X. Lery, Dr C.M. Limoli, Ms G.N. Mahlangu, Dr J. Miller, Dr H. Okuda, Mrs L. Paleshnuik, Dr J. Sabartova, Dr B. Santoso, Professor G. Scriba, Dr M. Smid, Dr V. Dias Sousa, Dr L. Stoppa and Dr Sun J. reported no conflict of interest.

Professor A. Nicolas reported that he provides consulting for analytical development to pharmaceutical companies. This disclosure does not constitute a conflict of interest as these companies do not manufacture any specific product linked to the topic of the meeting.

Dr A.J. van Zyl reported that he has worked as an independent consultant and auditor to assess compliance with good manufacturing practices for the pharmaceutical industry, as well as organizing training workshops. This disclosure does not constitute a conflict of interest as these companies do not manufacture any specific product linked to the topic of the meeting.

Introduction

The World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) met in Geneva from 16 to 20 October 2017. Dr Suzanne R. Hill, acting Assistant Director of the Health Systems and Innovation Cluster and Director of the Department of Essential Medicines and Health Products (EMP) at WHO, welcomed the participants on behalf of the new WHO Director-General, Dr Tedros Adhanom Ghebreyesus. Dr Hill emphasized the vision of Dr Tedros for “a world in which everyone can live healthy, productive lives, regardless of who they are or where they live”. His strategic leadership aims for an enhanced and independent WHO to take a science-led and innovation-based approach to making health care available to people everywhere. WHO Member States are full and equal partners in this process, and the Organization will guide them in making the decisions that will affect the health of their populations. The Committee was informed about the new Senior Leadership Team that has been announced at WHO. The activities related to the ECSP will be under Dr Mariângela Batista Galvão Simão, Assistant Director-General for Drug Access, Vaccines and Pharmaceuticals, with a strong focus on ensuring access to health products for populations in all WHO Member States.

Dr Hill then spoke about EMP’s new Strategic Framework, which aims to reinforce WHO’s support to Member States for improved access to safe and quality-assured health products. She outlined the links between different WHO programmes and how they work together to achieve the objectives of this framework. The work is the backbone of WHO’s function for medicines. Dr Hill highlighted the fundamental role of the Expert Committee’s standard-setting work in acting on the 2017 World Health Assembly resolutions on antimicrobial resistance, medicines and vaccine shortages, access to medicines, and substandard and falsified medical products. The Expert Committee also provides the platform for other forums, such as the international meetings of world pharmacopoeias. Dr Hill outlined some of the topics to be discussed at the fifty-second meeting. She reminded the Expert Committee that its members participate in their personal capacity to provide independent advice, and that the decisions at the meeting would be made by the Committee members and agreed on the last day of the meeting. She thanked the experts and collaborating centres for their major contributions to the Committee’s work.

The Expert Committee elected Dr Joey Gouws as Chairperson, Professor Jin Shaohong as Co-Chairperson, and Dr Budiono Santoso and Dr Michelle Limoli as Rapporteurs. Dr Gouws then took the chair and welcomed the members, technical advisers and observers to the open session of the Expert Committee.

Ms Emer Cooke, Head of the WHO Regulation of Medicines and other Health Technologies (EMP/RHT) unit, described the strategic collaboration of

the four groups working within RHT: the Technical Standards and Norms (TSN) team coordinates standard-setting work, the Regulatory Systems Strengthening (RSS) team supports regulatory authorities and convergence initiatives, the Prequalification Team (PQT) prequalifies medicines, vaccines, certain diagnostics and vector control products, and the Safety and Vigilance (SAV) team supports monitoring of adverse reactions and the fight against substandard and falsified medicines. The Committee was informed that Dr François-Xavier Lery would join WHO from 2 November 2017 as Coordinator of TSN.

RHT aims to support WHO's global efforts by ensuring that its four groups work in an integrated way. While the focus is on high priority products in the areas of malaria, HIV, tuberculosis and reproductive health, the aim is to build functional regulatory systems that can oversee all products. Collaboration and reliance mechanisms are in place in many areas, for example, for laboratory testing and inspections. Convergence and reliance also have huge potential to minimize duplication of effort in the area of pharmacopoeial standards and are promoted through good pharmacopoeial practices.

Ms Cooke thanked the Committee members, temporary advisers and the WHO Secretariat for their major contributions, emphasizing that their work is key to the development of the WHO strategy to ensure universal access to quality-assured health products.

The Committee took note of the updates.

Open session

The open session had been arranged in response to earlier expressions of interest by the diplomatic missions. The Committee welcomed Dr Yang Xiaochen, Health Focal Point at the Permanent Mission of the People's Republic of China to the United Nations Office at Geneva to its open session.

Introduction to the ECSP

Dr Sabine Kopp, Secretary of the Expert Committee, gave an introduction to the role, functions and procedures of the ECSP. The ECSP was established in 1948 by the first World Health Assembly. It advises the WHO Director-General on norms and standards for pharmaceuticals and some related medical products. It maintains *The International Pharmacopoeia* for medicines, including radiopharmaceuticals, and provides technical guidance at all stages of the product life cycle. The Committee members are selected from the WHO expert advisory panels. Strict rules and procedures apply to their selection.

A wide collaborative network and an interactive public consultation process are in place for guidelines development. The report of each annual Expert Committee meeting is presented to the WHO Governing Bodies and published in the WHO Technical Report Series, with the adopted guidelines as annexes.

A total of 85 current WHO guidelines and good practice documents and 50 training modules are available on the WHO website and on CD-ROM. Examples include the interagency model quality assurance system for procurement agencies, which has come to be implemented by all major international funders and procurers of medicines, and the guidance on good review practices which were developed in collaboration with the Asia-Pacific Economic Cooperation.

In the discussion that followed, it was explained that translations of specific guidelines are made available in various languages depending on demand and available resources. It was also reiterated that WHO provides norms and standards in line with internationally accepted standards with the aim of ensuring the safety, efficacy and quality of medical products. While WHO recognizes that the implementation of these standards in Member States may be challenging, the Organization will not support any compromise on the standards.

1. General policy

1.1 Cross-cutting pharmaceutical quality assurance issues

1.1.1 Expert Committee on Biological Standardization

Dr Ivana Knezevic gave an update on the activities of the Expert Committee on Biological Standardization (ECBS), which works on standardization of vaccines, blood products (including antivenoms), biotherapeutics and in vitro diagnostics. At its sixty-eighth meeting from 17 to 20 October 2017 the ECBS would consider a number of physical standards for establishment, including an antiserum to respiratory syncytial virus, anti-typhoid capsular Vi polysaccharide immunoglobulin and typhoid Vi polysaccharide. Measurement standards for antibodies to Ebola virus, malaria antigen and Chikungunya virus RNA would also be considered. The Committee would also discuss written standards to be published as annexes to the WHO Technical Report Series, including guidance on evaluating the quality, safety and efficacy of Ebola vaccines, and on post-approval changes for biotherapeutic products. To facilitate the use of guidelines in Member States, WHO conducts implementation workshops. Successful events have been held on human papillomavirus and typhoid conjugate vaccines as well as on biotherapeutics including biosimilars. The ECBS also works on blood regulation and a review of the activities in the field, such as assessment performed in Zambia is part of the discussion.

The ECBS is working on a number of cross-cutting issues of interest to other groups. The global benchmarking tool to assess the functionality of regulatory authorities has been harmonized and an update would be presented. Currently the regulation of blood and blood products is being integrated into the tool as another product stream, and medical devices will follow. Definition of a “stringent regulatory authority” is of interest because of the part played in the prequalification of various biological products. A pilot study on biotherapeutic products is intended to facilitate prequalification of biosimilars and key aspects of that project would be presented to the ECBS. Also, a harmonized model template has been proposed for lot release of prequalified vaccines. The recent activities in different WHO departments in the field of snake-bite envenoming, including antivenoms, would be briefly presented. Dr Knezevic emphasized the importance of standards established by the ECBS as a basis for regulatory convergence. Information exchange mechanisms have been established in a growing number of networks of regulators, manufacturers and academia.

The Committee noted the update.

1.1.2 Traditional and complementary medicines

Ms Yukiko Maruyama of the WHO Traditional, Complementary and Integrative Medicine team and Dr Sabine Kopp, Secretary of the Expert Committee, presented two draft guidance documents developed for herbal medicines. The Committee noted the report. The discussion of the two guidelines was deferred to the private session reserved for the Expert Committee Members.

1.1.2.1 Good herbal processing practices

Ms Maruyama introduced a document titled *Proposed WHO guidelines on good herbal processing practices for herbal medicines* to the Expert Committee. The guidelines were developed in response to a suggestion submitted to the WHO Expert Committee in 2001. The proposal was subsequently supported by recommendations made at various international meetings and by World Health Assembly Resolution 56.31, requesting WHO to provide normative guidelines for ensuring and monitoring the quality, efficacy and safety of herbal medicines.

This is the last of four new WHO guidelines in the area of quality assurance and control of herbal medicines. Good herbal processing practices (GHPP) are a new concept. The aim of this document is to provide general and specific technical guidance on processing of herbal materials at the different stages of the production process of herbal medicines. The proposed WHO GHPP guidelines are intended to bridge the gap between guidance provided in the *WHO good agricultural and collection practices (GACP) for medicinal plants*⁸ and the *Good manufacturing practices (GMP) for herbal medicines*.⁹ The draft document was developed through the usual wide consultative process. Approximately 570 reviewers had provided national information and comments on the first and second drafts. The Expert Committee was updated on progress in 2014 and 2016 and responded with guidance and comments. The document presented to the Committee at its fifty-second meeting represented the third revised draft and had been finalized on the basis of discussions during the third WHO consultation on quality control of herbal medicines held in Hong Kong SAR, China, from 4 to 6 September 2017.

The Committee adopted the proposed WHO guidelines on GHPP for herbal medicines and recommended that they should be published as an annex to its report (Annex 1), and possibly also as a stand-alone WHO publication to enable a wide distribution.

⁸ WHO good agricultural and collection practices (GACP) for medicinal plants. Geneva: World Health Organization; 2003 (<http://apps.who.int/medicinedocs/en/d/Js4928e/>; <http://apps.who.int/medicinedocs/pdf/s4928e/s4928e.pdf>).

⁹ WHO guidelines on good manufacturing practices (GMP) for herbal medicines. Geneva: World Health Organization; 2007 (<http://apps.who.int/medicinedocs/en/m/abstract/Js14215e/>; <http://apps.who.int/medicinedocs/documents/s14215e/s14215e.pdf>).

1.1.2.2 Good herbal manufacturing practices

Dr Kopp introduced a document proposing a maintenance process of the existing good manufacturing practices (GMP) for herbal medicines. At the third WHO consultation on quality control of herbal medicines held in Hong Kong SAR, China, in September 2017, the experts advised that the existing *Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines*¹⁰ are still appropriate in terms of technical content, but that the references and definitions should be updated.

The Committee recommended that a maintenance process should be initiated to align the references and definitions in the guidance on GMP for herbal medicines with other current WHO guidance as relevant. The Committee agreed that the document would be published as Annex 2 to the report of its fifty-second meeting.

1.1.3 Expert Committee on Selection and Use of Essential Medicines

Ms Bernadette Cappello of the WHO Innovation, Access and Use team presented an update from the Expert Committee on Selection and Use of Essential Medicines, which held its twenty-first meeting from 27 to 31 March 2017. The Expert Committee had considered more than 90 applications for addition, deletion or changes to medicines on the 20th Model List of Essential Medicines (EML) and the 6th Model List of Essential Medicines for children (EMLc). A total of 30 medicines were added to the EML, including 25 medicines for children, bringing the totals to 433 and 314 medicines on the EML and EMLc, respectively.

To support WHO's global action plan on antimicrobial resistance, the Expert Committee considered a comprehensive review of antibiotics for treatment of 25 common, important infectious syndromes. The Committee recommended a novel approach of classifying antibiotics into three categories – Access, Watch and Reserve (AWaRe). “Access” antibiotics are first- and second-choice treatments for a wide range of infections, The “Watch” category includes antibiotics and antibiotic classes that have higher resistance potential and are recommended as first- or second-line treatments only for a specific, limited number of infections, and “Reserve” antibiotics are “last-resort” options that should be accessible, but whose use should be reserved for highly specific patients and settings, when no alternative options exist or are suitable. The AWaRe classification of antibiotics is a tool for effective antimicrobial stewardship that optimizes access to essential antibiotics.

Other changes to the Model Lists in 2017 include the addition of new cancer medicines dasatinib, nilotinib and zoledronic acid; addition of fentanyl and a new indication for methadone for treatment of cancer pain; addition of

¹⁰ WHO Technical Report Series, No. 937, 2006, Annex 3.

dolutegravir and raltegravir for treatment of HIV infection, and the addition of erythropoiesis-stimulating agents as a pharmacological class for the treatment of anaemia in patients with renal disease. New uses were specified for nine previously listed products, including pre-exposure prophylaxis of HIV infection for tenofovir-containing antiretroviral medicines. Applications requesting the deletion of bevacizumab, misoprostol and oseltamivir from the Model Lists were rejected by the Expert Committee and these medicines remain listed; however, oseltamivir was moved from the core to the complementary list.

The full report of the Expert Committee, including the updated Model Lists is available on the WHO website. The Committee noted the update.

1.1.4 **Antimicrobial resistance**

Dr Arno Muller provided an oral update on the work of the WHO Innovation, Access and Use team to achieve the objective of WHO's global action plan on antimicrobial resistance by optimizing the use of antibiotics in humans. A list of 13 priority pathogens was published in February 2017. WHO published the status of the new antibiotics and biologicals in clinical development to treat these pathogens. It was found that of 59 products in the pipeline only nine were likely to add value to the current treatment arsenal. WHO and the Drugs for Neglected Diseases Initiative have set up the Global Antibiotic Research and Development Partnership to support the development of new treatments. The newly introduced antibiotic classification used in the 20th EML is based on 23 priority syndromes; WHO plans to expand the list of syndromes for the next EML revision in 2019. There is also a focus on supporting the development of needed rapid diagnostic tests for antimicrobial resistance, and on ensuring that these are included in the proposed new WHO Model List of Essential Diagnostics (EDL).

Since 2016 WHO has been collecting data on sales of antimicrobials in the public and private sectors of WHO Member States. A report on the results of this monitoring exercise is expected to be published in 2018. Information is also being gathered on pricing and availability of antibiotics. Furthermore WHO supports stewardship programmes in countries to promote better prescribing and works with other groups to strengthen regulatory control in Member States. It was emphasized that quality assurance of antibiotics, including implementation of GMP together with environmental controls, is important to combat antimicrobial resistance.

The Committee noted the update.

1.1.5 **Member State Mechanism on substandard and falsified products, and their surveillance and monitoring**

Mr Michael Deats presented an update on the Member State Mechanism for dealing with substandard and falsified medical products, formerly referred to

as substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products. Created in 2012, this Mechanism is open to all Member States and is overseen by a steering committee composed of 12 WHO Member States from all WHO regions collaborating to combat substandard and falsified medical products from a public health perspective. A recent review of the Mechanism recommended that it should continue its activities in the areas of prevention, detection and response, that coordination, communication and dissemination should be enhanced, and that national and regional capacities should be mobilized across all sectors. The Mechanism would discuss the 2018–2019 workplan at its November 2017 meeting and it was likely to include the following activities: develop training materials, maintain a global focal point network within national medicines regulatory authorities, work on rapid detection technologies, and explore the links between reduced access to products – for example, during stock-outs – and the emergence of substandard and falsified products. Two studies were to be launched in November 2017: one to estimate the prevalence, cost and socioeconomic impact of such products; and another to highlight some causes, consequences and possible solutions.

The Expert Committee heard an update on the WHO Global Surveillance and Monitoring System (GSMS). This system was launched in 2013 and maintains a searchable database accessible to regulatory focal points. To date, reports from 106 countries on more than 1500 suspect products had been collected. A wide range of health products are affected, with anti-infective medicines and antiparasitics being the most frequently reported categories. A global alert system is triggered in the case of significant threats to public health, a notification service is available through an RSS feed available on the Programme's website.¹¹

WHO provides technical and strategic support to Member States in evaluating the incidents reported to the GSMS and in building up evidence for policy-making and targeted investment of resources. WHO also organizes national and regional workshops; to date more than 600 regulatory staff have been trained.

The Committee noted the report.

1.1.6 Regulatory support

Dr Samvel Azatyan presented an update about WHO's regulatory support activities on behalf of Dr Mike Ward, Head of the WHO Regulatory Systems Strengthening (RSS) team.

RSS provides support to several regulatory networks, including the paediatrics regulatory network, the African Vaccine Regulators Forum and the African Medicines Regulators Harmonization initiative, as well as two new

¹¹ www.who.int/medicines/regulation/ssffc.

initiatives: the South-East Asia Regulatory Network and the WHO-National Control Laboratory Network on Biologicals, which aims to promote reliance on lot testing of vaccines conducted by the regulatory laboratories in the countries of production.

RSS supports facilitated pathways for regulatory reliance as part of good regulatory practices. It oversees work on the Global Benchmarking Tool (GBT), which originated as a tool to assess vaccine-related regulatory functions in producing countries as a prerequisite for prequalification of vaccines. The GBT is being unified and extended to assess the maturity of regulatory authorities more generally, to support decisions on reliance. This work has led to a proposal by RSS to establish guidelines on quality management systems for regulatory authorities (see section 8.6). A new approach to supporting regulatory systems was presented at the seventeenth International Conference of Drug Regulatory Authorities (ICDRA) and pre-ICDRA held in South Africa in 2016, namely the formation of a Coalition of Interested Partners to provide joint, coordinated support to RSS in Member States.

ICDRA is a biennial conference organized since 1980 as a platform for international consensus-building on regulatory matters. After almost 40 years, ICDRA continues to be an important forum for discussion and harmonization. The seventeenth ICDRA, held in South Africa from 29 November to 2 December 2016, was the first ICDRA to be held on the African continent. More than 360 delegates participated actively. The meeting recommendations are available in the *WHO drug information journal*.¹² The eighteenth ICDRA will take place from 3 to 7 September 2018 in Dublin, Ireland, under the theme “Smart safety surveillance: A life-cycle approach to promoting safety of medical products”.

The members thanked the South African regulatory authority for organizing a successful and vibrant ICDRA conference. The Expert Committee highlighted the vital role of RSS in ensuring that patients in WHO Member States have access to safe, quality-assured medical products.

The Committee noted the update.

Update on the WHO certification scheme

Dr Samvel Azatyan provided an update on the WHO certification scheme on the quality of pharmaceutical products moving in international commerce. Created in 1969, this scheme is supported by a number of World Health Assembly resolutions and was last endorsed in 1997. In 2008 the Expert Committee

¹² 17th International Conference of Drug Regulatory Authorities. WHO Drug Info. 30;2016:547–7 (http://www.who.int/entity/medicines/areas/quality_safety/regulation_legislation/icdra/2016ICDRA_Recommendations.pdf?ua=1).

recommended that the scheme should be reviewed and updated in line with recent developments. A question-and-answer (Q&A) document was provided and feedback was sought from Member States about their implementation of the scheme; however, very few responses were received. A revised version of the Q&A document was made available in 2015.

Current membership includes 148 national regulatory authorities and the European Medicines Agency. The primary document delivered under the scheme is the certificate of pharmaceutical product, which serves to confirm the regulatory status of a product in the exporting country. The scheme is still considered to be valuable in principle, but issues of misuse have been noted in global pharmaceutical markets. In view of the feedback received from the users of the scheme, the Expert Committee was asked to consider supporting a revision of this scheme, to be submitted to the World Health Assembly for endorsement.

The Committee noted the update and recommended that the Secretariat should prepare a proposal for revision of the scheme for public consultation.

1.2 International collaboration

1.2.1 Global Fund to Fight AIDS, Tuberculosis and Malaria

Dr Amélie Darmon described the Global Fund's quality assurance policies, which have been harmonized with those of other international organizations. The Global Fund relies on WHO norms and standards in the procurement of pharmaceuticals and other health products by grant recipients. Products must meet clinical criteria based on WHO treatment guidelines and must be authorized for use in recipient countries. Key categories of pharmaceuticals, i.e. antiretrovirals and medicines to treat tuberculosis, malaria and hepatitis, must in principle be WHO-prequalified or authorized by a stringent regulatory authority (SRA). Almost all Global Fund-financed antiretrovirals, 89% of antimalarials and 68% of first-line antituberculosis medicines meet these criteria. For needed key products for which such an assessment has not yet been completed, time-limited opinions from the WHO-hosted Expert Review Panel (ERP) are sought. The ERP conducts two reviews per year, based on an assessment of key quality data submitted in a product questionnaire¹³ and information on the GMP status of the manufacturing site. The opinions take the form of a risk-based classification according to publicly available criteria.¹⁴ The outcomes are also used by other

¹³ Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies, Appendix 6 to Model quality assurance system for procurement agencies. In: WHO Expert Committee on Pharmaceutical Preparations. Forty-eighth report. Geneva: World Health Organization; 2014: Annex 3 (WHO Technical Report Series, No. 986).

¹⁴ WHO/PQT: medicines. The Expert Review Panel. Information note, 9 February 2016 (https://extranet.who.int/prequal/sites/default/files/documents/73%20ERP_Feb2016_1.pdf).

international organizations. The ERP pathway continues to be important for certain needed product categories, such as paediatric formulations and certain antituberculosis and antimalarial treatments.

The Global Fund requires principal recipients to monitor the quality of all categories of pharmaceuticals procured with grant funds through risk-based quality control testing at WHO-prequalified or International Organization for Standardization (ISO)-accredited laboratories, in close collaboration with national regulatory authorities. For ERP-reviewed products the Global Fund organizes pre-shipment testing. Principal recipients are also strongly encouraged to monitor adverse drug reactions in line with WHO recommendations on pharmacovigilance. A responsible person is nominated for each grant to coordinate this monitoring, and funding for monitoring can be made available under the grant agreements.

Ongoing quality-related challenges include the lack of harmonization of analytical methods for quality control testing, the lack of qualified sources of active pharmaceutical ingredients (APIs) for consistent product quality, and non-compliance with GMP observed at numerous manufacturing sites. Furthermore, the outcomes of ongoing discussions to redefine the term “stringent regulatory authority” will impact the Global Fund’s quality assurance mechanisms.

The Committee noted the report.

1.2.2 United Nations Development Programme

Dr Jean-Michel Caudron presented an update on the activities of the United Nations Development Programme (UNDP) in delivering quality-assured health products and services to WHO Member States. The mandate of UNDP is to contribute to the development of Member States. Collaboration with the Global Fund was established in 2003, and to date UNDP has assisted more than 50 countries to access funds and assistance. The strengthened supply chain and procurement systems established by Global Fund grant programmes also benefit the procurement of health products funded with national funds, including medicines for noncommunicable diseases, as well as medicines for treatment and palliative care of cancer patients. The demand for these products is expected to increase rapidly. UNDP is currently developing a quality assurance policy for medicines for noncommunicable diseases. The policy, which was expected to be published in late 2017, is consistent with the United Nations Children’s Fund (UNICEF), United Nations Population Fund (UNFPA) and Global Fund policies and WHO guidelines, and foresees reliance on the assessments done by SRAs, PQT and ERP. Given the increasing demand for medicines for chronic diseases, including biosimilars, UNDP is looking to the WHO Expert Committee to provide guidance on quality assurance for these product categories.

The Expert Committee noted the report.

1.2.3 United Nations Children's Fund

Dr Peter Svarrer Jakobsen presented an update on the work of the UNICEF Supply Division, which works with about 900 logistics staff in some 100 countries to bring quality-assured medicines and other supplies to children and their families. More than 80% of UNICEF's procurement is in collaboration with other United Nations (UN) agencies. In 2016, total expenditure for supplies and services worldwide was US\$ 3.5 billion, including US\$ 1.64 billion for vaccines – making UNICEF the largest procurer of vaccines in the world – US\$ 161 million for pharmaceuticals and US\$ 139 million for medical supplies.

The UNICEF Supply Division operates in compliance with WHO guidelines and other international good practices. The Supply Division works according to the WHO Model quality assurance system for procurement agencies.¹⁵ UNICEF relies on WHO prequalification for vaccines, antiretrovirals, antimalarials and antituberculosis products. A UNICEF prequalification process is in place for needed products that are not WHO-prequalified or otherwise stringently assessed. This process involves the review of an abbreviated product dossier based on Appendix 6 to the Model quality assurance system for procurement agencies¹⁵ by qualified pharmacists as well as risk-based GMP inspections to verify compliance with WHO GMP and good distribution practice guidelines. Since 2006 UNICEF has been a partner to the Pharmaceutical Inspection Co-operation Scheme (PIC/S). From 2012 to 2016, UNICEF inspectors carried out some 160 GMP inspections. Joint inspections are performed with WHO-PQT, the International Committee of the Red Cross and Médecins sans Frontières. Collaboration and information-sharing processes are in place with international partners. For vaccines and medicines eligible for prequalification, UNICEF relies on the outcomes of WHO inspections. UNICEF's quality assurance system includes a risk-based annual plan of sampling and quality control testing at WHO-prequalified laboratories.

The Committee noted the report.

1.2.4 Pharmacopoeial Discussion Group

Dr Kevin Moore presented an update from the Pharmacopoeial Discussion Group (PDG), an informal body of representatives from the European Directorate for the Quality of Medicines & HealthCare (EDQM), the Japanese Ministry of Health, Labour and Welfare/Pharmaceuticals and Medical Devices Agency (MHLW/PMDA) and the United States Pharmacopeia (USP), which represent

¹⁵ Model quality assurance system for procurement agencies. In: WHO Expert Committee on Pharmaceutical Preparations. Forty-eighth report. Geneva: World Health Organization; 2014: Annex 3 (WHO Technical Report Series, No. 986).

the pharmacopoeias of Europe, Japan and the United States, respectively. In 2001 WHO joined as an observer. PDG was linked to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) through the ICH Q4B Expert Working Group from around 2004 until its conclusion in 2011. The group's current work focuses on retrospective harmonization of excipient monographs and general chapters. To date, 28 of 31 general chapters and 45 of 62 excipient monographs have been harmonized. An overview was provided of the current status of new and revised texts. The PDG has adopted a streamlined and simplified five-stage working procedure. PDG has begun a strategic review of harmonization areas and of individual work items currently in progress and for future consideration. Harmonization of several items will be continued in other collaborative forums, such as bilateral discussion or adopt/adapt mechanisms as mentioned in the good pharmacopoeial practices (GPhP). The next meeting of the PDG will be held in Strasbourg, France, in October 2018.

The Committee noted the report.

2. Quality control – specifications and tests for *The International Pharmacopoeia*

2.1 Update and workplan

Dr Herbert Schmidt presented an overview of progress since the fifty-first meeting of the Expert Committee. The seventh edition of *The International Pharmacopoeia* had been made available on the WHO website¹⁶ and on CD-ROM. The new edition includes new or revised texts for six monographs on pharmaceutical substances, seven monographs on specific dosage forms, three methods of analysis and two texts for the Supplementary information section. A new chapter on *Colour of liquids* reproduced from the European Pharmacopoeia has been included; the permission for reproduction of the text “colour of liquids” granted by the European Pharmacopoeia was gratefully acknowledged. Dr Schmidt thanked all individuals and groups that contributed to maintaining up-to-date monographs and reference standards for *The International Pharmacopoeia*.

The Committee noted the report and congratulated the Secretariat of *The International Pharmacopoeia* on these achievements.

At its fifty-first meeting the Expert Committee had approved the two-year workplan 2016–2017 for elaboration of monographs. The workplan identifies 34 finished products that are included in the WHO EML and/or invited for prequalification, and 31 related APIs, for which no monograph is available in the British Pharmacopoeia, the European Pharmacopoeia, the Japanese Pharmacopoeia or the USP. These substances and specific dosage forms comprise the priority list for elaboration of new monographs. This work is ongoing.

The workplan also listed 80 monographs on medicines that are no longer included in the EML or invited for prequalification. A survey conducted by the WHO Secretariat had not identified any reason to keep them in *The International Pharmacopoeia*. These monographs have been transferred to a publicly accessible archive section on the WHO website.¹⁷

The Committee took note of the update.

2.2 General policy

2.2.1 Replacement of titration methods using mercuric acetate in *The International Pharmacopoeia*

At its fiftieth meeting the Expert Committee had endorsed the proposal by the Secretariat of *The International Pharmacopoeia* to replace the obsolete use of mercury salts in non-aqueous titration by alternative methods. Alternative

¹⁶ <http://apps.who.int/phint>.

¹⁷ http://www.who.int/medicines/publications/pharmacopoeia/pharm_int-omissions/en/.

general procedures have been described in the revised general chapter 2.6 *Non-aqueous titration*, which was adopted at the fifty-first Committee meeting. Revised provisions for assay have been developed for inclusion in 32 monographs that currently prescribe the use of mercuric acetate for titrations. The proposed alternative procedures are predominantly based on suitable methods identified in other pharmacopoeias; in one case experimental laboratory investigations were performed. The revised assay methods were discussed at an informal consultation held in May 2017, and sent out for public consultation in July 2017. The draft document and comments received were presented to the Committee.

The Committee approved the alternative titration methods and endorsed the revision of 32 monographs affected by this transition.

2.2.2 **Transition from microbiological to chromatographic assay of antibiotics: capreomycin**

In 2009 the Expert Committee recommended that microbiological assays mentioned in monographs for antibiotics in *The International Pharmacopoeia* should be replaced by chromatographic methods, where possible and appropriate. While the transition has been largely completed for monographs for single-component antibiotics, it remains challenging for multi-component compounds.

One such compound is capreomycin, a priority medicine used to treat multidrug-resistant tuberculosis according to WHO treatment guidelines. Capreomycin consists of a mixture of four structurally related components with different activities in the microbiological assays. *The International Pharmacopoeia* is the first to require chromatographic assay methods for capreomycin APIs and finished products, whereas the Chinese Pharmacopoeia (ChP), the Indian Pharmacopoeia Commission (IPC) and USP describe a microbiological assay. The strength of capreomycin products is currently being stated in terms of its microbiological activity; however, the WHO International Standard for Antibiotics (ISA) defining the activity of capreomycin was discontinued in 2000. The re-establishment of the WHO ISA for capreomycin may need to be investigated. The Expert Committee had endorsed the release of a capreomycin sulfate International Chemical Reference Substance (ICRS) at its fifty-first meeting, together with a cautionary note in the leaflet stating that the substance is suitable for the quantitative determination of the four capreomycin components, but that a correlation between the concentration of the components and the activity of the substance, determined with microbiological methods, has not been established. The Committee recommended at its fifty-first meeting that information should be sought from manufacturers on the composition and microbiological activity of their capreomycin products, and that an analytical comparison of available pharmacopoeial standards for capreomycin should be conducted.

A draft concept paper was developed in January–April 2017, proposing the next steps for gathering the data requested by the Committee. The draft

concept paper was discussed at an informal consultation held in May 2017, further revised and sent out for public comment in July 2017. The concept paper was presented to the Expert Committee together with a compilation of comments received, and the Committee was informed of the steps taken by WHO and the initial outcomes of the above-mentioned surveys.

An intercompendial collaboration to move to chromatographic assays for capreomycin was suggested at a side meeting during the eighth international meeting of world pharmacopoeias. A road map for this initiative was circulated for comment to ChP, IPC, USP and to EDQM, as well as a working group established at the informal consultation on new medicines, quality control and laboratory standards held in May 2017. The road map was presented to the Expert Committee together with comments received. It proposes a joint pilot study to link the microbiological activity of capreomycin with the mass of its components. Initial findings of investigations performed by the ChP were also presented at the meeting. The results of the pilot study and the landscape analysis may enable a joint transition to a chromatographic assay for capreomycin, and the insights gained may facilitate future transitions to physicochemical methods for other antibiotics.

Results were presented for the National Institutes for Food and Drug Control's investigation of the antimicrobiological activity of capreomycin sulfate ICRS at five collaborating laboratories according to the current provisions in the ChP. No relationship could be established between the mass of capreomycin components in samples and the microbiological activity. The expert suggested re-establishing the WHO ISA for capreomycin.

Guidance was sought from the Committee on the next steps for the collaborative studies.

The Expert Committee appreciated the work done and the outcomes achieved. It also noted some gaps that still need to be addressed. The Committee recommended that the working group established at the informal consultation in May 2017 should analyse the situation and advise on the way forward.

2.2.3 General policy for drafting of monographs

At its fifty-first meeting the Expert Committee recommended that new guidance should be developed on policies for drafting monographs for *The International Pharmacopoeia*, including naming of monographs, setting of limits, design of identity tests and other relevant topics. A comprehensive guidance document was drafted and discussed at an informal consultation on quality control held in May 2017, and circulated within a group of experts for comment. Dr John Miller presented the draft text and the feedback received and outlined the main issues that remain to be resolved.

The Committee noted the update.

2.2.4 Proposed chapter on polymorphism

A chapter on polymorphism for inclusion in the Supplementary information section of *The International Pharmacopoeia* under “Notes for guidance” was drafted in March 2017. The draft chapter was discussed at an informal consultation on quality control held in May 2017, and sent out for public consultation in July 2017. Numerous technical comments had been received and were being reviewed.

The Committee noted the update.

2.3 General chapters

2.3.1 Proposed chapter on capillary electrophoresis

In response to discussions during an informal consultation on quality control laboratory tools and specifications for medicines held in May 2017, a new chapter on capillary electrophoresis was drafted, based on the internationally harmonized texts developed by the PDG. The draft chapter was sent out for public consultation in July 2017 and was presented to the Committee together with feedback received.

The Committee was informed of further changes envisaged to ensure that the text will be harmonized with the texts of other pharmacopoeias.

The Committee adopted the proposed chapter, subject to its finalization by the working group overseeing its development.

2.4 General monographs for dosage forms and associated method texts

2.4.1 General chapter on radiopharmaceuticals

A general chapter on radiopharmaceuticals was developed by the International Atomic Energy Agency (IAEA) and was discussed by the Expert Committee together with several monographs for specific radiopharmaceutical dosage forms (see section 2.5.9).

2.5 Specifications for medicines, including children’s medicines and radiopharmaceuticals

2.5.1 For antimalarials

Pyrimethamine (revision)

Pyrimethamine tablets

A revised monograph on pyrimethamine and a new monograph on pyrimethamine tablets were presented to the Expert Committee, together with supporting laboratory reports. The texts were developed in collaboration with

the British Pharmacopoeia. They were discussed at an informal consultation held in May 2017 and would be sent out for public consultation after the fifty-second Committee meeting.

The Committee adopted both monographs, subject to their circulation for public consultation, and subject to their finalization by a group of experts in line with comments received.

2.5.2 For antiviral medicines, including antiretrovirals

Atazanavir sulfate (revision)

Atazanavir capsules (revision)

The monographs on atazanavir sulfate and atazanavir capsules had been revised in line with a proposal by the ICRS custodian centre, and to reflect the information given on atazanavir capsules in the 20th WHO EML. The revised monographs would be sent out for public consultation after the fifty-second Committee meeting.

The Committee adopted the revised monographs, subject to their finalization by a group of experts during the next informal consultation and taking into account any comments that might be received during the public consultation.

Efavirenz, emtricitabine and tenofovir tablets (revision)

Revisions to the monograph on efavirenz, emtricitabine and tenofovir disoproxil fumarate tablets were requested by users of *The International Pharmacopoeia* and were discussed at an informal consultation held in May 2017. The revised monograph was circulated for public comment in August 2017, then further revised and presented to the Committee together with comments received.

The Committee adopted the revised monograph.

The Committee also accepted the proposal to update the titles of two other monographs to specify the salt form of tenofovir (tenofovir disoproxil fumarate), i.e. (1) tenofovir tablets, and (2) emtricitabine and tenofovir tablets.

Ganciclovir

Ganciclovir for injection

Ganciclovir for injection is an HIV-related medicine invited for WHO prequalification. New monographs on ganciclovir and ganciclovir for injection were drafted by a collaborating centre and were discussed at informal consultations held in 2016 and 2017, as well as at the fifty-first Expert Committee meeting. The draft monographs were circulated for public comment in January 2017 and July 2017. They were presented to the Committee together with a compilation of comments received in the two rounds of public consultation.

The Committee adopted both monographs and released the ganciclovir reference substance for system suitability (containing impurities A, B, C, D, E and F) established by the European Pharmacopoeia for use according to the provisions described in the respective monographs.

Ritonavir (revision)

Ritonavir tablets (revision)

Ritonavir oral solution

Draft revisions of the monographs on ritonavir and ritonavir tablets were prepared in March 2017, and a new monograph on ritonavir oral solution was drafted. This work was undertaken in collaboration with the British Pharmacopoeia, enabling sharing of work and data and alignment of standards. All three monographs were discussed at an informal consultation held in May 2017. Laboratory investigations are ongoing. The monographs were presented to the Expert Committee for information, pending their circulation for public comment.

The Committee noted the update and provided input on the monographs.

2.5.3 For antituberculosis medicines

Capreomycin sulfate (revision)

Capreomycin powder for injection (revision)

Revisions of the draft monographs on capreomycin sulfate and capreomycin powder for injection had been proposed, including the addition of a new reference substance for identification tests, the addition of a note on the ongoing discussions about transition from microbiological to physicochemical assays for antibiotics (see section 2.2.2), and to determine the percentage content of capreomycin per sealed container. The revised monographs were discussed at an informal consultation in May 2017 and were sent out for public consultation in June 2017. The draft monographs and comments received were presented to the Committee.

The Committee adopted the monographs, subject to the amendments agreed.

Levofloxacin

Levofloxacin tablets

New monographs on levofloxacin and levofloxacin tablets are being developed for inclusion in *The International Pharmacopoeia*. Laboratory investigations are

ongoing, and the draft monographs are yet to be circulated for public consultation. The monographs were presented to the Expert Committee for information.

The Committee took note of the update and provided input on the monographs.

Moxifloxacin hydrochloride

Moxifloxacin tablets

New monographs on moxifloxacin hydrochloride and moxifloxacin tablets were drafted in 2016. The monograph on moxifloxacin tablets was developed in collaboration with the British Pharmacopoeia. Both monographs were discussed at informal consultations held in 2016 and 2017, and comments were provided by the Expert Committee at its fifty-first meeting. The draft monographs were presented to the Committee at its fifty-second meeting, pending their circulation for public comment.

The Committee provided input and adopted the monographs, subject to the amendments agreed at the meeting and finalization of the monographs by a group of experts that will take into account any comments received during the public consultation. The Committee also released moxifloxacin for peak identification reference substance (containing moxifloxacin and the impurities A, B, C, D and E) established by the European Pharmacopoeia for use according to the provisions described in the respective monographs.

Protionamide (revision)

Protionamide tablets

A revised monograph on protionamide and a new monograph on protionamide tablets were developed by a collaborating centre and circulated for public comment in July 2017. The two monographs and a compilation of comments received were presented to the Committee.

The Committee adopted the monographs, subject to the amendments agreed at the meeting.

2.5.4 For medicines for tropical diseases

Ivermectin

Ivermectin tablets

New monographs on ivermectin and ivermectin tablets were drafted for inclusion in *The International Pharmacopoeia* based on information found in other monographs, information provided by manufacturers and laboratory investigations, which are ongoing. The draft monographs were discussed at an informal consultation held in May 2017, and were presented to the Expert Committee pending their circulation for public comment.

The Committee took note of the update and provided input on the draft monographs.

2.5.5 For medicines for infectious diseases

Amoxicillin trihydrate (revision)

Clavulanate potassium

Amoxicillin and clavulanic acid tablets

A draft revised monograph on amoxicillin trihydrate was prepared in 2016 based on provisions found in other pharmacopoeias and laboratory investigations, and a new monograph on amoxicillin and clavulanic acid tablets was drafted. The two texts were discussed at an informal consultation held in May 2016. A new monograph on clavulanate potassium was subsequently drafted. All three draft monographs were presented to the Expert Committee at its fifty-first meeting for information, and were discussed at an informal consultation held in May 2017. The latest drafts were presented to the Committee at its fifty-second meeting, pending their circulation for public consultation.

The Committee adopted the monographs, subject to finalization by a group of experts that will take into account any comments received during the public consultation.

Clindamycin palmitate hydrochloride

Clindamycin palmitate powder for oral solution

New draft monographs developed by a collaborating centre were discussed at an informal consultation on quality control laboratory tools and specifications for medicines in May 2016. They were circulated for public comment in July 2016, further revised in consultation with the laboratory that had prepared the draft, and presented to the Committee for information at its fifty-first meeting. They were then discussed at an informal consultation in May 2017, leading to further laboratory investigations being carried out. Revised drafts of the two monographs were presented to the Expert Committee, pending their circulation for a second round of public consultation in November 2017.

The Committee adopted the two monographs, subject to finalization by a group of experts that will take into account any comments received during the public consultation.

Tetracycline hydrochloride

A revised monograph on tetracycline hydrochloride was prepared with proposed replacement methods for the assay using titration with mercury acetate (see also section 2.2.1) and the microbiological assay (see also section 2.2.2). The

draft monograph was presented to the Committee, pending its circulation for public consultation.

The Committee noted the monographs and provided input. It was agreed that the monographs should be further revised to take into account any comments received, and presented to the Expert Committee at its fifty-third meeting.

2.5.6 For medicines for chronic diseases and for mental health

Atenolol (revision)

Following a request from the WHO custodian centre for ICRS, the monograph on atenolol was revised based on information found in the European Pharmacopoeia and in the scientific literature. The monograph was discussed at an informal consultation in May 2017 and sent out for public consultation in June 2017. It was further revised and presented to the Expert Committee together with a compilation of the comments received.

The Committee adopted the revised monograph, subject to the amendments agreed at the meeting.

Dacarbazine (revision)

A revision of the monograph on dacarbazine was drafted following a request from the custodian centre for ICRS, based on information found in the European Pharmacopoeia, the USP and the scientific literature. The draft revised monograph was discussed at an informal consultation in May 2017, and was sent out for public consultation in August 2017. It was further revised and presented to the Expert Committee, together with a compilation of the comments received.

The Committee adopted the revised monograph as presented at the meeting.

2.5.7 For medicines for maternal, newborn, child and adolescent health

Norethisterone enantate (revision)

Norethisterone enantate injection

A revision of the monograph on norethisterone enantate and a new monograph on norethisterone enantate injection were prepared by a collaborating laboratory. The monographs were sent out for public consultation in July 2017. Thereafter they were further revised in view of the comments received, and were presented to the Committee together with a compilation of the comments.

The Committee considered the comments received and agreed to develop the monographs further for presentation to the informal consultation to be held in 2018 and subsequently to the Expert Committee at its fifty-third meeting.

2.5.8 For other medicines

Ciclosporin

A revision of the monograph on ciclosporin was proposed to align it with the requirements of other pharmacopoeias. The draft revised monograph was discussed at an informal consultation in May 2017 and sent out for public consultation in August 2017. The monograph was further revised and was presented to the Expert Committee together with a compilation of the comments received.

The Committee adopted the revised monograph as presented at the meeting.

2.5.9 For radiopharmaceuticals

The IAEA representative was unfortunately unable to attend the meeting. In his absence Dr Sabine Kopp presented an update of the current collaborative project with regard to the development of monographs for radiopharmaceuticals.

In line with the procedure “Updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*” (WHO Technical Report Series, No. 992, Annex 2) the following monographs had undergone a wide consultation process since 2012.

At its fifty-first meeting the Committee had been informed that a number of monographs had been updated by IAEA, pending review and finalization by a senior expert. Draft monographs on the radionuclides listed below were finalized during 2017 and submitted to the public consultation process of the Expert Committee in September 2017 in accordance with the agreed procedure for the elaboration of radiopharmaceutical monographs for *The International Pharmacopoeia*.¹⁸ They were presented to the Expert Committee at its fifty-second meeting.

A general chapter on radiopharmaceuticals and a series of specific dosage form monographs were also presented to the Expert Committee at its fifty-second meeting. These were draft revisions of current texts published in *The International Pharmacopoeia*. The revisions are intended to align the texts with current technologies. A number of them had completed the stages required prior to adoption, including two rounds of public consultation; the third round was expected to be finalized shortly.

The WHO Secretariat proposed that comments received on the monographs listed below should be discussed with IAEA and finalized in

¹⁸ Updating mechanism for the section on radiopharmaceuticals in *The International Pharmacopoeia*. In: WHO Expert Committee on Pharmaceutical Preparations. Fiftieth report. Geneva: World Health Organization; 2015: Annex 2 (WHO Technical Report Series, No. 992).

collaboration with IAEA experts, in line with Phases 6 and 7 of the published procedure.

The following set of monographs (Table 1) was drafted as a revision of published monographs in *The International Pharmacopoeia*.

Table 1

Set of monographs drafted as a revision of published monographs in *The International Pharmacopoeia*

General monograph	Radiopharmaceuticals
Specific monographs	
Radionuclides	
^{99m} technetium	(^{99m} Tc)technetium bismuthate complex injection (^{99m} Tc)technetium colloidal sulfur injection (^{99m} Tc)technetium colloidal tin injection (^{99m} Tc)technetium mebrofenin complex injection (^{99m} Tc)technetium medronate complex injection (^{99m} Tc)technetium mertiatide complex injection (^{99m} Tc)technetium pentetate injection sodium pertechnetate (^{99m} Tc) injection (fission) sodium pertechnetate (^{99m} Tc) injection (nonfission) (^{99m} Tc)technetium sestamibi complex injection (^{99m} Tc)technetium succimer complex injection (^{99m} Tc)technetium tetrofosmin complex injection
¹⁸ fluor	(¹⁸ F)fludeoxyglucose injection
⁶⁷ gallium	(⁶⁷ Ga)gallium citrate injection
¹²³ iodide	sodium (¹²³ I)iodide capsules iobenguane (¹²³ I) injection
¹²⁵ iodide	sodium (¹²⁵ I)iothalamate injection
¹³¹ iodide	iobenguane (¹³¹ I) injection
³² phosphor	sodium phosphate (³² P) injection

Table 1 *continued*

¹⁵³ Sm(samarium)	(¹⁵³ Sm)samarium lexidronam complex injection
⁸⁹ Sr(strontium)	(⁸⁹ Sr)strontium chloride injection
⁹⁰ Y(yttrium)	(⁹⁰ Y)yttrium silicate injection

The Committee adopted the monographs for inclusion in the 2018 edition of *The International Pharmacopoeia*, pending their finalization according to the procedure for developing radiopharmaceutical monographs. If any major technical issue is identified, the respective monographs will be presented again to the Expert Committee.

3. Quality control – international reference materials (International Chemical Reference Substances and Infrared Reference Spectra)

3.1 Report of the custodian centre

Dr Stefan Almeling presented a report on the activities of EDQM as the custodian centre in charge of ICRS in *The International Pharmacopoeia*. He provided an overview of the most frequently distributed ICRS and of progress achieved. Seven new ICRS have been established. Two laboratory studies have been completed and two others are ongoing.

Dr Almeling thanked all collaborating individuals and groups for their contributions to the development of ICRS by the custodian centre.

The Committee noted the report.

3.2 Update on International Chemical Reference Substances, including report of the dedicated Expert Committee on Specifications for Pharmaceutical Preparations subgroup on International Chemical Reference Substances

Dr Herbert Schmidt reported on progress made with the following ICRS that have been developed and are being distributed:

- Artesunate ICRS 2
- Atazanavir sulfate ICRS 2
- Capreomycin sulfate ICRS 1
- Lopinavir ICRS 1
- Lumefantrine ICRS 2
- Medroxyprogesterone acetate ICRS 2
- Medroxyprogesterone acetate impurity F ICRS 1

The Expert Committee confirmed the release of the above-mentioned ICRS.

The ICRS workplan 2017–2018 was presented to the Expert Committee. New ICRS will be established for metacycline hydrochloride, albendazole, levamisole hydrochloride, misoprostol, methylthioninium chloride and cycloserine. New intended uses will be introduced for the ICRS for ethinylestradiol, sulfamethoxazole, trimethoprim and mebendazole. The ICRS for quinidine sulfate, tenofovir disoproxil fumarate and ritonavir will be replaced.

The Secretariat thanked EDQM, the ICRS Board and laboratories participating in collaborative trials to determine the assigned content of quantitative ICRS for their support in establishing, maintaining, distributing and monitoring ICRS for use with the monographs of *The International Pharmacopoeia*.

The Committee adopted the proposed workplan. It was recommended to consider ways of expediting the development and release of ICRS to ensure that monographs newly published in *The International Pharmacopoeia* can be used without delay.

3.3 General policy

Following earlier Committee decisions, monographs in *The International Pharmacopoeia* that refer to pharmaceutical preparations that are no longer included in the WHO EML or invited for prequalification are transferred to a publicly accessible archive section on the WHO website, together with a note on their use reading as follows:

These monographs will neither be updated or revised nor will the prescribed International Chemical Reference Substances be further monitored. Users will need to ensure that the substance complies with current rules and regulations governing medicines in their respective territories and that the prescribed reference substances are still suitable for the intended use.

The Secretariat, after consultation with the custodian centre, proposed that ICRS included in such monographs should be made available for one year after the transfer of the respective monographs to the archive page on the WHO website, and they would then be removed from the ICRS catalogue. This period will enable users of *The International Pharmacopoeia* to identify an alternative reference substance.

In the discussion on this issue, it was noted that while the pharmaceutical products covered by the retired monographs are no longer on the EML or invited for prequalification, they may still be included in some national EMLs. It is therefore important that they remain available on the WHO website.

The Expert Committee agreed to the proposed procedure, including a phasing out period of one year. The Committee further noted that the term “omitted” monographs may be misleading and could be replaced by an alternative term, based on an analysis of terms used in other pharmacopoeias.

The Expert Committee agreed that the last statement in the note on the use of omitted monographs (“...and that the prescribed reference substances are still suitable for the intended use”) should be deleted.

4. Quality control – national laboratories

4.1 External Quality Assurance Assessment Scheme

WHO offers proficiency testing through its External Quality Assurance Assessment Scheme (EQAAS), enabling laboratories to assess and demonstrate the reliability of the data that they are producing. Since 2010, EQAAS has been organized with assistance from EDQM.

A total of 31 laboratories from all six WHO regions participated in Phase 7 of the EQAAS studies. Participants were required to perform a dissolution test and an assay by liquid chromatography on a single test sample, which was sulfadoxine and pyrimethamine tablets. In the dissolution study, 29 of 31 participating laboratories (94%) showed satisfactory results for pyrimethamine. For sulfadoxine, 74% of the laboratories provided results that could be considered satisfactory. In the assay study, 97% of participants reported satisfactory results for sulfadoxine and 87% for pyrimethamine. For both studies, possible sources of errors were identified, and laboratories with unsatisfactory results were invited to investigate their procedures and share the findings with WHO. A first round of responses had been received and advice provided accordingly.

Expressions of interest have been invited to participate in Phase 8 of WHO's EQAAS, which is expected to entail assay and the test for related substances on a single test sample of clindamycin hydrochloride.

During the discussion it was explained that the laboratories with unsatisfactory results were invited to share details of their failure investigations and corrective action plans. Some, but not all, laboratories did so. For prequalified laboratories, the outcome is shared with WHO-PQT and followed up during inspections.

WHO offers participation in EQAAS against a fee, which is below cost and preferential rates are available for participants from low- and middle-income countries based on the World Bank classification of income. WHO regional and country offices have been approached about including an amount for Phase 8 in their budgets for capacity-building plans.

The Committee noted the update and recommended that this important work should continue.

4.2 Considerations for requesting analysis of medicines samples and model certificate of analysis

4.2.1 Considerations for requesting analysis of samples

During an informal consultation on regulatory guidance held in July 2016 a suggestion was made to revise and update the 2002 WHO guidance on *Considerations for requesting analysis of drug samples*. A draft update was

presented to the Committee at its fifty-first meeting and circulated for public comment in November 2016. A revised draft was circulated for a second round of public comment in May 2017 and was presented to the Committee at its fifty-second meeting. No comments were received in response to the second round of public consultation.

The Expert Committee discussed the text and made some comments. The Committee then adopted the guidelines, subject to the amendments agreed (Annex 3).

4.2.2 Revision of the model certificate of analysis

Similar to the above, an update of the WHO model certificate of analysis, which was published in 2002 was suggested, to take into account new trends and international developments. A revision was proposed at an informal consultation held in 2016. A draft update was presented to the Committee at its fifty-first meeting and circulated for public comment in November 2016. The draft was revised further and circulated once more for public comment in May 2017 and was presented to the Committee at its fifty-second meeting. No comments had been received in response to the second round of public consultation.

The Committee discussed the guidelines and made some comments. The Committee then adopted the guidelines, subject to the amendments agreed (Annex 4).

4.3 Guidance on testing of “suspect” falsified medicines

At its forty-ninth meeting, the Expert Committee recommended that a general text on testing of “suspect” falsified medicines should be developed. The need for such a text had been expressed in the responses to a survey conducted among more than 50 quality control laboratories (QCLs). A first draft was circulated in August and September 2015 among the laboratories that had participated in the survey, and was presented to the Committee at its fiftieth meeting. The draft was then further revised and supplemented based on input from various groups and experts. The second draft was circulated for public comment in October 2016, and an update was provided to the Committee at its fifty-first meeting. The proposed text was further revised based on discussions at an informal consultation in May 2017 and on input from experts, including from those participating in the Member State Mechanism on SF medical products, and a third draft was circulated for comments in August 2017. The draft guidance and a compilation of comments were presented to the Committee at its fifty-second meeting.

The Committee adopted the new guidance, subject to the amendments agreed (Annex 5).

5. Prequalification of quality control laboratories

5.1 Update on the prequalification of quality control laboratories

Mr Rutendo Kuwana presented an update on the procedure for prequalification of QCLs to the Expert Committee. A total of 44 laboratories have been prequalified to date, of which five achieved prequalification during 2016 and two during 2017; a further 47 laboratories are working towards prequalification. He also highlighted some major areas in which laboratories often fail to comply with requirements. Technical assistance had been provided to 64 laboratories since 2006, with six audits or technical assistance visits having been conducted in 2017. In addition, 12 peer audits had been conducted since 2015, as well as training for auditors that was organized in June 2017. Peer audits have a capacity-building effect for both the auditing and the audited laboratory. Training has been organized on data integrity and on handling and maintenance of equipment; further training events are planned as a follow-up to the WHO-EQAAS proficiency studies (see section 4.1).

The Committee noted the update.

5.2 Update on WHO quality monitoring projects

As part of a sample-testing survey of WHO-prequalified antiretrovirals conducted in 2015, the accompanying product information was assessed. The Committee was provided with a preliminary overview of the findings. Overall, 82% of the samples were not in line with the information published in the WHO public assessment report, mainly due to changes in the order and the wording of the sections. Some differences were also noted in the indication and posology sections. Twenty-five per cent of the samples did not have a patient information leaflet. Of those that did, none of the leaflets met the criteria of readability and user-friendliness set in this survey.

A two-phase survey on the quality of antimalarials is under way. Phase I served to evaluate the feasibility of using near-infrared (NIR) and Raman spectroscopy in generating a reference library for prequalified products. This phase has been completed. NIR was found to be more suitable than Raman spectroscopy and will be used in Phase II of the survey, which is planned to start in the first quarter of 2018. In Phase II, market samples will be screened using the NIR technology applied in Phase I and fully tested at prequalified laboratories. The results will then be compared.

The Expert Committee noted the update.

6. Quality assurance – collaboration initiatives

6.1 International meetings of world pharmacopoeias

Since 2012 WHO, in cooperation with a world pharmacopoeia, has organized international meetings of world pharmacopoeias to facilitate convergence of pharmacopoeial standards and collaboration. The eighth international meeting of world pharmacopoeias was co-hosted by ANVISA (the regulatory authority of Brazil) and the Brazilian Pharmacopoeia, and was held in the WHO office in Brasilia, Brazil from 11 to 12 July 2017. Twenty-six representatives from 13 pharmacopoeias, including the European Pharmacopoeia, representing 38 national pharmacopoeias and pharmacopoeial authorities, participated actively in the meeting. The agenda included discussions on two Supplementary chapters to the main good pharmacopoeial practices (GPhP) (see section 6.2). The pharmacopoeias represented at the eighth international meeting issued a joint statement on the important role of public quality control standards in fighting antimicrobial resistance.¹⁹ The Brazilian Pharmacopoeia expressed its appreciation of the opportunity to host this important meeting.

In conjunction with the eighth international meeting of world pharmacopoeias, ANVISA organized its ninth Brazilian Pharmacopoeia meeting, which served as an opportunity to update a wide range of stakeholders on the collaborative work of the world pharmacopoeias.

The ninth international meeting of world pharmacopoeias will be hosted by the National Institute of Drug Quality Control of Viet Nam and the Vietnamese Pharmacopoeia. The Indian Pharmacopoeia Commission expressed interest in hosting the tenth meeting.

The Expert Committee noted the report and thanked Brazil for hosting the eighth international meeting of world pharmacopoeias. The Committee also thanked the authorities of Viet Nam and India for their willingness to host the ninth and tenth meetings, respectively.

6.2 Good pharmacopoeial practices

The primary objective of GPhP is to define approaches and policies for establishing pharmacopoeial standards, with the ultimate goal of harmonization. The main text of the GPhP guidance, which describes general principles for the design, development and maintenance of pharmacopoeial standards, had

¹⁹ Statement by Brazil, national, regional and international pharmacopoeias on the occasion of the 8th international meeting of the world pharmacopoeias, 21 August 2017. Available on the website of the regulatory authority of Brazil (ANVISA) via <https://goo.gl/nxyj82> at: <http://portal.anvisa.gov.br/documents/219201/3322895/Declaracao+A7+A3o+Farmacopeia+Ing+AAs.pdf/a46a93ba-3b16-4a4d-ac81-64b293ead1e1>.

been adopted by the Committee at its fiftieth meeting in 2015. Chapters on compounded preparations and on herbal medicines have also been developed (see sections 6.2.1 and 6.2.2). Once adopted, the additional GPhP texts will be published as annexes to the WHO Technical Report Series.

The Committee noted the report and thanked all representatives of the world pharmacopoeias that contributed to this important work.

Survey on GPhP

During the eighth international meeting of world pharmacopoeias it was decided to conduct a survey on the use of the GPhP. The survey questions were developed and sent out by several agencies including by Brazil, the European Pharmacopoeia, USP and WHO to their stakeholders.

Dr Sabine Kopp presented the outcomes of a survey on the use of the new GPhP guidance, which was coordinated by WHO in collaboration with the world pharmacopoeias. Approximately two thirds of the respondents identified in the survey stated that they were aware of the GPhP. Some stated that elements of the GPhP guidance had been incorporated into national practice, and a number of other uses of the GPhP were described. There did not seem to be a great demand for more technical detail or illustrative examples.

The USP presented an overview of the responses received through the survey link sent out to the USP's marketing research distribution list. Responses came predominantly from industry. The feedback received through the survey suggested that the GPhP guidance is of interest to a limited group of professionals. The European Pharmacopoeia and the Brazilian Pharmacopoeia had presented the responses they received to this survey at the eighth meeting of world pharmacopoeias.

The Committee noted the update. It was recommended that the use of GPhP guidance, as well as *The International Pharmacopoeia* and national pharmacopoeias, should be more widely advocated within WHO and among stakeholders and partners.

6.2.1 Draft chapter on compounding

Pharmacopoeial monographs for compounded preparations are generally developed by a pharmacopoeia and its expert committees rather than based on information received from specific manufacturers. The proposed text aims to define good practices for developing pharmacopoeial monographs for compounded preparations, including medicines prepared extemporaneously for a specific patient and those that are prepared in advance and held in stock in appropriate facilities.

Drafting of this chapter started in 2015 under the leadership of the British Pharmacopoeia, the Russian Pharmacopoeia and the USP. The proposed

text was discussed at the sixth, seventh and eighth international meetings of world pharmacopoeias, underwent several rounds of comments by world pharmacopoeias, and was posted on the WHO website for public comment. The draft chapter was presented to the Committee at its fifty-second meeting together with the most recent round of comments received.

The Committee adopted the proposed chapter as an annex to the WHO Technical Report Series, subject to its final revision and adoption by the pharmacopoeias by the end of 2017 (Annex 6).

6.2.2 Draft chapter on monographs on herbal medicines

This proposed text of the chapter on monographs on herbal medicines defines the principles to be observed when drafting a general chapter and specific monographs for herbal medicines. An initial draft was prepared by the IPC Committee in 2013, circulated several times for comment among world pharmacopoeias, discussed during the sixth, seventh and eighth international meetings of world pharmacopoeias and presented to the Expert Committee at its fiftieth and fifty-first meetings. It was posted for public comment on the WHO website in July 2017. At the eighth international meeting of world pharmacopoeias it was suggested that the definitions on herbal medicines should be aligned with those discussed at the third WHO consultation on quality control of herbal medicines organized by the WHO Traditional, Complementary and Integrative Medicine team and hosted by the Department of Health, Hong Kong SAR, China. The proposed draft supplementary chapter on monographs for herbal medicines was presented to the Expert Committee, together with comments received during the consultation process.

The Committee adopted the proposed chapter as an annex to the WHO Technical Report Series, subject to its final review and adoption by the pharmacopoeias by the end of 2017 (Annex 7).

6.3 Inspection guidelines and good practices

An oral update was provided by Dr Sabine Kopp on a collaboration for updating international guidance on GMP for sterile pharmaceutical products. WHO is actively participating in the joint revision process being undertaken by PIC/S and the European Medicines Agency. Draft revised guidelines have been prepared with technical input from the PQT inspection team and submitted to the European Commission. The guidelines will be circulated by the three above-mentioned parties for public consultation.

The Expert Committee noted the update.

7. Quality assurance – good manufacturing practices

7.1 Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems

A draft revision of WHO guidance on heating, ventilation and air-conditioning systems (HVAC) was prepared in 2015 to align the text with current guidance and practice. The document was further revised based on the outcomes of discussions at a technical consultation held in May 2016 and two rounds of public consultation, which each generated numerous comments. At its fifty-first meeting the Committee reviewed the revised text and agreed that, given the difficulty of maintaining specialized technical examples, the text should be split into two documents. One would be a guidance text containing WHO recommendations for HVAC systems for non-sterile products including their validation, and the other would be an illustrative document with design and implementation examples, to be published at a later stage. A revised guidance text was prepared and discussed at an informal consultation in April 2017, revised further and circulated for public consultation in July 2017. The draft guidance was amended to take into account the feedback received and was presented to the Committee at its fifty-second meeting together with a compilation of the comments received.

The Committee discussed the revised WHO guidance on HVAC and provided input on the remaining questions. The Committee adopted the revised guidelines with the amendments agreed (Annex 8). The Committee recommended that the illustrative part of the HVAC guidance be finalized and published as soon as possible.

7.2 WHO good manufacturing practices: validation, including main principles and specific texts (water, cleaning, computerized systems, qualification of systems and equipment, non-sterile)

Work to update the WHO guidance on validation and its seven appendices started in 2013. The revised Appendix 7, *Non-sterile process validation*, was adopted by the Expert Committee in October 2014. Draft revisions of the main text and of Appendices 4 (*Analytical method validation*), 5 (*Validation of computerized systems*) and 6 (*Qualification of systems and equipment*), were subsequently prepared, discussed at an informal consultation in May 2016, and circulated for public comment.

At its fifty-first meeting in October 2016 the Expert Committee adopted the revised main text of the validation guidelines with amendments as agreed during the meeting, and recommended that the revised main text should be published together with its revised appendices as follows: a cross-reference to

the main text on HVAC²⁰ in lieu of Appendix 1; a cross-reference to existing guidance on water for pharmaceutical use²¹ in lieu of Appendix 2, the republished Appendices 3 (*Cleaning*) and 7 (*Non-sterile process validation*) as they stand, and revisions of Appendices 4, 5 and 6.

The revisions of Appendices 4, 5 and 6 were discussed at an informal consultation on good practices for health products manufacture and inspection held in April 2017. All three appendices are at different stages of consolidation of comments and further revision, and will be circulated for a second round of public consultation. The revised appendices are expected to be presented to the Committee at its fifty-third meeting.

The Committee noted the update.

7.3 **Guidance on good practices for desk review for good manufacturing practices, confirmation in lieu of on-site assessment**

Good regulatory practices call for risk-based prioritization of regulatory inspections, with reliance, where appropriate, on desk review of inspection information from trusted sources. The need for new guidance on good practices for desk review of inspection information became apparent during a training symposium held in 2016 for national medicines authorities involved in collaborative registration. At its fifty-first meeting the Committee had discussed a concept paper and the proposed outline of this guidance prepared by PQT's inspection group in consultation with stakeholders. The guidance was developed by an expert with input from GMP inspectors working for regulatory authorities of the East African Community, and was discussed at an informal consultation on good practices for health products manufacture and inspection held in April 2017. Revised drafts were posted for public comment on the WHO website in May and in August 2017. The text was further revised and presented to the Expert Committee at its fifty-second meeting, together with the comments received.

The Committee adopted the guidelines, subject to the amendments agreed (Annex 9).

7.4 **Update and recommendations from the inspectors' meeting**

At an informal consultation on good practices for health products manufacture and inspection held in April 2017, it was noted that new technologies were being adopted for the manufacture of water for injections. The monograph on

²⁰ See section 7.1.

²¹ Water for pharmaceutical use. In: WHO Expert Committee on Pharmaceutical Preparations. Forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970).

“Water for injections” included in *The International Pharmacopoeia* describes a distillation process, whereas other technologies, such as reverse osmosis, have been included in other pharmacopoeias.

The Committee noted the report and recommended that the WHO Secretariat should collect feedback on whether to revise the WHO specifications and GMP in relation to the production of water for injections.

8. Regulatory guidance

8.1 Regulatory requirements on stability testing of active pharmaceutical ingredients and finished pharmaceutical products

The revised guidelines on stability testing were introduced to the Expert Committee. The 2009 update of the WHO guidelines on stability testing²² included cross-references to various related guidelines, as well as a separate Appendix 1 on *Long-term stability testing conditions as identified by WHO Member States*, which is updated continuously upon receipt of new information from national regulatory authorities. It is important to note that a decision was taken by the ICH Steering Committee to withdraw its ICH Q1F guidelines on storage conditions in Climatic Zones III and IV and to refer instead to the WHO guidelines. It was noted that ICH should be informed that the link on the ICH website section for ICH Q1F²³ refers to the 2009 WHO guidelines and needs to be updated once the revised guidelines are published.

Some queries on stability requirements stated in earlier WHO publications triggered an analysis to identify the areas of the stability guidelines in need of revision. In July 2016 the participants of a joint meeting of WHO and regulatory experts confirmed the needs for revision identified in the analysis, and at its fifty-first meeting the Expert Committee recommended that the guidelines should be updated as proposed. A revised text was prepared and was circulated for public consultation in January 2017. The feedback was compiled and discussed at a joint meeting on regulatory guidance held in July 2017. The draft was further revised, circulated for a second round of public consultation, and presented to the Committee at its fifty-second meeting together with a compilation of the comments received.

The Committee adopted the guidelines, subject to the amendments agreed (Annex 10).

8.2 Biowaiver list based on the WHO Model List of Essential Medicines

The Expert Committee was given an update on the revision of the WHO biowaiver list and the procedures envisaged for generating scientific data as a basis for this revision.

²² Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Pharmaceutical Preparations. Forty-third report. Geneva: World Health Organization; 2009: Annex 2 (WHO Technical Report Series, No. 953).

²³ International Council for Harmonisation (ICH). Q1A - Q1F Stability. Q1F. Stability data package for registration applications in climatic zones III and IV (<http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>).

8.2.1 Revision of the biowaiver list

As part of its 2006 guidance on waiving of bioequivalence requirements for immediate-release oral solid dosage forms on the WHO EML, WHO had provided a list of APIs that are eligible for biowaivers. The intention is for this list to be updated and maintained as a living document on the WHO website. In 2016 it was agreed that the list should be based on verified laboratory data instead of a literature-based approach.

The WHO Secretariat intends to coordinate a new multicentre project to determine the solubility profiles of APIs contained in medicines on the WHO EML to enable an informed decision on whether a biowaiver could safely be granted. The WHO Secretariat proposed that the Expert Committee contribute to updating the biowaiver list by proposing appropriate laboratories to perform the tests, review experimental protocol templates, review laboratory results, determine the APIs' Biopharmaceutics Classification System (BCS) class, and/or participate in the publication of results.

A number of members responded positively to the WHO Secretariat's call for support for the envisaged studies.

The Committee noted the report on the update of the WHO biowaiver list. WHO gratefully acknowledged the support offered by the members of the Expert Committee.

8.2.2 Conduct of solubility studies

During the design of studies to support the revision of the WHO biowaiver list, it became apparent that more guidance was needed on how to design and conduct solubility studies for the purpose of classifying APIs within the BCS. A guidance text was drafted in March 2017, building on recently adopted WHO guidance on equilibrium solubility experiments²⁴ and on the general chapter on solubility measurements included in the Brazilian Pharmacopoeia in 2016. The proposed guidance was discussed with relevant specialists and at a joint meeting on regulatory guidance held in July 2017. The proposal was further revised and circulated for public consultation in September 2017. It was presented to the Committee at its fifty-second meeting together with comments received.

The Committee noted the update on this draft guidance and endorsed the proposed approach to conducting the solubility studies, using this guidance as part of the protocol.

²⁴ Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the biopharmaceutics classification system, Appendix 2 to Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Pharmaceutical Preparations. Fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003).

8.3 Collaborative procedure for the assessment and accelerated national registration of medicines and vaccines approved by stringent regulatory authorities

Based on experience gained with the collaborative registration procedure for WHO-prequalified products,²⁵ a pilot procedure for collaborative registration of pharmaceutical products approved by an SRA was developed in 2014. The pilot procedure provides a mechanism for confidential sharing of detailed assessment information for a specific product, generated by the relevant reference SRA. The applicant submits the SRA's information to the regulatory authority in the target country, and the SRA will provide authentication on request. The information may include a bridging report relating to the use of the product in the target country, as opposed to its use in the country over which the SRA has jurisdiction.

At its fifty-first meeting the Expert Committee endorsed the WHO Secretariat's proposal to develop WHO guidelines for collaborative registration of SRA-approved products in line with the principles adopted during the pilot study. Such a procedure can shorten the time needed to gain approval, promote collaboration and support regulatory convergence and capacity-building. WHO will facilitate applications only for products needed in public treatment programmes of interest to the Organization. The principles of the procedure were discussed by participating regulators at the fourth annual meeting on collaborative registration of prequalified products, held in Cape Town, South Africa, in December 2016. A draft text was prepared and underwent two rounds of public consultation in March and August 2017. The proposed guidance was further revised and presented to the Committee together with a compilation of comments received.

The Committee noted that this procedure will be very useful to increase access to quality-assured medicines (both innovative and generic), particularly biotherapeutic products, in Member States.

The Committee adopted the guidelines, subject to the amendments agreed (Annex 11).

²⁵ Collaborative procedure between the World Health Organization (WHO) prequalification team medicines and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. In: WHO Expert Committee on Pharmaceutical Preparations. Fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996).

8.4 Good practices for implementing the collaborative procedures

The need for collaboration and reliance to achieve effective regulation of medical products is well recognized. The WHO collaborative registration procedure for prequalified products²⁶ and the pilot procedure for products approved by an SRA (see section 8.3) have been implemented for this purpose. Experience with the implementation of these two procedures has shown that clear procedures for regulatory authorities are critical. A concept paper was presented to the Expert Committee proposing the development of new guidance for regulators on implementing the collaborative procedures in line with relevant WHO guidance on regulatory best practices. An outline of such a guidance document was proposed by RSS and was included as an annex to the concept paper. The aim of the guidance is to support national regulatory authorities in making effective use of accelerated pathways for registration of medical products.

The Expert Committee endorsed the proposal to develop a good practice guidance document on implementing accelerated registration procedures.

8.5 Good regulatory practices

The importance of RSS is widely recognized and is reflected in World Health Assembly Resolution 67.20. Delegates at the fourteenth ICDRA called for the development of guidelines on good regulatory practices (GRP). A number of workshops were held with representatives of WHO Member States and public health stakeholder organizations, leading to the production of high-level guidelines that adapt internationally recognized GRP principles to the regulation of medical products. In October 2016 the draft text was sent out for public consultation. The comments received were considered by both the ECBS and the ECSP, which had welcomed the development of this much-needed guidance at its fifty-first meeting. The draft text was discussed at an informal consultation on regulatory matters held in July 2017, and was presented to the Expert Committee at its fifty-second meeting for information. The document will be revised further and circulated for a second round of public consultation. A revised draft will be presented to the Expert Committee and to the ECBS at their 2018 meetings.

The Expert Committee noted the update.

²⁶ Collaborative Procedure between the World Health Organization (WHO) Prequalification Team and National Regulatory Authorities in the Assessment and Accelerated National Registration of WHO-prequalified Pharmaceutical Products and Vaccines. In: WHO Expert Committee on Pharmaceutical Preparations. Fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996).

8.6 Quality management systems for national regulatory authorities

A quality management system (QMS) is an instrument to comply with good regulatory principles for the development, implementation and maintenance of laws, regulations and guidelines and all other regulatory functions. Generic guidance on quality management is available, notably from the International Organization for Standardization (ISO) 9001:2015 and its related guidance documents. ISO provides guidance on a maturity assessment of quality management with four levels: Level 1 (no formal approach), Level 2 (reactive approach), Level 3 (stable formal approach) and Level 4 (continual improvement emphasized).

National regulatory authorities (NRAs) of 23 countries in four WHO regions have assessed their QMS against the indicators of the Global Benchmarking Tool (GBT). The results showed that the authorities' QMSs were not fully implemented, suggesting that specific guidance on the subject may be useful for NRAs. RSS therefore proposed the development of a WHO guidance document to support and facilitate the implementation of QMS for regulatory authorities. An update would be presented to the Committee in 2018, and a mature draft would be submitted to the Committee in 2019.

The Expert Committee endorsed the proposal to undertake this work.

9. Prequalification of priority essential medicines and active pharmaceutical ingredients

9.1 Update on the prequalification of medicines

Mr Deus Mubangizi gave an update on PQT. He thanked the Expert Committee for its work in reviewing and adopting the norms and standards that underlie prequalification and pointed out that PQT provides feedback on its experience with implementation of the guidance. The common standards developed in this way are promoting harmonization across WHO regions in the area of pharmaceutical quality management. Mr Mubangizi gave some examples of the specific tools and procedures used in prequalification, which have had positive spin-offs in regulatory capacity-building, promotion of unified standards and awareness of quality among all stakeholders.

WHO prequalification is now widely acknowledged as a guarantee of quality and as a global public health good. Prequalification encompasses vaccines, medicines and in vitro diagnostic products. A work stream on vector control products was added in 2017. Calls are increasing for it to be extended to additional therapeutic areas.

With respect to the long-term financing of WHO diagnostics, medicines and vaccines prequalification, a new fee structure was introduced in January 2017 for medicines.

The Committee noted the report and expressed its sincere appreciation of this team.

9.2 Update on the prequalification of active pharmaceutical ingredients

A brief update on the API prequalification procedure was provided by Dr Antony Fake. It was highlighted that API assessment is undertaken either in the context of a finished pharmaceutical product for which prequalification is being sought, or in the independent API prequalification procedure. It was noted that there is now a strong preference for use of the API prequalification as a means for supplying API information as illustrated by the fact that 60 of the 64 API master files (APIMFs) under evaluation are in support of an API for which prequalification is sought. Significant reductions in the time taken to complete the initial assessment of an APIMF have occurred, down from 155 days in 2015 to 50 days in 2017. However, it was also noted that work associated with post-prequalification changes continues to increase proportionally to the total number of prequalified APIs. Implementation of ICH Q3D and acceptance of documentation via file transfer protocol sites are under discussion.

The Committee noted the update.

10. Nomenclature, terminology and databases

10.1 Definition of “stringent regulatory authority”

The WHO prequalification procedure and several other WHO guidance documents provide for mechanisms to rely on SRAs, defining an SRA as a regulatory authority which is a member or an observer of ICH, or is associated with an ICH member through a legally binding mutual recognition agreement. Following the expansion of ICH to include organizations and associations at the global level, the Committee adopted an interim definition of an SRA proposed by the WHO Secretariat, which includes the same elements as the current definition, each qualified by the added statement “*as before 23 October 2015*”. It was also noted that work is advancing towards a new approach to assessment of NRAs based on their maturity, using the GBT of NRAs.

Following discussions within WHO and with participants at a joint meeting on regulatory guidance held in July 2017, a proposal was drafted and posted for public comment on the WHO website and in the *WHO Drug Information journal*.

The proposed approach sets out four principles to apply in qualifying regulatory authorities as “on the list” (the term “stringent” will also be revisited): (1) grandfathered SRAs: authorities meeting the criteria of the interim definition should continue to be “on the list”; (2) the process and outcomes used to include additional NRAs should be made publicly available; (3) the WHO-GBT maturity level 4 assessments and risk-based reassessment should be used as criteria for adding and maintaining NRAs “on the list”; and (4) a modular approach should be used to enable NRAs to be included “on the list” for a specific function and/or product group. The proposal, a compilation of comments received and a summary of the main issues were presented to the Committee at its fifty-second meeting.

The topics for discussion that were raised in the summary of comments received in response to the public consultation were:

- firstly, an appropriate term to replace the term “stringent”;
- secondly, the desired characteristics of the authorities to be listed and the process to be followed for including them in the list, and
- thirdly, whether global stakeholders should be guided by a generic description of what constitutes a “recognized” regulatory authority or by the actual WHO list of authorities.

It was further suggested that this list could be drawn up taking a phased approach, by starting with the authorities meeting the interim definition and adding additional ones when the criteria have been agreed and the GBT or other relevant tools have been validated. It was noted that the ultimate responsibility and decision on use of the list (as applied to any specific NRA) resides with the user of the list and depends on the specific context of its intended use.

It was recommended that this be a voluntary process initiated by a request from the authority concerned. Details of the GBT should be made publicly available. An authority may be listed with respect to specific functions and/or product groups. The list of authorities should be periodically updated.

The Committee recommended:

- that the term “stringent regulatory authority (SRA)” be replaced by “WHO-listed authority”;
- that those NRAs currently identified as “SRAs” in accordance with the current interim definition be regarded as WHO-listed authorities;
- that the designation of additional NRAs as WHO-listed authorities should be based on an assessment against the GBT, as well as successful completion of an agreed and transparent confidence-building process;
- that a procedure for listing be developed through the usual public consultation process.

10.2 Quality assurance terminology

The Committee was informed that the list of terms and definitions used in medicines quality assurance had been updated to include those from the guidance texts published in the WHO Technical Report Series, up to and including no. 1003 of 2017.

The Committee noted the report and thanked the Secretariat for its efficiency in maintaining this list.

10.3 Guidelines and guidance texts adopted by the Committee

The Committee was informed that an article on 70 years of the ECSPP had been published in the *WHO Drug Information journal*.²⁷ The article contains a list of all current guidelines adopted by the Committee. A database of guidelines is maintained by WHO.

The Committee noted the update and thanked the Secretariat for this work.

10.4 International Nonproprietary Names for pharmaceutical substances

Dr Raffaella Balocco provided an update from the WHO International Nonproprietary Names (INN) Programme, which assigns unique names to new

²⁷ 70 years of WHO standards on medicines quality. Expert Committee on Specifications for Pharmaceutical Preparations, 1947-2017: Addressing changing public health challenges. WHO Drug Info. 31;2017:15–26.

pharmaceutical substances. In recent years, an increasing number of applications had been received for naming of biological substances, and particularly monoclonal antibodies. Brief written updates were presented to the Committee on the nomenclature scheme for monoclonal antibodies, the work of the fusion protein working group and the nomenclature schemes for advanced therapies. The Committee was further informed that WHO plans to establish a School of INN to promote the use of INN by all stakeholders globally, as a common nomenclature for all pharmaceutical substances. A steering committee for this project has been appointed. The Committee was informed of the outcomes of a brief online survey conducted in 2016 to explore the current use of INNs in practice and education.²⁸ The School of INN will be a virtual school delivering training and education through the Internet. An electronic platform is in development. The School will be promoted through a leaflet to be included in major pharmacological textbooks.

The Expert Committee noted the update.

10.5 **Guidance on the graphic representation of pharmaceutical substances**

Guidance on representation of graphic formulae in *The International Pharmacopoeia* and on the list of INN was first published in 1996.²⁹ At its fiftieth meeting the Expert Committee confirmed that an update of this guidance would be useful. At the Committee's fifty-first meeting some examples of graphic representation of formulae for biological products were presented, highlighting the need for a harmonized approach in this area. Thereafter a working document was prepared and circulated among INN experts, the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, world pharmacopoeias and the WHO collaborating centres working on the development of monographs for *The International Pharmacopoeia*. The draft text and the comments received were presented to the Committee for input. Once feedback from all relevant parties has been compiled and addressed, the document will be circulated for public consultation.

The Committee noted the report.

²⁸ An article presenting the main survey findings was submitted for publication in Issue 4 (2017) of the *WHO Drug Information* journal (www.who.int/medicines/publications/druginformation).

²⁹ Guidelines for the graphic representation of chemical formulae. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report. Geneva: World Health Organization; 1996: Annex 1 (WHO Technical Report Series, No. 863).

11. Miscellaneous

11.1 WHO Department of Essential Medicines and Health Products: Strategic vision

As mentioned by Dr Sue Hill in her introduction to the meeting, the WHO-EMP department has adopted a strategic framework entitled “Towards Access 2030”.

The new 2030 development agenda and increasing globalization of health products development and supply have generated a need – and an opportunity – for WHO to adjust and strengthen its work in this area at all three levels of the Organization. WHO needs to ensure that headquarters, regional and country offices function more organically to deliver on development targets, and that health systems strengthening activities result in tangible progress for people everywhere. This new long-term framework for 2016–2030 aims to provide a broad vision and strategic direction to focus and reinforce WHO’s ability to help Member States achieve universal access to safe and quality-assured health products and universal health coverage.

12. Closing remarks

The Chair thanked the Committee for its standard-setting work, which has an impact for many people in all of WHO's Member States. She thanked the observers for their active participation and contributions. Ms Emer Cooke thanked all participants for their contributions and for the high-quality discussions held at the meeting. She thanked the Chair, the Vice-chair and the Rapporteurs for contributing to an efficient meeting.

The Chair closed the meeting and wished the participants a safe journey.



13. Summary and recommendations

The WHO Expert Committee on Specifications for Pharmaceutical Preparations advises the Director-General of WHO in the area of medicines quality assurance. The Committee oversees the maintenance of *The International Pharmacopoeia* and provides guidance for use by relevant WHO units and regulatory authorities in WHO Member States to ensure that medicines meet unified standards of quality, safety and efficacy. The Committee's guidance documents are developed through a broad consensus-building process, including an iterative public consultation phase. Representatives from international organizations, non-state actors, pharmacopoeias and relevant WHO departments are invited to the Committee's annual meetings to provide updates and input to its discussions.

At its fifty-second meeting held from 16 to 19 October 2017 in Geneva, Switzerland, the Expert Committee heard updates on cross-cutting issues from other WHO bodies including the Expert Committee on Biological Standardization, the Expert Committee on the Selection and Use of Essential Medicines, the Traditional, Complementary and Integrative Medicine team, the programme working to combat antimicrobial resistance, the Member State Mechanism on substandard and falsified medical products, the International Nonproprietary Names (INN) Programme, and the Regulatory Systems Strengthening (RSS) unit. Updates were also presented by partner organizations including the United Nations Children's Fund, the Global Fund to Fight AIDS, Tuberculosis and Malaria, the United Nations Development Programme and the Pharmacopoeial Discussion Group.

Progress updates on quality control activities were presented by the European Directorate for the Quality of Medicines & HealthCare as the custodian centre in charge of International Chemical Reference Substances (ICRS) for use with monographs of *The International Pharmacopoeia*, and from the International Atomic Energy Agency on the development of radiopharmaceutical monographs. Briefings were also provided on the outcomes of the eighth international meeting of world pharmacopoeias, which was co-hosted by WHO and the Brazilian Pharmacopoeia and ANVISA, and on the results of proficiency testing studies conducted in Phase 7 of the WHO External Quality Assurance Assessment Scheme (EQAAS).

Progress updates were provided on prequalification of medicines, active pharmaceutical ingredients and quality control laboratories, and on completed and planned surveys to monitor the quality of medicines circulating on the markets of Member States.

The Expert Committee reviewed new and revised specifications and general texts for quality control testing of medicines for inclusion in *The International Pharmacopoeia*. The Committee adopted 11 guidelines and 77 pharmacopoeial texts (one general chapter, 10 new and 11 revised monographs for

pharmaceutical dosage forms, 32 revised monographs with alternative methods replacing titration with mercuric acetate, and 24 revised radiopharmaceutical monographs), and confirmed the release of seven new ICRS established by the custodian centre for ICRS.

At its fifty-second meeting the Expert Committee made the decisions and recommendations listed below.

The following guidelines were adopted and recommended for use:

- WHO guidelines on good herbal processing practices for herbal medicines (Annex 1)
- WHO good manufacturing practices for herbal medicines (revision) (Annex 2)
- Considerations for requesting analysis of medicines samples (revision) (Annex 3)
- WHO model certificate of analysis (revision) (Annex 4)
- WHO guidance on testing of “suspect” falsified medicines (Annex 5)
- Good pharmacopoeial practices: Chapter on compounding (Annex 6)
- Good pharmacopoeial practices: Chapter on monographs on herbal medicines (Annex 7)
- Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems (revision) (Annex 8)
- Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions (Annex 9)
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (revision) (Annex 10)
- Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (Annex 11)

The Committee endorsed the proposed approach to conducting solubility studies for the purpose of revising the WHO biowaiver list.

For inclusion in *The International Pharmacopoeia*

The following general texts were adopted by the Committee:

General chapters

- General chapter on capillary electrophoresis

Monographs

For antimalarials

- pyrimethamine (revision)
- pyrimethamine tablets

For antiviral medicines, including antiretrovirals

- atazanavir sulfate (revision)
- atazanavir capsules (revision)
- efavirenz, emtricitabine and tenofovir disoproxil fumarate tablets (revision)
- ganciclovir
- ganciclovir for injection

The Committee also adopted revised titles for the monographs on tenofovir disoproxil fumarate tablets, and emtricitabine and tenofovir disoproxil fumarate tablets.

For antituberculosis medicines

- capreomycin sulfate (revision)
- capreomycin powder for injection (revision)
- moxifloxacin hydrochloride
- moxifloxacin tablets
- protionamide (revision)
- protionamide tablets

For medicines for infectious diseases

- amoxicillin trihydrate (revision)
- amoxicillin and clavulanic acid
- clavulanate potassium
- clindamycin palmitate hydrochloride
- clindamycin palmitate powder for oral solution

For medicines for chronic diseases and for mental health

- atenolol (revision)
- dacarbazine (revision)

For other medicines

- ciclosporin (revision)

In addition, the Committee approved the alternative titration methods and endorsed the revision of the following 32 monographs that currently prescribe titrations using mercuric acetate:

- amiloride hydrochloride
- amitriptyline hydrochloride
- biperiden hydrochloride
- chlorhexidine dihydrochloride
- chlorpromazine hydrochloride
- dopamine hydrochloride
- edrophonium chloride
- ephedrine hydrochloride
- ethambutol hydrochloride
- fluphenazine hydrochloride
- homatropine hydrobromide
- homatropine methylbromide
- ketamine hydrochloride
- lidocaine hydrochloride
- loperamide hydrochloride
- metoclopramide hydrochloride
- morphine hydrochloride
- naloxone hydrochloride
- neostigmine bromide
- pilocarpine hydrochloride
- procarbazine hydrochloride
- proguanil hydrochloride
- propranolol hydrochloride
- pyridostigmine bromide
- pyridoxine hydrochloride
- quinine dihydrochloride
- quinine hydrochloride
- suxamethonium chloride

- tetracycline hydrochloride
- thiamine hydrobromide
- thiamine hydrochloride
- verapamil hydrochloride

For radiopharmaceuticals

- General monograph on radiopharmaceuticals (revision)
- fludeoxyglucose (18F) injection (revision)
- gallium (67Ga) citrate injection (revision)
- iobenguane (123I) injection (revision)
- iobenguane (131I) injection (revision)
- samarium (153Sm) lexidronam complex injection (revision)
- sodium (125I) iothalamate injection (revision)
- sodium iodide (131I) capsules (revision)
- sodium pertechnetate (99mTc) injection (fission) (revision)
- sodium pertechnetate (99mTc) injection (non-fission) (revision)
- sodium phosphate (32P) injection (revision)
- strontium (89Sr) chloride injection (revision)
- technetium (99mTc) bicisate complex injection (revision)
- technetium (99mTc) colloidal sulfur injection (revision)
- technetium (99mTc) colloidal tin injection (revision)
- technetium (99mTc) mebrofenin complex injection (revision)
- technetium (99mTc) medronate complex injection (revision)
- technetium (99mTc) mertiatide complex injection (revision)
- technetium (99mTc) pentetate complex injection (revision)
- technetium (99mTc) sestamibi complex injection (revision)
- technetium (99mTc) succimer complex injection (revision)
- technetium (99mTc) tetrofosmin complex injection (revision)
- technetium (99mTc) tin pyrophosphate complex injection (revision)
- yttrium (90Y) silicate injection (revision)

International Chemical Reference Substances

The Committee confirmed the release of the following ICRS that have been newly characterized by the custodian centre, the European Directorate for the Quality of Medicines & HealthCare:

- Artesunate ICRS 2
- Atazanavir sulfate ICRS 2
- Capreomycin sulfate ICRS 1
- Lopinavir ICRS 1
- Lumefantrine ICRS 2
- Medroxyprogesterone acetate ICRS 2
- Medroxyprogesterone acetate impurity F ICRS 1

The Committee furthermore released the following reference substances for use according to the provisions described in the related monographs:

- ganciclovir reference substance for system suitability (containing impurities A, B, C, D, E and F) established by the European Pharmacopoeia;
- moxifloxacin for peak identification reference substance (containing moxifloxacin and the impurities A, B, C, D and E) established by the European Pharmacopoeia.

The Committee adopted the ICRS workplan for 2017–2018.

Recommendations

The Expert Committee made the recommendations listed below in the various quality assurance-related areas. Progress on the suggested actions will be reported to the Committee at its fifty-third meeting.

The International Pharmacopoeia

The Committee recommended that the Secretariat, in collaboration with experts as appropriate, should:

- request the working group that was established at the informal consultation in May 2017 on the transition from microbiological to chromatographic assay of capreomycin to analyse the situation and advise on the way forward.
- Consider ways of further expediting the development and release of ICRS to ensure that monographs newly published in *The International Pharmacopoeia* can be used without delay.
- Introduce a “phasing out period” of one year for the distribution of ICRS related to monographs that are no longer included in *The International Pharmacopoeia*, starting from the date when the

monographs are transferred to the WHO webpage for omitted monographs. Note that the term “omitted” may be replaced by an alternative term in line with wording used by other pharmacopoeias.

- Delete the statement requiring users of monographs that are no longer included in *The International Pharmacopoeia* to verify that the reference substances prescribed in the monographs are still suitable for the intended use.

Quality control – national laboratories

- Continue offering the External Quality Assurance Assessment Scheme (EQAAS)

Quality control – collaboration initiatives

- Advocate the use of good pharmacopoeial practices guidance, as well as the use of *The International Pharmacopoeia* and national pharmacopoeias through communication within WHO and with Member States, stakeholders and partners.
- Continue the efforts with the European Union and PIC/S towards jointly updated GMP for sterile products.

Quality assurance – good manufacturing practices

- Initiate a maintenance process to align the references and definitions in the guidance on GMP for herbal medicines with other current WHO guidance as relevant.
- Finalize and publish the illustrative part of the guidance on heating, ventilation and air-conditioning as soon as possible.
- Collect feedback on whether to revise the WHO specifications and good manufacturing practices in relation to the production of water for injections.

Regulatory guidance

- Prepare a proposal for revision of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, for public consultation.
- Develop a good practice guidance document on implementing accelerated registration procedures.

- Develop a guidance document to support and facilitate the implementation of quality management systems for national regulatory authorities.

Nomenclature, terminology and databases

With regard to the definition of stringent regulatory authorities, the Committee recommended:

- that the term "stringent regulatory authority (SRA)" be replaced by "WHO-listed authority";
- that those NRAs currently identified as "SRAs" in accordance with the current interim definition be regarded as WHO-listed authorities;
- that the designation of additional NRAs as WHO-listed authorities should be based on an assessment against the Global Benchmarking Tool, as well as successful completion of an agreed and transparent confidence-building process; and
- that a procedure for listing be developed through the usual public consultation process.

Continue the updating of the WHO nomenclature database, including terms and definitions adopted by the ECSP and of principles used when representing graphic formulae.

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Yogyakarta, Indonesia; Food and Drugs Control Laboratories, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran; Caribbean Regional Drug Testing Laboratory, Kingston, Jamaica; Mission for Essential Drugs and Supplies, Nairobi, Kenya; National Quality Control Laboratory for Drugs and Medical Devices, Nairobi, Kenya; Food and Drug Quality Control Center, Ministry of Health, Vientiane, Lao People's Democratic Republic; Laboratoire de Contrôle de Qualité des Médicaments, Agence du Médicament de Madagascar, Antananarivo, Madagascar; Centre for Quality Control, National Pharmaceutical Control Bureau, Petaling Jaya, Selangor, Malaysia; Laboratoire National de la Santé du Mali, Bamako, Mali; Laboratoire National de Contrôle des Médicaments, Rabat, Morocco; Quality Surveillance Laboratory, Windhoek, Namibia; National Medicines Laboratory, Department of Drug Administration, Kathmandu, Nepal; Laboratoire National de Santé Publique et d'Expertise, Niamey, Niger; Central Quality Control Laboratory, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Drug Control and Traditional Medicine Division, National Institute of Health, Islamabad, Pakistan; Instituto Especializado de Análisis, Universidad de Panamá, Panama; Centro Nacional de Control de Calidad, Instituto Nacional de Salud, Lima, Peru; Bureau of Food and Drugs, Department of Health, Muntinlupa City, Philippines; Laboratory for Quality Control of Medicines, Medicines Agency, Ministry of Health, Chisinau, Republic of Moldova; National Drug and Cosmetic Control Laboratories, Drug Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Laboratoire National de Contrôle des Médicaments, Dakar Etoile, Senegal; Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Centre for Quality Assurance of Medicines, Faculty of Pharmacy, North-West University, Potchefstroom, South Africa; Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; National Drug Quality Assurance Laboratory, Ministry of Health, Colombo, Sri Lanka; National Drug Quality Control Laboratory, Directorate General of Pharmacy, Federal Ministry of Health, Khartoum, Sudan; Pharmaceutical Analysis Laboratory, R&D, The School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, United Republic of Tanzania; Tanzania Food and Drug Authority, Dar-es-Salaam, United Republic of Tanzania; Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Laboratoire National de Contrôle des Médicaments, Tunis, Tunisia; National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; Central Laboratory for Quality Control of Medicines of the Ministry of Health of Ukraine, Kiev, Ukraine; Laboratory of Pharmaceutical Analysis, State Pharmacological Centre, Ministry of Health of Ukraine, Kiev, Ukraine; Laboratorio Control de Productos MSP, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; Instituto Nacional de Higiene "Rafael Rangel", Caracas, Venezuela; National Institute of Drug Quality Control, Hanoi,

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Annex 1

WHO guidelines on good herbal processing practices for herbal medicines

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1. Introduction

1.1 Background to development of guidelines

1.1.1 Needs

Over the past three decades, there has been a constant, and at times, exponential growth in global interest in the use of herbal medicines. This increase in popularity and usage of herbal medicines is evident in the global market. Herbal medicines, including finished herbal products and the starting materials for their production, such as medicinal plants, herbal materials, herbal preparations and herbal dosage forms, are moving into international commerce and global trade, which reflects their increased economic value and importance.

Adverse events reported to the regulatory authorities in relation to the use of herbal products are often attributable to poor quality of source material and manufacturing and processing factors, among others. Correct identification of source plant species and the selection of appropriate parts for use in herbal medicines are basic and essential steps for ensuring safety, quality and efficacy of herbal medicines. Hence, the safety and quality of herbal medicines at every stage of the production process have become a major concern to health authorities, health care providers, the herbal industries and the public.

The safety and efficacy of herbal medicines largely depend on their quality. Unlike pharmaceutical products formulated from single-molecule chemicals produced synthetically or by isolation from natural source materials employing reproducible methods, herbal medicines consist of simple processed herbs or finished herbal products prepared from source materials containing a multiplicity of chemical constituents, the quality and quantity of which can vary from batch to batch due to intrinsic and extrinsic factors. Consequently, the quality of finished herbal products is greatly influenced by the quality of the raw materials and the intermediates; and the requirements and methods for quality control of finished herbal products, particularly for mixed herbal preparations, are far more complex than those employed for single-molecule chemical medicines.

A number of World Health Assembly (WHA) resolutions relating to traditional medicine have requested the World Health Organization (WHO) to provide technical support to develop methodology to monitor or ensure the safety, quality and efficacy of herbal medicines. The International Conferences of Drug Regulatory Authorities, and annual meetings of International Regulatory Cooperation for Herbal Medicines, as well as the Meetings of the National Centres Participating in the WHO International Drug Monitoring Programme have also requested WHO to develop and continuously update the technical guidelines on quality, safety and efficacy of herbal medicines.

1.1.2 Process and context

Participants of the WHO informal meeting on methodologies for quality control of finished herbal products (held in Ottawa, Canada in July 2001) looked at the overall picture of herbal medicines: from raw materials to the distribution and supply of finished herbal products, including key steps at which quality control is required.

One of the main recommendations of the meeting was that WHO should prepare a series of technical guidelines and documents covering quality control issues (from raw materials to finished herbal products), as well as to update existing documents.

Following the meeting's recommendations, and as a part of the implementation of relevant WHO strategies (notably, WHO traditional medicine strategies and WHO medicines strategies) and WHA resolutions, WHO undertook the development of four new guidelines and updated other existing documents. Their aim is to provide technical guidance on quality control required at key steps in the production of herbal medicines to support Member States in their efforts to ensure the quality of herbal medicines. These guidelines are:

- *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants (1);*
- *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues (2);*
- *WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines (3); and*
- *WHO guidelines on good herbal processing practices for herbal medicines (present document).*

WHO has also updated two key technical guidance documents:

- *WHO good manufacturing practices (GMP): supplementary guidelines for the manufacture of herbal medicines (4), which was also reproduced in WHO guidelines on good manufacturing practices (GMP) for herbal medicines (5) and further updated (6); and*
- *Quality control methods for herbal materials (7), which includes the WHO good practices for pharmaceutical quality control laboratories as an annex.*

1.1.3 Preparation of the guidelines

The original title suggested for these guidelines was "Good processing practices for herbal materials". The working draft guidelines were reviewed, and the objectives, scope and proposed contents were discussed and agreed to at the

second WHO consultation on quality control of herbal medicines (Hong Kong SAR, China in November 2014). The first draft guidelines were drafted and revised twice, through a global review process. The second revised draft was reviewed and discussed at the third WHO consultation on quality control of herbal medicines held in Hong Kong SAR, China, in September 2017. The draft was then further revised based on the discussion and consensus reached at the third WHO consultation.

1.2 Scope

Herbal processing encompasses the unique procedures of preparing herbal materials and herbal preparations, and it may be extended to the production of finished herbal products, with the ultimate goal of assuring herbal medicines quality. Thus, within the context of quality assurance and control of herbal medicines, the *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants (1)* cover the cultivation and collection of medicinal plants, together with certain post-harvest operations in which the concept of “post-harvest processing” is laid down. The good herbal processing practices (GHPP) set out in the present guidelines are intended to complement, and should be used in conjunction with, the GACP guidelines. On the other hand, the *WHO guidelines on good manufacturing practices (GMP) for herbal medicines (4–6)* have established general technical requirements for quality assurance and control in the manufacture of herbal medicines. In general, they cover the production steps following “post-harvest processing”, including steps known as “processing”. The GHPP guidelines are thus intended to supplement technical guidance on processing in the post-harvest stages.

In this scenario, GHPP is integrally linked to GACP and GMP, by elaborating on the post-harvest processing procedures (which are dealt by the former) and supplementing the latter on processing procedures for the production and manufacture of herbal medicines. These guidelines will provide technical guidance on GHPP in the:

- processing of herbs into herbal materials;
- processing of herbal materials into herbal preparations; and
- processing of herbal materials or herbal preparations into herbal dosage forms.

1.2.1 Processing of herbs into herbal materials

The concept of post-harvest processing set out in the GACP encompasses the immediate treatments accorded to herbs obtained from cultivation or field collection to free them from foreign matter, untargeted or extraneous plant

materials and other contaminants. Integral to the preparation of herbal materials are the procedures of “inspection” and “sorting”, as well as “primary processing” procedures such as washing, disinfection, primary cutting, cooling, freezing and “drying”. These processes are described in detail in these GHPP guidelines.

In addition, various other “primary processing” procedures are applied to herbs, as a single processing procedure or as combined procedures. These include a well-defined series of procedures intended to alter their toxicity or modify their medicinal activity. These procedures include advanced cutting and comminution (fragmentation), ageing, sweating (fermentation), baking/roasting, boiling/steaming, stir-frying and primary distillation. Technical information on these *primary processing* procedures, applied during the *post-harvest processing* process are also elaborated on in the present GHPP guidelines.

1.2.2 Processing of herbal materials into herbal preparations

The herbal materials described above may be used as herbal medicines. Such (processed) herbal materials intended for direct therapeutic use should be produced under GACP and GMP conditions. In many other cases, herbal materials will undergo further “processing” treatment procedures before being used to manufacture the finished herbal products. The active ingredients are usually processed together with other components of the herbal materials. Sometimes these active ingredients are further concentrated by the removal of inactive and/or undesirable substances. The herbal preparations thus obtained include extracts, decoctions, tinctures, essential oils and others. The processes involved include extraction, distillation, fractionation, concentration, fermentation, or other chemical or biological methods.

General guidelines for good practices in the production of herbal preparations and/or finished herbal dosage forms as set out in the GMP requirements prescribed by WHO guidelines (4–6, 8) should be followed. Technical information on the key processes is supplemented in the present GHPP guidelines.

1.2.3 Processing of herbal materials or herbal preparations into herbal dosage forms

Depending on the intended use, herbal materials could be regarded as starting materials and herbal preparations could be regarded as intermediates in the process of producing finished herbal products, or as herbal dosage forms for therapeutic applications. In the latter case, simple herbal dosage forms may be prepared either from herbal materials (such as unprocessed seeds or plant exudates) or herbal preparations (such as ground powders and dried extracts) ready for administration to patients. These herbal dosage forms, produced under

GMP conditions, include decoctions, tea bags, granules, syrups, ointments or creams, inhalations, patches, capsules, tablets and pills, among others. Supplementary technical information on the key processes is included in these GHPP guidelines.

1.3 Objectives of the guidelines

These guidelines will provide technical guidance on GHPP for the production of herbal materials, herbal preparations and, ultimately, herbal dosage forms (guided by GMP). Under the overall context of quality assurance and control of herbal medicines, the main objectives of these guidelines are to:

- provide general and specific technical guidance on GHPP for herbal medicines;
- provide technical information on general as well as specific good herbal processing techniques and procedures applied to the preparation of herbal materials from herbs;
- provide technical information on good herbal processing techniques and procedures applied to the production of herbal preparations from herbal materials;
- provide supplemental technical information on good herbal processing techniques and procedures applied to the production of dosage forms of herbal medicines;
- provide a model for the formulation of national and/or regional good herbal processing practices guidelines and monographs for herbal materials, as well as for herbal preparations, and related standard operating procedures (SOP); and
- contribute to the quality assurance and control of herbal materials, herbal preparations and herbal dosage forms to promote safety, efficacy and sustainability of herbal medicines.

1.3.1 Use of these guidelines

These guidelines should be considered in conjunction with the existing WHO technical documents and publications relating to the quality assurance of herbal medicines and medicinal plants (for details, see references 1–16).

The *WHO guidelines on good herbal processing practices for herbal medicines* is one of a series of guidance documents concerned with control measures necessary to produce quality herbal medicines for safe and efficacious use as directed by the regulatory authority concerned. The present document concerns the assurance of the quality of the herbal materials prepared by various

methods and processing steps from the herbs obtained under GACP. It also covers the herbal preparations prepared using various methods and processing steps from the herbal materials, as well the herbal dosage forms produced through various methods and processing steps from herbs, herbal materials or herbal preparations. Herbal materials and herbal preparations can be used directly as herbal medicines (when produced under GMP conditions), or can serve as source materials for the production of finished herbal products in accordance with GMP. These guidelines are applicable to the processing operations from post-harvest to herbal dosage forms. The processing of herbs, herbal materials and herbal preparations should meet all applicable national and/or regional quality standards. Adherence to local legislation, rules and practice in each Member State is mandatory. Each Member State should develop its own national guidelines on GHPP for herbal medicines that are appropriate to the country's situation.

1.4 Definitions of terms

The terms used in these guidelines are defined below. The terms and their definitions have been selected and adopted from other WHO documents and guidelines that are widely used by WHO Member States, as well as from other reference sources, publication details of which can be found in the reference list. These definitions may differ from those included in national regulations and are, therefore, for reference only.

It should be noted that as a consequence of the various types of “herbal medicines” produced, the same type of material may be classified in different ways (for example, powdered plant material may be both “herbal material” and “herbal preparation” or, in a packed form, “herbal dosage form” or “finished herbal product”).

1.4.1 Terms relating to herbal medicines

Herbal medicines include herbs and/or herbal materials and/or herbal preparations and/or finished herbal products in a form suitable for administration to patients (3).

Note: In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (for example, animal and mineral materials, fungi, algae or lichens, among others).

Herbs (16)

Herbs include crude plant materials such as leaves, flowers, fruits, seed, stem wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

***Herbal materials*¹ (16)**

Herbal materials include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other plant materials.

***Herbal preparations* (16)**

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.

***Finished herbal products* (3)**

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”).

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be “herbal”.

Herbal dosage forms

Herbal dosage forms are the physical form (liquid, solid, semi-solid) of herbal products produced from herbs, with or without excipients, in a particular formulation (such as decoctions, tablets and ointments). They are produced either from herbal materials (such as dried roots or fresh juices) or herbal preparations (such as extracts).

Medicinal plants are plants (wild or cultivated) used for medicinal purposes (1, 4–6).

Medicinal plant materials: see Herbal materials

¹ The participants of the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that latex and exudates can be included.

1.4.2 Terms relating to herbal processing practices

Herbal processing

Herbal processing refers to the overall treatment in the course of production of herbal materials, herbal preparations and herbal dosage forms. For the purpose of the present guidelines, herbal processing includes “post-harvest processing” described in the *WHO guidelines on GACP for medicinal plants* (1), as well as “processing” procedures and protocols set out in the *WHO guidelines on GMP for herbal medicines* (4–6, 8).

Post-harvest processing

Post-harvest processing covers any treatment procedures performed on the herbs after harvest or collection when they are being processed into herbal materials. It includes processes such as inspection, sorting and various primary processing and drying. Often, well-defined combined or serial procedures are applied to herbs before they can be used in therapeutic treatment or as intermediates for manufacturing finished herbal products. These treatment processes are considered important pharmaceutical techniques in the herbal industry, through which purity and/or quality of raw herbs is assured (such as prevention of microbial and insect infection or infestation), and the therapeutic properties of raw herbs are altered (such as enhancement of effectiveness or reduction of toxicity). These primary processing procedures may vary from one herbal material to another, depending on its chemical and pharmacological characteristics, as well as the intended therapeutic purposes.

Adjuvants

Adjuvants are adjunctive substances added during the herbal processing procedures for the purpose of altering the pharmacological or therapeutic properties of the herbal materials, neutralizing or reducing toxicity, or masking the taste, assisting formulation into suitable herbal dosage forms, maintaining stability or extending the storage time. Common adjuvants include water, wine, vinegar, honey, milk and clarified butter, among other materials.

1.4.3 Terms relating to quality control

A comprehensive list of terms relating to the quality control of herbal medicines can be found in the *WHO guidelines on GMP for herbal medicines* (5, 6), *Good manufacturing practices for pharmaceutical products: main principles* (8), *Quality control methods for herbal materials* (7), and *WHO guidelines for selecting substances of herbal origin for quality control of herbal medicines* (3). The following terms are more applicable to the present guidelines.

active ingredients refer to constituents with known therapeutic activity, when they have been identified. When it is not possible to identify the

active ingredients, the whole herbal medicine may be considered as an active ingredient (3).

batch (or lot)² (5, 8, 17). A defined quantity of starting material, packaging material or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

batch number (or lot number) (5, 8, 17). A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

chemical reference substance (or standard) (17). An authenticated, uniform material that is intended for use in specified chemical and physical tests, in which its properties are compared with those of the product under examination, and which possesses a degree of purity adequate for its intended use.

constituents (3). Chemically defined substances or group/group(s) of substances found in a herbal material or herbal preparation.

contamination³ (5, 8, 17). The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

cross-contamination (5, 8, 17). Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

good manufacturing practice (GMP) (8). GMP is that part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP is concerned with both production and quality control. GMP is aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

in-process control (5, 8, 17). Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product

² The participants at the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that in case of terminal sterilization, the batch size should be determined by the capacity of the autoclave or any other sterilization equipment.

³ The participants at the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017 recommended that the term “physical” should be added before the term “chemical”.

conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

markers (marker substances) (3). Reference substances that are chemically defined constituents of a herbal material. They may or may not contribute to their therapeutic activity. However, even when they contribute to the therapeutic activity, evidence that they are solely responsible for the clinical efficacy may not be available.

master formula (5, 8, 17). A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

specification (5, 8, 17). A list of defined requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

standard operating procedure (5, 8, 17). An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (for example, equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

2. Good herbal processing practices for the production of herbal materials

2.1 General information

Post-harvest processing is often specific to the herb and may involve unique procedures. The particular processing method may be a practice based on a tradition as old as the use of medicinal plants, and/or it may be based on proprietary procedures. In either case, herbal processing procedures should be subjected to good practice standards.

Herbs obtained from field collection or cultivation should be subjected to a series of good practice post-harvest processing procedures set out in the GACP guidelines (1). In general, post-harvest processing of herbs includes inspection and sorting, primary processing and drying. The exact herbal processing procedures may vary from one herb to another. Thus, some procedures consist of only a few simple steps of primary processing such as cleaning, primary cutting and sectioning, before being dried. Others may require more complicated steps such as advanced cutting and sectioning (for example, decoction pieces processing), comminuting, ageing, sweating (fermentation), baking/roasting, boiling/steaming and stir-frying, for the purpose of improving

the quality, preventing damage from mould and other microorganisms, detoxifying intrinsic toxic ingredients or enhancing therapeutic efficacy. The present GHPP guidelines elaborate and supplement the GACP guidance.

In all cases, good in-process control measures should be employed to assure the quality of the end-product. National and/or regional botanical and chemical quality standards for each processed herbal material should be met. In the absence of national standards, regional or international pharmacopoeial standards may be adopted. Guidance on compliance measures can be found in the annex to the *Quality control methods for herbal materials* (7), *WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines* (3), *WHO guidelines on GACP for medicinal plants* (1), *WHO guidelines on GMP for herbal medicines* (4–6, 8), and the present guidelines.

2.2 Purposes and functions of primary processing

Simple post-harvest processing (such as sorting, washing and leaching) serves to remove dirt and other unwanted materials from the herbs after they have been harvested or collected from the growing site. Unless intended for use in its fresh form, the herb is subjected to a drying procedure, immediately or shortly after harvesting, in order to minimize damage from mould and other microbial infestation.

Through experience gained over the centuries, knowledge has been acquired for the development of various primary processing procedures for maximizing the quality and therapeutic value of herbal medicines. The final form of a herbal material depends upon the nature of the herb and its intended use. In general, primary processing of herbs serves several purposes, such as concentrating the ingredients; removing undesirable substances; modifying the therapeutic properties; reducing toxicity; facilitating dispensing, compounding and storage. The major objectives of primary processing of herbal materials are summarized below.

2.2.1 Neutralization of toxicity and diminishing side-effects

Herbal materials that possess significant toxicity, highly potent pharmacological activity or are known to cause severe side-effects, should be pretreated in specific manners in order to neutralize the toxicity or to reduce the side-effects prior to use. Such a detoxifying process is particularly important for those herbs that are known to contain toxic or undesirable chemical components; they must be properly processed to remove those unwanted substances. Through the primary processing processes such as steaming and frying, heat-sensitive toxic components will be degraded. In other cases, processes such as sweating (for example, fermentation) and ageing result in enzymatic degradation of the toxic ingredients. For example, raw aconite (*Aconitum carmichaelii* Debeaux or

related species) root, containing significant amounts of toxic alkaloids such as aconitine, must be boiled or steamed for hours to hydrolyse aconitine into less toxic derivatives. In the case of cascara (*Frangula purshiana* Cooper), the bark that has been collected or harvested should be kept (aged) for at least one year before use. This is to allow oxidation to occur, by which the strongly purgative hydroxyanthracene glycosides are converted to oxidized compounds with lower laxative potencies.

2.2.2 Modification of therapeutic properties

Some herbal materials require primary processing to alter their therapeutic properties. For example, rhubarb (rhizome of *Rheum* spp.) in its raw form possesses purgative action and is useful as a cathartic. After being steamed with wine, however, the purgative action is attenuated and the processed rhubarb can be used for other purposes such as reducing inflammation.

The specific medicinal property of some herbal materials may be changed through primary processing. For example, the unprocessed raw rehmannia (*Rehmannia glutinosa* (Gaertn.) DC.) root is used to treat fever, hypertension and skin eruptions. After being cooked in wine, however, the processed rehmannia is often used for tonic and anti-ageing purposes in some traditional medicine contexts.

In the case of ginseng (*Panax ginseng* C.A. Mey.) roots, different primary processing procedures give rise to several processed products, such as white ginseng and red ginseng. White ginseng is the herbal material dried in the sun or by heat, whereas red ginseng is prepared through a series of steaming and cooking steps. These two types of ginseng products have different therapeutic uses in some traditional medicine contexts, red ginseng being more potent than white ginseng in its warming or energizing effects.

2.2.3 Enhancing efficacy and reinforcing therapeutic effects

The therapeutic efficacy of certain herbal materials can be augmented through primary processing in some traditional medicine contexts. For instance, the pain-relieving property of corydalis (*Corydalis yanhusuo* W.T. Wang) rhizomes is believed to increase when they are stir-fried with rice vinegar.

2.3 Post-harvest processing procedures

Raw herbs should be inspected and sorted immediately following harvest or collection. They are then subjected to a series of on-site primary processes, and in most cases, subjected to further processes at a processing facility. The exact processing methods may differ from one herb to another, and the guidelines therefore may need to be adjusted on a case-by-case basis.

An example of a model format for a GHPP monograph/SOP protocol is given in Appendix 1.

2.3.1 **Sorting (garbling)**

The sorting process serves as the first step to ensuring the purity and cleanliness of the herbs. After the bulk amount of the desired plant part has been harvested or collected, all extraneous and unwanted matter including dirt (for example, soil, dust, mud and stones), impurities (for example, insects, rotten tissues, untargeted/extraneous medicinal plant(s) and/or plant part(s)), and residual non-medicinal as well as toxic part(s) must be removed from the medicinal part(s). Depending on the herb, the process may involve procedures such as:

- removing dirt and foreign substances;
- discarding damaged parts;
- peeling (to separate unwanted plant part(s) from the medicinal plant part(s) such as removing unwanted root bark from the roots or collecting stem bark from the stem);
- sieving, trimming, singeing (to remove hairs or rootlets);
- removal of residues of unwanted plant part(s) (for example, removing unwanted seeds from fruits and stripping leaves from stems).

Although in some cases sorting may be done by mechanical means, it is usually done by hand. Only staff who are suitably trained and equipped (for example, wearing gloves and a dust mask, etc. as appropriate) should carry out this work.

2.3.2 **Primary processing**

Washing

Raw herbs, especially roots, rhizomes and tubers, are usually washed with clean water and dried soon after harvest or collection. During the washing process, scraping and brushing may be necessary. It is generally recommended not to soak the herbs in water for an unnecessarily long period. Water should be changed as frequently as required. The use of water containing a low concentration of chlorine (for example, sodium hypochloride, bleach) to prevent microbial fermentation is recommended where and when possible or practical.

Leaching

Some impurities can be removed by the action of running water over the raw herbs (leaching). The duration of leaching has to be controlled in order to prevent excessive loss of active ingredients.

Primary cutting

Bulky raw herbs that have been harvested or collected may require primary cutting to reduce their size before transportation to the processing or manufacturing facility. Primary cutting is usually performed at or near the harvest or collection site.

Ageing

The ageing process refers to storing the herbal materials for a period of time after harvesting or collection from the field prior to use. Herbs are generally aged in the sun or in the shade, depending on the specific herbal material. During the process of ageing, excessive water is evaporated and enzymatic reactions (such as hydrolysis of the glycone portion of glycosides) or oxidation may occur to alter the chemical composition of the herbal material. For example, in cascara (*Frangula purshiana* Cooper) bark, after proper ageing (at least one year, or having been artificially heated to speed up the process), the reduced forms of the emodin glycosides in the fresh bark are converted to monomeric oxidized emodin glycosides. The latter form of glycosides are milder cathartic agents, with reduced irritating effects that may cause vomiting and stomach upsets, and hence, are more suitable as a therapeutic agent.

Sweating

A similar process known as sweating (for example, fermentation) involves keeping the herbal materials at a temperature of 45–65 °C in conditions of high humidity for an extended period, from one week to two months, depending on the plant species. The sweating process is considered a hydrolytic and oxidative process in which some of the chemical ingredients within the herbal materials are hydrolysed and/or oxidized.

The herbal materials are usually densely stacked between woollen blankets or other kinds of cloth. For example, vanilla beans (*Vanilla planifolia* Jacks. ex Andrews) are well known to undergo repeated sweating between woollen blankets in the sun during the day and packed in wool-covered boxes at night for about two months. During this process, the vanilla pods lose up to 80% of their weight and take on the characteristic colour and odour of vanilla.

Parboiling (blanching)

After washing, certain herbal materials may undergo a parboiling or blanching process in which they are put into boiling water for a brief period without being fully cooked. Such a heating procedure may serve several purposes, such as improving storage life of the processed materials by gelatinizing the starch, preventing mould or insect contamination, easily drying, destroying enzyme

activity to prevent the alteration of certain chemical constituents, and facilitating further processing such as removal of the seed coat of almonds.

Boiling or steaming

The boiling process involves cooking the herbal materials in water or another liquid such as vinegar, wine, milk or other vehicle.

In the steaming process, herbal materials are kept separate from the boiling water but have direct contact with the steam, resulting in a moist texture of the herbal materials. Often, the herbal materials are placed in a steamer or in a special utensil equipped with a flat frame suspended over boiling water. In some cases, the herbal materials are pre-mixed with excipient substances such as wine, brine or vinegar before being steamed. The boiling or steaming process serves to soften plant tissues, to denature enzymes present in the herbal materials, and/or to thermally degrade selected chemical constituents. At the same time, the excipient, if used, is absorbed into the plant tissues to become an integral part of the processed herbal materials. For example, *Reynoutria multiflora* (Thunb.) Moldenke (synonym *Polygonum multiflorum* Thunb.) root is often steamed in the presence of a black bean (*Phaseolus vulgaris* L.) decoction in order to enhance its tonic effects. Boiling the raw herbs such as *Croton tiglium*, *Abrus precatorius*, *Nerium oleander* and *Gloriosa superba* L., in cow's milk is practised in some traditional medicine contexts to reduce the levels of their toxic ingredients and thus diminish the toxicity of the herbal materials.

Baking or roasting

The baking or roasting process is a dry-heating using indirect, diffused heat, where the herbal materials are put in a heating device. The herbal materials are often embedded in bran or magnesium silicate (talc) powder to ensure even heating over the entire surface at an elevated temperature for a specified period of time. Some herbal materials are wrapped in moistened papers during the roasting process. The exact temperature used and duration of baking or roasting vary from one herbal material to another. Some are baked or roasted until the surface colour turns yellowish brown; some may be further heated until charred. For example, nutmeg (*Myristica fragrans* Houtt.) and kudzu (*Pueraria montana* var. *lobata* (Willd.) Sanjappa & Pradeep) root require roasting before they are used for medicinal purposes.

Stir-frying

Stir-frying is a process in which the herbal materials are put in a pot or frying pan, continuously stirred or tossed for a period of time under heating until the external colour changes, charred or even carbonized. Depending

on the plant species, the stir-frying process may require the addition of adjuvants such as wine, vinegar, honey, saline and ginger juice, which would be infused into the herbal matrix to become an integral part of the processed herbal material.

To ensure even heating over the surface of the herbal materials, sand, rice, bran, talc or clay can be admixed with the herbal material during stir-frying.

For example, liquorice (*Glycyrrhiza glabra* L. and *G. uralensis* Fisch.) root and rhizome and Astragalus roots (*Astragalus mongholicus* Bunge or *A. membranaceus* (Fisch.) Bunge) are often stir-fried with honey for the preparation of decoction slices, whereas the *Salvia miltiorrhiza* Bunge root is stir-fried with wine. Fresh ginger is often stir-fried with sand until the surface colour turns brown. In other instances, ginger can be further stir-fried over intense fire to a carbonized state for use as decoction pieces.

Fumigation

Fumigation with sulfur dioxide has been employed in post-harvest handling of some herbs for the purpose of preserving colour, improving fresh-looking appearance, bleaching, preventing the growth of insects and inhibiting decay caused by moulds. Thus, the process has been frequently applied to herbal materials of light and bright colours to avoid “browning”. Due to concerns about the undesirable residues, this process should be avoided as far as possible. When a real need is identified, treatment should be carried out at the earliest possible stage and exclusively by adequately trained and qualified personnel, according to the specific recommendations for use. All relevant regulations (for example, limits on sulfite residue) should be complied with.

Irradiation

In some cases, irradiation or ultraviolet light can be used to eliminate or reduce microbial load of the herbal materials. The use of these procedures has to comply with the national and/or regional regulations.

Advanced cutting, sectioning and comminution

When thoroughly dried, the herbal materials are processed by cutting and sectioning into convenient or specific sizes and shapes or forms for storage, direct use as decoction slices or pieces, and/or for further processing for the manufacture of herbal preparations or herbal dosage forms. Decoction slices or pieces are available in many Member States for direct use as herbal medicines. Where applicable, the entire, sectioned or cut herbal materials are comminuted or pulverized into powder form in accordance with common herbal medicines practice, for use as herbal dosage forms.

White and/or red ginseng products presented as root pieces, slices or in powder form prepared from appropriately dried roots of *Panax ginseng* C.A. Mey., marketed as herbal medicines, are good examples of herbal materials derived from simple processing procedures.

Other primary processing procedures

Other primary processing procedures may be applied to raw herbs at an early stage for the production of herbal materials, such as collection of gums or resins. Also included under the term primary processing are primary distillation of raw herbs to obtain crude essential oils and expression to obtain fresh juice. Such procedures are usually performed in the processing facility under GMP conditions.

2.3.3 Drying

Unless used in the fresh state, the raw herbal materials need to be dried after being sorted and washed. In general, they must be dried as soon as possible to protect them from mould and other microbial infestation. Drying will also prevent tissue deterioration and phytochemical alteration caused by the actions of enzymes and microbial organisms. It will also facilitate grinding and milling, and converts the herbal materials into a convenient form for further processing. However, attention must be given to the potential loss of volatile (for example, essential oil) constituents present in the fresh material.

The final moisture content for dried herbal materials varies depending on the tissue structure, but should ideally be below 12%. Information on the appropriate moisture content for a particular herbal material may be available from pharmacopoeias or other monographs.

Proper drying involves four major aspects: control of temperature, humidity, airflow and cleanliness of the air. The drying conditions are determined by the nature of the raw medicinal plant material to be dried (tissue structure and chemical composition) and by the desired appearance of the final form. The drying method used may have considerable impact on the quality of the resulting herbal materials. Hence, the choice of a suitable procedure is crucial. Information on appropriate drying methods and procedures for particular herbal materials may be available from pharmacopoeias or other authoritative monographs. Raw herbal materials are most often dried by sun-drying, shade-drying or by artificial heat.

The drying conditions chosen should be appropriate to the type of the herbal material. They are dependent on the characteristics (for example, volatility and stability) of the active ingredients and the texture of the plant part collected (for example, root, leaf or flower). Generally, one of the following drying processes can be adopted.

Sun-drying

Some herbal materials can be dried in the open air under direct sunlight, provided the climate is suitable. The duration of the drying process depends largely on the physical state of the herbal material and the weather conditions.

For natural drying in the open air, medicinal plant materials should be spread out in thin layers on drying frames and kept away from sources of possible contamination such as vehicle exhaust, heavy dust and rain. They should also be protected from insects, rodents, birds and other pests, livestock and domestic animals. The material should be turned periodically to achieve uniform drying. The drying frames should generally be set up at a sufficient height (for example, 15 cm) above the ground. Efforts should be made to achieve uniform drying within the shortest possible time to avoid mould formation.

Shade-drying

Herbal materials can be dried in the shade with or without artificial airflow to avoid direct exposure to strong sunlight. The drying process is slow, but it is preferred when it is necessary to maintain (or minimize loss of) colour of leaves and flowers. Low temperatures (relative to heat-drying) will also preserve most of the volatile and aromatic components by reducing evaporation.

Drying by artificial heat

Drying by artificial heat can be faster than open-air drying and is often necessary on rainy days or in regions where the humidity is high. Drying of herbal materials may be done using ovens, stoves, rack dryers, solar dryers, tunnel dryers, belt dryers, other heating devices or open fires. The use of an open fire should be avoided as much as possible, as residues of combustion may introduce contamination. When an open fire is used, the area must be well ventilated.

For artificial heat-drying, the temperature, humidity and other conditions should be governed by the physical nature of the herbal material being dried and the physical/chemical properties of its active ingredients. Over-heating may lead to an excessive loss of the volatile components and/or decomposition of chemical constituents. In general, the temperature should be kept below 60 °C for bark and root and below 40 °C for leaves, herbs and flowers.

2.4 General issues

2.4.1 Selection of processing method

Herbal materials derived from the same species but processed by different methods may show significant differences in quality and therapeutic properties, owing to the influence of the treatment process on the chemical composition.

It is not uncommon to find different processing methods being used for the same herb or herbal material, depending on intended use. For example, raw (unprocessed) liquorice is used as an antitussive and expectorant; but after being stir-fried with honey or ghee, the processed liquorice becomes a tonic drug to be used for replenishing body strength.

Prior to processing, it is important to consult the national or regional regulatory standards and other literature sources to decide on the most appropriate method to use. Once a method has been adopted, adherence to the SOP is necessary to ensure batch-to-batch consistency. For industrial production, method validation should be adopted as part of the SOP.

Only suitably trained staff should carry out the work, which should be conducted in accordance with the SOP and national and/or regional regulations in the countries where the plants are grown/collected and manufactured and in which the end-users are located.

2.4.2 Temperature

With in-processing procedures that involve heating, the temperature used is critical. It is necessary to ensure that the required temperature is achieved during the process. In some cases, preheating the equipment (for example, oven, frying pan and steamer) and/or the additives (such as sand, bran and rice) is required before putting in the herbal materials. When heating equipment is used, it should be regularly calibrated.

2.4.3 Duration of procedure/treatment

It is also critical to control the duration of the procedure or treatment of the herbal materials. Both over- and under-treatment will affect the quality of the resulting materials. Duration of the procedure or treatment should be monitored through adequate in-process controls performed on the basis of organoleptic alterations (such as changes in colour, odour, taste and texture) or changes in the contents of active chemical constituents with appropriate instruments or testing.

2.4.4 Use of adjuvants

Common adjuvants used during the processing procedures include water, wine (for example, rice wine, wheat wine and sorghum wine), vinegar, honey, ginger juice, liquorice extract, ghee, brine and so on. Under special circumstances, other adjuvants such as cow's milk, goat's milk, animal bile, goat fat, cow's urine, butter, black bean extract, coconut water, tamarind juice, turmeric, lemon juice and mineral materials (for example, borax) have been used.

The quality of adjuvants must be clearly defined and controlled (according to pharmacopoeial and/or relevant regulatory requirements). The exact amounts and quality of these adjuvants used (the ratio of herbal material and the adjuvant) should also be consistent from batch to batch. In addition, the use of any materials derived from animals or animal products in any processing procedures should be evaluated for safety and contamination, especially with pathogens, prior to use. General guidance is available in *Safety issues in the preparation of homeopathic medicines* (9).

2.5 Documentation

All processing procedures that could affect quality and safety of herbal materials should be documented. Guidance for good documentation can be found in *Good manufacturing practices for pharmaceutical products: main principles* (5, 8, 17), as well as *WHO guidelines on good agricultural and collection practices for medicinal plants* (1). Thus, it is important to establish a record-keeping system so that all records are up to date, maintained and traceable for the entire processing procedures for each batch of herbal materials.

Written processing records should include, but not be limited to, the following information:

- name of herbal material – botanical name (binomial – genus, species, with the authority (abbreviations, if used, should follow internationally accepted rules)) and the plant family name of the medicinal plant are essential. If required by national legislation, synonyms and applicable subspecies, variety, cultivar, ecotype or chemotype should be documented; if available, the local and English common names should also be recorded;
- plant part(s) of the medicinal plant or herb;
- stage of vegetative development, for example, flowering and fruiting, vegetative maturation;
- site/geographical location (if possible, based on GPS data,) and time of harvesting/collection;
- state of the medicinal plant or herb (for example, fresh or dried);
- batch number, batch size and any other identification code;
- name of supplier;
- dates of receipt of the material, processing of the material, and completion of the process;
- name of person in charge of the processing, and person in charge of batch release;

- general processes that the plant material has already undergone (for example, drying, washing and cutting, including drying time and temperatures, and size of herbal material);
- gross weight of the plant material before and after processing;
- method used for special processing;
- details of the procedures (master formula), including descriptions of the utensil and equipment used, steps of operation, manufacturer, specification, amount and quality grade of the adjuvant (for example, wine or vinegar) and/or other substances (for example, sand, bran) used, temperature control, length of processing time, after-process steps (for example, cooling, drying, cutting), and other relevant information;
- details of animal-derived materials or adjuvants used and their microbiological certificates, if applicable;
- batch production – detail deviations from or modifications of the master formula;
- in-process control, for example, organoleptic changes of the herbal material before and after processing (such as change in colour, shape, texture, odour and taste);
- quality control parameters, grades and/or specifications, and assay results, where appropriate, of active ingredient(s), markers or chemical reference standard(s);
- storage conditions and containers; and
- shelf life/retest period.

3. Good herbal processing practices for the production of herbal preparations

3.1 General information

The herbal materials described in section 2 of these guidelines may be ready to serve as the starting materials for use as herbal medicines. In some cases, they are cut into sections or ground into powder and used directly as the final dosage form. But often the herbal materials will undergo further treatment processes before being used to manufacture the finished herbal products. The ingredients are usually not purified and the extracts are further concentrated by the removal of inactive and/or undesirable substances.

Herbal preparations are thus obtained by subjecting the herbal materials to treatments such as extraction, distillation, fractionation, concentration,

fermentation, or other physicochemical or biological methods. The resulting preparations include extracts, decoctions, tinctures, essential oils and others.

3.1.1 Preparation of herbal materials for processing

- The quality of herbal materials should meet the requirements specified in the national pharmacopoeia or recommended by other documents of the end-user's country.
- Authentication of herbal materials should be performed prior to extraction. Purity (absence of contaminants) should also be ensured.
- Proper documentation on the herbal material should be available as recommended in section 2.5.
- The herbal material should be cleaned, dried (unless fresh material is required), and comminuted into an optimal size for extraction.
- The herbal materials should be processed as soon as possible after arrival at the processing facility. Otherwise they must be properly stored to avoid contamination, damage and deterioration (for example, loss of active constituents).
- All operational steps should be reproducible and performed hygienically, in accordance with the processing SOP.

In general, for processes such as extraction, fractionation, purification and fermentation, the rationale for the guidelines should be established on a case-by-case basis. An example of a model format for a good herbal processing practice monograph/SOP protocol to produce a herbal preparation is given as Appendix 2. General guidance is provided below.

3.2 Extraction

Extraction is a process in which soluble plant chemical constituents (including those which have therapeutic activity) are separated from insoluble plant metabolites and cellular matrix, by the use of selective solvent (which is sometimes called the menstruum). The purpose of extraction of herbal material is to eliminate unwanted materials and to concentrate other chemical constituents in a soluble form. Herbal extracts include liquid (fluid) extracts, soft extracts, oleoresins, dry extracts and others. The herbal preparations so obtained may be ready for use as medicinal agents, or they may be further processed into herbal dosage forms such as tablets and capsules.

Various techniques are used for extraction, including maceration, infusion, digestion, percolation – including hot continuous (Soxhlet) extraction – and decoction. Other extraction techniques can also be applied, for example,

heat reflux extraction, counter-current extraction, microwave-assisted extraction, ultrasonic extraction (sonication) and supercritical fluid extraction.

3.2.1 Common methods of extraction

In order to produce herbal preparations of defined quality, the use of appropriate extraction technology, extraction conditions, extraction solvents, ratio between herbal material and solvents, and type of equipment are crucial. Some common methods of extraction are described below.

Maceration

Maceration involves the procedures of mixing the properly comminuted herbal materials with the solvent and allowing the mixture to stand at a certain temperature for a defined period of time, agitating as necessary. During the maceration process, chemical constituents are extracted from the plant tissues through a dissolution process into the liquid solvent. Often the herbal material is put in a container and solvent added until the herbal powder is thoroughly moistened. An additional quantity of solvent is then introduced. The mixture is agitated at regular intervals for a defined period of time, strained, and the marc (the solid material) is pressed, to collect residual extract. All liquids are collected, combined and separated by decantation, centrifugation, straining or filtration. The maceration process may be repeated with fresh solvent if desired. In the process of maceration, the herbal materials are macerated in definite quantities of a solvent (at an optimal ratio of the amounts of herbal material to solvent), for a specified duration of time. Exhaustive bulk extractions via maceration can be quite time-consuming and require large volumes of solvent.

In specific cases, a modified maceration procedure involves pre-soaking the herbal material in water for a period of time to induce fermentation. In other cases, maceration can be performed by gentle heating in order to enhance the extraction efficiency in a process known as “digestion”.

“Sonication-assisted extraction” and “microwave-assisted extraction” are modified methods of maceration, in which ultrasound or microwaves are utilized to enhance the extraction efficiency, to reduce the amount of solvent used, and to shorten the extraction time.

For *sonication*, the herbal material is placed in a container together with a solvent, which is in turn put in an ultrasonic bath. The ultrasound provides sufficient power to break down the cell walls of the herbal material and facilitates the solubilization of metabolites into the solvent. The frequency of ultrasound, length of treatment and temperature of sonication are important factors affecting the extraction yield.

For *microwave-assisted extraction*, the herbal material is placed in a container together with water, or another suitable solvent and subjected to

microwave treatment. Heat generated by the microwave energy facilitates the dissolution of compounds from the herbal matrix into the solvent.

Sonication-assisted and microwave-assisted extraction are rarely applied to large-scale extraction; they are used mostly for the initial extraction of a small amount of material.

Infusion

Infusion refers to an extraction procedure in which boiling water is poured on the herb or herbal material to produce a dilute liquid preparation. Typically, the herb or herbal material is allowed to stand for some time (usually 5–20 minutes). Sometimes another quantity of hot water is added and allowed to stand for additional time. The extracted plant material is removed by straining and the infusion is ready for use. Infusion is commonly employed to make herbal teas.

Percolation

Percolation is the procedure in which the solvent is allowed to continuously flow through the herbal material in a percolator (a vessel with an outflow at the bottom end). Typically, the properly comminuted herbal material is moistened with an appropriate amount of solvent and allowed to stand (macerate) for a few hours before being packed into the percolator. Additional solvent is added to totally wet the comminuted herbal material for some time. The bottom end (valve) of the percolator is then opened (adjusted), with fresh solvent being replenished from the top of the percolator to maintain a steady flow of solvent through the bed of herbal material. The flow rate of the liquid is controlled by adjusting the valve of the outlet. The extraction liquid is collected from the bottom outlet of the percolator. When the process is completed, the marc may be pressed and all liquids pooled to obtain the percolate. In addition to the solvent used for the extraction, the flow rate and the temperature influence the extraction yields and they have to be carefully controlled. Percolation is often used for an exhaustive extraction of the herbs and is applicable to both initial and large-scale extraction. In some cases, the process of percolation can be modified by applying vacuum to increase the flow of solvent.

A special technique of percolation is the “continuous (Soxhlet) extraction” process using the Soxhlet or Soxhlet-like apparatus. Usually, 50–60 cycles are necessary for complete extraction. Due to the continuous extraction, this method is more efficient than simple percolation and consumes less solvent. However, due to continuous heating at the boiling-point of the solvent used, thermolabile compounds may be damaged and/or artefacts may be formed. Besides the laboratory-scale setup for continuous extraction, industrial-scale stainless steel extractors and high-pressure extraction are commonly used in many manufacturing facilities.

Decoction

Decoction is the most common method for making herbal preparations in various traditional medicine contexts. It involves boiling the herbal material in water, during which time the chemical constituents are dissolved or extracted into the hot liquid. This procedure is suitable for extracting soluble and heat-stable active constituents of the herb or herbal material.

Supercritical fluid extraction

Supercritical fluid extraction is a modern technique making use of the solvating property of a fluid in its supercritical state (carbon dioxide is the most common supercritical solvent) to dissolve the chemical constituents in herbal materials. The density of the supercritical fluid (thus its solvating property) can be adjusted by altering the temperature and pressure, or by the addition of modifiers (for example, ethanol) to change the polarity of the supercritical fluid.

3.2.2 Steps involved in the extraction of herbs and herbal materials

The following steps are generally involved in the extraction procedures.

Comminution, fragmentation, grinding or milling (see also section 2.3.2)

Prior to extraction, the herb is generally dried and reduced to a size of 30–40 mesh sieves (the actual size can be adjusted if necessary). If fresh material is used for extraction, it is necessary to perform extraction as soon as possible after collection to avoid deterioration (microbial fermentation). The purpose of powdering the herbal material is to rupture its tissues and cell structures so that the chemical ingredients are more readily exposed to the extraction solvent. Moreover, size reduction increases the surface area, which in turn enhances the mass transfer of chemical ingredients from plant tissue to the solvent. However, excessive grinding can degrade the herbal material through mechanical heating and oxidation from exposure to air. Further, an excessively fine powder may block the pores of the extraction filter, slowing down or preventing the passage of the filtrate; it may even coalesce in the presence of the extraction solvent to form solid lumps, cakes or bricks, not amenable to being extracted.

Extraction

The extraction process is carried out in the selected solvent at a desirable temperature for an optimal period of time. Depending on the polarity of the desired chemical constituents, water or other solvents can be used, either at room temperature (“cold” extraction) or at an elevated temperature (“hot” extraction).

Sequential extraction with a series of solvents of differing polarity is sometimes done to create a series of extract fractions. In this procedure, the

herbal material is subjected to organic and aqueous solvents in a sequence of increasing polarities, for example, n-hexane, dichloromethane, ethyl acetate, water-saturated n-butanol and water. As a result, chemical constituents possessing different polarities are transferred from the herbal material to different solvent fractions according to the principle of “like dissolves like”. For example, the initial step of extraction using non-polar solvents (such as n-hexane or petroleum ethers) removes lipophilic constituents (such as alkanes, fatty acids and sterols) from the herbal material in a process sometimes referred to as “defatting”. The compounds with intermediate polarity (such as flavonoid and quinone aglycones) will dissolve in the medium-polarity solvents (such as dichloromethane and ethyl acetate), whereas more polar compounds (such as glycosides and polyphenols) will be concentrated in the more polar solvents (such as butanol or water). Fractionation as a secondary processing step applied to herbal extracts is described in section 3.4.

Separation techniques

After the completion of extraction, the liquid so obtained is separated from the marc by filtration through a filter cloth or filter-paper to remove any particulate insoluble residues. Other separation techniques, including decantation, centrifugation or straining, may be used depending on the method of extraction and composition of the matrix.

Concentration

The extract is often concentrated by the removal of excessive solvent to a thick concentrated extract or to a solid mass. The concentration procedures may involve evaporation under reduced pressure, freeze-drying or spray-drying.

3.2.3 Common herbal preparations obtained by extraction

The extraction process using suitable solvents can yield herbal extracts of liquid, semi-solid or solid consistency. There are four general categories of herbal extracts, i.e. liquid (fluid) extract, soft extract, oleoresin and dry extract.

3.2.3.1 Liquid (fluid) extract

Liquid (fluid) extract is a liquid preparation of herbal materials obtained using water, alcohol or other extraction solvents. Common preparations include:

- **Fluidextract**

Fluidextract is an alcoholic liquid extract produced by percolation of herbal material(s) so that 1 mL of the fluidextract contains the extractive obtained from 1 g of the herbal material(s).

- **Decoction**

Decoction is a water-based herbal preparation made by boiling herbal materials with water, and is commonly utilized in various traditional medicine contexts. In some cases, aqueous ethanol or glycerol can also be used to prepare decoctions. However, decoctions may be prepared by a programmable decocting machine that processes the herbal material at a specific temperature for a specific duration and then dispenses the decoction in hermetically sealed plastic pouches of a specified single-dosage volume that can be refrigerated for subsequent reheating and consumption. The amounts of herbal material and solvent used, as well as the length of the decocting process, should be specified.

- **Infusion**

Infusion is a dilute solution prepared by steeping the herbal materials in boiling water for a short time. Infusions prepared in edible oil or vinegar are also available.

- **Tincture**

As a general rule, a “tincture” is an alcoholic or hydroalcoholic extract of a herbal material, typically made up of 1 part herbal material and 5–10 parts solvent (for example, ethanol or wine). Tinctures can be prepared by extracting herbal materials usually with ethanol of a suitable concentration. The ratio of water to alcohol should be recorded.

- **Macerate**

Macerate is a liquid preparation prepared by soaking the herbal material(s), reduced to a suitable size, in water at room temperature for a defined period of time, usually for 30 minutes, when not otherwise specified.

3.2.3.2 **Soft extract**

Soft extract is a semi-solid preparation obtained by total or partial evaporation of the solvent from a liquid extract.

3.2.3.3 **Oleoresin**

Oleoresin is a semi-solid material composed of a resin in solution in an essential and/or fatty oil obtained by evaporation of the excess solvent.

3.2.3.4 **Dry extract**

Dry extract is a solid preparation obtained by evaporation of the solvent from a liquid/fluid extract. Dry extract can also be prepared by spray-drying with or without the use of an adsorbent (such as methyl cellulose), or by drying and milling to produce a powder. This may be further processed by compression or with use of a binding agent or granulation liquid to produce multiparticulate granules.

3.2.4 Factors influencing extraction of herbal materials

A number of factors influence the efficiency and reproducibility of the extraction process. Issues to consider include the solvent used to make an extract, particle size of the herbal material, the herb-to-solvent ratio, extraction process used (for example, percolation or maceration), extraction time, temperature and other relevant conditions. All these factors should be optimized and set out in the SOP, and be strictly adhered to.

3.2.5 Selection of extraction methods

- The choice of extraction method is governed by the nature (stability, solubility, structural complexity and other properties of the chemical constituents) and amount of material to be extracted. For large amounts, the feasibility of extracting on a bulk scale should be considered.
- The extraction method should be as exhaustive as possible, i.e. removing as much of the desired chemical constituent as possible from the plant matrix.
- It should be fast, simple, economical, environment-friendly and reproducible.

3.2.6 Extraction conditions and procedures

Solvent

- Depending on the nature of the target compounds or undesirable compounds, an appropriate solvent (or solvent mixture) should be selected. While water has been, and is, most commonly used as a solvent, organic solvents of varying polarities are often used in modern methods of extraction to exploit the various solubilities of phytochemical constituents. For example, an aqueous solution of alcohol (for example, 50–80% aqueous ethanol) can extract the majority of organic chemical constituents from herbal materials. Other solvents may apply for the extraction of specific types of constituents (such as proteins and polysaccharides).
- When selecting a solvent or solvent mixture, the following factors should be considered: solubility of the target compounds, stability and reactivity of the solvent, safety (low toxicity, low flammability, non-corrosiveness), cost, ease of subsequent solvent removal and solvent recovery (low boiling-point), and environmental friendliness.

- Before using a solvent, the safety data sheet⁴ should be reviewed and appropriate protective measures should be implemented. Precautions must be taken to minimize the risk of fire and explosion. Care should be taken to reduce environmental contamination and to protect workers and other people in the vicinity from exposure to chemical hazards.
- Toxic solvents and those that are damaging to the environment, for example, benzene, toluene and carbon tetrachloride, should be avoided. Diethyl ether should also be avoided as it is highly flammable and can lead to the formation of explosive peroxides. The use of chlorinated solvents is discouraged; if used, dichloromethane is preferred to chloroform, the latter being more toxic. Ethanol is preferred over methanol; the latter has higher toxicity.
- Solvents are classified into three classes according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH),⁵ with respect to their potential risk as follows:
 - class 1 (solvents to be avoided such as benzene);
 - class 2 (limited toxic potential such as methanol or hexane); and
 - class 3 (low toxic potential such as ethanol) (18).
- Solvents of general-purpose grade available in plastic containers are often contaminated by plasticizers, and minimizing contamination is especially important when carrying out bulk extraction requiring large volumes of solvent. It is advisable to distil solvents prior to use.
- The amounts of solvent used must be optimized to ensure batch-to-batch conformity.
- The quality and specification of solvent used should be specified and controlled.
- Solvents should be properly stored in non-plastic containers in a well ventilated, fire and explosion containable area; and protected from direct exposure to sunlight.

⁴ United Nations (2015) Globally Harmonized System of Classification and Labelling of Chemicals (GHS), Sixth revised edition. Available at: https://www.unece.org/trans/danger/publi/ghs/ghs_rev06/06files_e.html.

⁵ International Council for Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use. ICH Harmonized Guideline – Impurities: Guideline for Residual Solvents (Q3C (R6) dated October 20, 2016). (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q3C/Q3C_R6__Step_4.pdf) accessed on 18 May 2017.

- When solvents are recycled, strength and purity must be confirmed prior to reuse. Recycled solvent should be used in the same extraction process only.
- Waste solvents must be disposed of safely and properly. National, local or institutional regulations on waste solvent disposal must be strictly followed.
- Limits for solvent residue in extracts or herbal preparations are important to observe especially when the solvent is not considered safe for general consumption.

Temperature

- To avoid thermal degradation of the chemical constituents, extractions are preferably performed at a temperature below 40 °C, unless evidence is available to support the use of higher temperatures.
- For heat-stable constituents, Soxhlet extraction or decoction can be used. In any case, higher than required temperatures should be avoided.
- Temperature during the entire extraction process should be controlled and recorded.

Length of treatment

- The length of extraction time depends on the purpose for which the extraction is performed and the nature of the active phytochemical constituents. Insufficient time will result in incomplete extraction, but prolonged extraction will lead to excessive extraction of the unwanted constituents and/or degradation of active chemical compounds.
- The number of repeated extraction cycles required for the complete removal of the desirable chemical constituents is as important as the length of time for each extraction.
- The length of extraction time and the number of cycles should be controlled and recorded.

3.3 Distillation

For the extraction of volatile components of herbal materials, such as essential (volatile) oils, the odorous and volatile principles of plants, techniques such as distillation, expression and enfleurage may be employed. Primary distillation

sometime takes place soon after the herb is harvested or collected to obtain crude oils. In other cases, herbal materials are distilled under well-controlled GMP conditions in the manufacturing facility.

Water or steam distillation is a method of choice for extracting volatile ingredients from herbs. In brief, the herbal material is packed in a still, a sufficient amount of water is added and brought to the boil (water distillation). Alternatively, a stream of steam is introduced to the herbal material that has been pre-soaked in water (water-steam distillation), or a stream of steam is introduced to herbal materials without water being added (direct steam distillation).

The method of distillation depends on the condition of the herbal materials. Water distillation can be applied to fresh herbs to avoid steam penetrating into the materials such as rose flowers, while direct steam distillation is often used for fresh or dried herbal materials. Freed from the plant tissue, the essential oil is carried away with the steam. Upon condensation, the water and oil are collected in liquid form, which then separates into two immiscible layers. During the process, the yield of essential oil can be quantified by using appropriate methods such as the Clevenger apparatus.

The yield and quality of essential oil obtained by distillation is affected by the process parameters. It is advisable to define optimal conditions in order to obtain the best results. Among the contributing factors are: mode of distillation, condition of raw herbal materials, loading of herbal materials, steam pressure and temperature and length of time for distillation.

3.3.1 Distillation procedures

- The distillation apparatus must be set up properly and safely according to the manufacturer's instructions.
- Distillation should be carried out in a well-ventilated room.
- Optimum distillation conditions, for example, heating rate, herb/solvent ratio and distilling rate, have to be specified and controlled.
- The equipment used should conform with the official safety standards and all procedures must be conducted in accordance with the operational instructions and safety requirements.
- The water used for distillation should at least comply with local requirements for drinking water.

3.3.2 Other methods

Volatile oils that may be decomposed during distillation can be obtained by expression (mechanical pressing), solvent extraction, supercritical carbon dioxide extraction or by the enfleurage process suitable for delicate flowers.

3.4 Fractionation

Fractionation is a separation process in which a mixture is divided into a number of smaller quantities (fractions) with higher content of target substances (chemical compounds). The crude extracts of herbal materials contain complex mixtures of chemical constituents with diverse chemical and physical characteristics. It is often desirable to divide the chemical constituents into different groups based on their similarities in terms of chemical and physical properties, such as a flavonoid- or alkaloid-rich fraction. Fractional separation of a herbal extract can be achieved by subjecting the extract to a variety of fractionation techniques such as liquid–liquid partition and various forms of chromatography. The method can be applied to produce preparations enriched in active compounds, or to remove inactive and/or toxic constituents.

3.4.1 Liquid–liquid partition

Herbal extracts may be fractionated by dissolving in a suitable solvent, if not already in liquid form, and partitioning with an immiscible liquid. One liquid phase is typically aqueous and the other is an organic phase such as dichloromethane or ethyl acetate. The chemical constituents will separate into the different liquid phases depending on their affinity according to the principle of “like dissolves like”. Manipulations of the pH of the aqueous phase combined with liquid–liquid partitioning can also be employed to separate a herbal extract into basic, neutral and acid fractions.

3.4.2 Chromatography

Further refinement of the extract fractions can be achieved by various chromatographic techniques, of which column chromatography is most commonly employed, particularly in the preparative scale. Column chromatography can be carried out using materials based on different mechanisms. Common modes are adsorption, partition, size exclusion, affinity and ion-exchange. The most frequently used stationary phases (solvents) are silica gel and alumina in adsorption chromatography. In size-exclusion and ion-exchange chromatography, polymeric gels and ion-exchange resins, respectively, are used. A proper column packed with the appropriate stationary phase and eluted by a mobile phase with suitable elution power is crucial to obtain optimized separation of chemical constituents in the herbal extract.

The counter-current techniques, such as high-speed counter-current chromatography and droplet counter-current chromatography, which also employs a liquid–liquid partitioning mechanism, can also be applied to separating constituents in the herbal extract.

3.4.3 Fractionation procedures

Liquid–liquid partition

- The storage, use and disposal of solvents must be done with care and in conformance with the national, local and institutional regulations.
- Experimental procedures should be carried out in certified facilities with sufficient ventilation and safety measures. Ideally, they should be performed inside fume hoods.

Chromatography

- The choice of stationary phase depends on the polarity, molecular size or the charge of the desired ingredients. It should be supported by a good rationale.
- The choice of mobile phase (solvent system) must be optimized.
- Column operation and development procedures (for example, column length and inner diameter, amount of stationary phase used, column packing, particle or bead size or macropore size, porosity and surface area, phase and support, sample application, elution gradient formation, flow rate, temperature, fraction collection and detection method), should be specified and standardized.

3.5 Concentration and drying

The herbal extracts or fractions enriched in active ingredients are often reduced to produce a more concentrated liquid by the removal of excess solvent. This can be achieved through evaporation or vaporization. Solvent (single) can be recovered and may be reused provided that appropriate quality control is ensured. Mixed solvents are not reusable. The concentration depends on the desired end-product.

Equipment for concentration may include descending film, thin layer or plate concentrators. Any method used to concentrate the extracts must avoid excessive heat because the active ingredients may be heat labile. The liquid preparation so obtained may be used as it is or further processed into a semi-solid or dry extract.

When complete drying is required, the drying process can make use of vacuum freeze-dryers (lyophilizers), cabinet vacuum dryers, continuously operating drum or belt dryers, microwave ovens or atomizers. The choice of technique for drying depends on the stability of the product and the amount of solvent that must be removed. The total removal of solvent results in a dry

extract, which may be less susceptible to microbial contamination than liquid extracts. Dry extract powders are often produced by drying the extract onto an inert carrier, such as methyl cellulose, maltodextrin or another excipient fit for the intended purpose, to facilitate processing into the final finished product.

3.5.1 Concentration and drying procedures

- The minimization of loss and/or damage to the chemical constituents of interest is critical to ensuring the effectiveness of the preparation. Therefore, the preservation of the active ingredients is of paramount importance during the concentration stage when heat is often applied to evaporate the solvent. Any concentration process should ensure that minimal thermal decomposition and chemical reactions (such as oxidation) occur. For organic solvents, evaporation under reduced pressure at a temperature below 40 °C is preferred.
- Solvent removal should be done as soon as possible after extraction. Prolonged exposure to sunlight should also be avoided.
- While evaporation is the most common and the most often applied technique for concentration, other approaches such as membrane technology and freeze-drying concentration are available.

3.6 Fermentation

In some cases, a herbal preparation is obtained after undergoing a process of fermentation of the comminuted herbal material or decoction. Fermentation can be either natural (“self-fermentation”) involving microbial cultures already present on the herb, enzymes naturally occurring in the herb (which may be activated by bruising the herb), or both, or by introducing an appropriate microbial organism (for example, *Lactobacillus* bacteria or yeast).

For natural fermentation, the dry comminuted herbal material, a decoction, or an extract of herbal material is often mixed with the juice of sugarcane, brown sugar or honey and the mixture is kept in an airtight utensil for several weeks for anaerobic fermentation to occur.

In some cases, herbal materials are mixed with a small amount of water and shaped into bricks, followed by microbial cultivation in an incubation room for a week or so, letting the mould grow on the surface of the herbal materials.

3.6.1 Fermentation procedures

- When fermentation is required to produce a herbal preparation, all utensils should be completely cleaned. A non-corrosive fermenter is required.

- The water to be used should comply with local requirement for potable water, not be alkaline and should be free of inorganic matter (deionized water).
- The temperature and length of fermentation should be optimized and controlled.
- When fermentation is complete, the solution should be filtered and stored in suitable containers.

3.7 Advanced cutting and powdering

Cutting and powdering (or grinding) of the crude drug has many advantages as this process facilitates reduction of the plant material to a desirable particle size. During the post-harvest processing stage, primary cutting takes place to reduce the size of large pieces of herb to facilitate transportation and cleaning or washing. In many cases, herbal materials are further cut into small pieces of particular size and shape following traditional practice. In other cases, size reduction of the herbal materials facilitates the process of extraction and the preparation of dosage forms such as capsules. The ground powder is usually subjected to sieve analysis to achieve uniform distribution of a desired particle size. Various types of grinding machines can be utilized depending on the hardness, size, heat stability, friability and structural features of the plant part and output characteristics.

3.7.1 Procedures

The appropriate particle size of a comminuted herbal material depends on its nature and its subsequent processing. When a national pharmacopoeia defines approved size ranges, those standards should be followed. In general, for dried leaves, flowers and whole herbaceous plants, an average particle size of 5–10 mm is adequate for extraction, while for harder materials such as wood, bark, roots, rhizomes and seeds, 0.5–5 mm is recommended. In special cases, such as the extraction of specific alkaloids, 50–500 μm particle size may be desirable. For encapsulation of powders, a particle size of about 1–50 μm is usually required. Very fine powders (for example, nanoparticles) should be avoided for extraction because they have a tendency to block the filters. Nanoparticles may also be used for encapsulation.

Usually particle size reduction is carried out using mills with varying operational functions. Hammer mills are the most commonly used for initial size reduction. They are suitable for pulverizing roots, barks and stems, but not for grinding soft materials such as flowers and leaves. Other types of mills such as crusher mills are good for crushing fibrous herbal materials, and further size reduction can be achieved by using cutter mills or disc mills.

3.8 Processing documentation

The general principles for documentation are set out in the *Good manufacturing practices for pharmaceutical products: main principles* (5, 8, 17).

In addition to the data called for in the above guidelines, the documentation for herbal preparations should as far as possible include, as a minimum, the following information:

- botanical information as specified in section 2.5;
- batch number, batch size, and any other identification code;
- supplier;
- dates of receipt of the herbal material, processing of the material, and completion of the process;
- name of person in charge of the processing;
- name of quality assurance manager; and person in charge of batch release;
- previous processes that the herbal material has already undergone;
- characteristics of the herbal preparation (such as type of preparation, ratio of the herbal material to the herbal preparation, organoleptic characters);
- methods used for processing to produce herbal preparation;
- details of the procedures (master formula), including quantity of herbal materials, extraction solvent, additive, descriptions of the steps of operation, operational conditions used during the process, and other relevant information;
- weight or amount of the herbal preparation;
- batch production: give details of deviations or modifications of the master formula;
- quality control parameters (such as identification tests, tests on water content and impurities, residual solvents, microbial contamination tests, shelf life), acceptance limits of the tests and quantitative assay results of active ingredients, markers or chemical reference standard(s);
- storage conditions and containers; and
- shelf life and retest period.

An SOP including all processing steps should be adopted and documented in the Master Record. Batch records should be kept and any deviations from the SOP should be fully recorded and investigated. Name(s) of all operators, and the dates and time at which each step or stage are carried out should be documented.

4. Good herbal processing practices for the production of herbal dosage forms

4.1 General information

In contrast to synthetic pharmaceutical preparations, certain herbal materials and herbal preparations may undergo simpler good practice processes to become suitable dosage forms and final products for administration. However, these dosage forms should be produced under applicable GMP (4–6, 8) conditions. Starting materials for the preparation and production of various herbal dosage/final dosage forms should consist of good quality medicinal plants cultivated or collected as prescribed by GACP (1). They should have been subjected to post-harvest processing, followed by further processing into herbal materials or herbal preparations under GHPP as described previously (sections 2 and 3).

Examples of a number of herbal dosage forms are presented in the *Japanese Pharmacopoeia*.⁶

The following describes some common dosage forms of herbal medicines. National and regional regulations and GMP guidelines must be followed for the production of finished products.

4.2 Preparation of liquid herbal dosage forms

Liquid herbal dosage forms as described here are oral preparations, including, but not limited to, the following product types or categories. These liquid herbal dosage forms may be prepared by dissolving the herbal preparation in an aqueous or non-aqueous solvent, by suspending it in an appropriate medium or by incorporating it into one of the two phases of an oil and water system.

4.2.1 Fluidextract

For description, see section 3.2.3.1

4.2.1.1 Preparation of fluidextracts

Fluidextracts are prepared by percolation of herbal material(s) using an aqueous alcoholic menstruum. After being thoroughly moistened, the mixture is packed firmly into a percolator and covered with additional menstruum. It is macerated for 24 hours, then percolated at a moderate rate, adding fresh menstruum as

⁶ Ministry of Health, Labour and Welfare, Government of Japan, General Rules for Preparations – [4] Monographs for Preparations Related to Crude Drugs, *Japanese Pharmacopoeia 17th edition*, 2016. <https://www.pmda.go.jp/files/000217650.pdf>.

necessary to completion. The first 700–800 mL of the percolate should be reserved for use to dissolve the residue from the additional percolate that has been concentrated to a soft extract at a temperature not exceeding 60 °C. The extract is adjusted with menstruum, if necessary, so that it satisfies the requirements for content of solvent (in a ratio of one part (1.0 mL) of liquid to one part (1.0 g) of the herbal material). They may be filtered, if necessary.

4.2.2 **Decoctions**

For description, see section 3.2.3.1

4.2.2.1 **Preparation of decoctions**

In many traditional medicine contexts, decoctions are prepared by boiling the herbal materials in water for a certain period of time, after which they are strained and taken directly by the patients. The amounts of water used and the length of boiling are generally specified by the practitioners on a case-by-case basis.

4.2.3 **Infusions**

For description, see section 3.2.3.1

4.2.3.1 **Preparation of infusions**

Infusions are prepared by macerating the herbal materials for a short period of time with warm or boiling water.

4.2.4 **Tinctures**

For description, see section 3.2.3.1

4.2.4.1 **Preparation of tinctures**

Tinctures are usually prepared by either maceration or percolation, using ethanol, wine or a hydroalcoholic mixture to extract the herbal material, or by dissolving a soft or dry extract of the herbal material in ethanol of the required concentration. Tinctures are adjusted, if necessary, so that they satisfy the requirement for content of solvent (1 part of herbal material and 5–10 parts of solvent). They may be filtered if necessary.

4.2.5 **Syrups**

Syrups are viscous liquids containing sugars or other sweetening agents. They are prepared by dissolving, mixing, suspending or emulsifying herbal extracts or decoctions in a solution of honey, sucrose or other sweetening agents.

4.2.5.1 Preparation of syrups

Syrups are usually prepared by adding sucrose (at least 45% m/m) to the herbal solution or decoction, and then heating and straining it. Other polyol sweetening agents may be used. Sufficient purified water is then added to yield a product of the desired weight or volume. Syrups should be made in quantities that can be consumed within a reasonable period of time. If necessary, syrups may contain approved preservatives to prevent bacterial and mould growth.

4.2.6 Oral emulsions

Oral emulsions are preparations consisting of a two-phase system composed of at least two immiscible liquids such as oil-in-water preparations that are rendered homogeneous and stabilized by the addition of emulsifying agent(s). For example, an oil obtained from herbs (for example, castor oil) is dispersed in water and emulsified with an emulsifying agent such as gum acacia.

4.2.6.1 Preparation of oral emulsions

Various techniques can be applied to uniformly disperse one liquid in another immiscible liquid in the form of small droplets throughout the other. When emulsions are prepared, energy must be expended to form an interface between the oily and aqueous phases. Emulsification equipment includes a wide variety of agitators, homogenizers, colloid mills and ultrasonic devices.

4.2.7 Aromatic waters

Aromatic waters are water preparations saturated with essential oils or other aromatic or volatile substances. Aromatic waters have a characteristic odour of the essential oil or volatile substances used.

4.2.7.1 Preparation of aromatic waters

Usually, an essential oil (1 part) is shaken in recently distilled water (999 parts) and set aside for 12 hours or longer after mixing with 10 parts of talcum powder. The solution is filtered and made up to a certain volume with water. Aromatic waters will deteriorate over time due to volatilization, decomposition or mould growth. They should, therefore, be made in small quantities for immediate use and protected from intense light, excessive heat and stored in airtight, light-resistant containers, if necessary.

4.3 Preparation of solid herbal dosage forms

Solid dosage forms as described here are those that are most commonly found in herbal medicine, but they are not limited to the following categories.

4.3.1 Herbal tea bags

Herbal tea bags are used in many traditional medicine systems as a dosage form. Each tea bag contains ground herbal materials (a single herb or a mixture of different herbs) sufficient for one dose for making into an infusion.

4.3.1.1 Preparation of herbal tea bags

Herbal materials (for example, dried roots, leaves or flowers) are put into paper or cloth bags. Herbal tea bags should be free of bleach, gluten and dioxin. Metallic pins, used for attaching a piece of thread to the tea bag, should be avoided as this may release unsafe cations into the solution. When used, boiling water is poured into the vessel or cup containing the bag.

4.3.2 Plant powders

In many traditional medicine systems, ground powders of herbal materials are taken directly by patients as a dosage form. Powders are ground into various coarse or fine particle sizes, excluding nanopowder.

4.3.2.1 Preparation of plant powders

Powders are prepared by grinding or pulverizing dried herbal materials to a suitable particle size. When used, they are suspended in warm water ready for ingestion, or more commonly, they are packed into capsules or sachets.

4.3.3 Dry extract powders (powdered extracts)

Dry extract powders are solid preparations with a powdery consistency, obtained by evaporation of the solvent used for extraction. They may contain suitable added substances such as excipients, stabilizers and preservative, and suitable for incorporation into a dry formulation as in capsules, tablets or granules.

4.3.3.1 Preparation of dry extract powders (powdered extracts)

Dry extract powders are prepared by spray-drying or freeze-drying of a fluid extract with or without the use of an adsorbent (such as methyl cellulose), or by drying and milling to produce a powder. Excipients are often used for purposes such as improving taste or facilitating the packaging step.

4.3.4 Granules

Granules are dried liquid (fluid) extracts processed into spherical particles composed of agglomerations of smaller particles. Typically, granules are reconstituted to a suspension or solution by the addition of water to make a “herbal tea” for administration, although they can be administered directly. They are also used in tablet compression or capsule filling.

4.3.4.1 Preparation of granules

In the typical manufacture of granules, the dried liquid extract is blended with diluents, binders or other suitable excipients, then wetted with an appropriate binding solution or solvent to promote agglomeration. The composition is dried and sized to yield the desired material properties.

4.3.5 Pills

Pills are dry extract powders in the form of small, spherical solids, similar to, as a rule, but larger than granules (size may vary in different traditional medicine contexts). In certain traditional medicine context, pills are also made from powdered herbs/herbal materials.

4.3.5.1 Preparation of pills

Pills may be prepared by trituration of dried powdered herbs or dry extract powders with suitable powdered excipients in serial dilution to attain a uniform mixture. Liquid excipients that act to bind and provide plasticity are added to the dry materials, and kneaded to form a mass. Typically, pills are swallowed with warm water.

4.3.6 Capsules

Capsules are solid dosage forms in which the herbal substance is enclosed in either a hard or soft, soluble shell of gelatin or other suitable materials. Hard-shell capsules (also known as two-piece capsules) consist of two pieces (a body and a cap) in a range of standard sizes; soft-shell capsules (also known as one-piece or gel capsules) comprise an outer case encapsulating a liquid or paste. The exact composition of the capsule varies with the nature of the content.

4.3.6.1 Preparation of capsules

Capsules are prepared by enclosing a plant powder, or homogeneous dry extract powder or granules with excipients in a suitable capsule base such as gelatin, of a particular shape and size. In the case of gel capsules, liquid extract or soft extract can also be encapsulated. The process is carried out using specialized equipment.

4.3.7 Tablets

Tablets are solid preparations in which the herbal extract powder, plant powder or granule is blended with excipients and formed into a defined shape and size by compression.

4.3.7.1 Preparation of tablets

Tablets are usually prepared by mixing the homogeneous dry extract powder, plant powder or granules with excipients such as diluents and binders, followed by compression into a defined shape and size. Tablets may be coated or uncoated.

4.3.8 Lozenges

Lozenges (compressed lozenges are referred to as “troches”) are solid dosage forms that are designed to dissolve slowly in the mouth to provide local action in the oral cavity or the throat, such as cough drops or pastilles, but may also provide systemic action. Lozenges often contain flavouring agents and sweetened bases.

4.3.8.1 Preparation of lozenges

In the typical preparation of lozenges, sucrose (or another excipient such as sorbitol) is cooked with the herbal extract and water. Flavouring and colouring agents are added and thoroughly mixed while cooling. Individual units of the desired shape are formed by filling the molten mass into moulds. Care should be taken to avoid excessive moisture during storage to prevent crystallization of the sugar base.

4.4 Preparation of other herbal dosage forms

4.4.1 Ointments, creams and salves

Ointments, creams and salves are topical preparations for application to the skin. They are usually semi-solid emulsions dissolved or dispersed in a suitable base. Salves are often solid at room temperature. They may contain emulsifiers or thickening agents.

4.4.1.1 Preparation of ointments, creams and salves

Ointments and creams can be formulated with a herbal extract or powder and a variety of oils and emulsifying agents. Preparation usually involves heating, mixing and stirring the lipid and aqueous portions until the mixture has congealed. They usually require the addition of preservative unless they are intended to be used within a relatively short period of time.

4.4.2 Inhalations

Inhalations are preparations intended for administration as aerosols to the bronchial tubes or lungs. They are usually either dry powder inhalers or inhalation liquid preparations. For administration of inhalations, suitable devices or apparatus are required. Steam inhalation of volatile substances from herbal teas or essential oils is used as a traditional inhalation method. The preparations

are also used at room temperature with suitable evaporating devices and as sticks when the volatile substance is incorporated in a suitable vehicle.

4.4.2.1 Preparation of inhalations

Dry powder inhalers are prepared by pulverizing dry extracts into fine particles. When necessary, lactose or other suitable excipients are added to make a homogeneous mixture. Inhalation liquid preparations are usually prepared by mixing dry herbal extracts with a vehicle and suitable pH-adjusting agents to make a solution or suspension. Suitable preservatives may be added to prevent the growth of microorganisms.

4.4.3 Plasters and patches

Plasters and patches contain herbal preparations such as dry or soft extracts on pieces of fabric or plastic elastomer sheets in such a way as to adhere to the skin and attach to the backing. When applied topically to the skin, they deliver the active ingredients through the skin to underlying tissues, usually for the relief of pain, backache or sore muscles.

4.4.3.1 Preparation of plasters and patches

A dry or soft extract of herbal preparation is spread uniformly on an appropriate support that is usually made of a rubber base or synthetic resin. Plasters are available in a range of sizes or cut to size to effectively provide prolonged contact with the site of application. They adhere firmly to the skin but can be peeled off without causing injury.

4.4.4 Medicated oils

Medicated oils are preparations formulated using fixed oils as base/vehicle where the prescribed herbal material, extract or fresh juice is mixed, macerated or boiled in oil. Different traditional methods are followed in the preparation of medicated oils but the aim is to obtain an oil enriched with fat-soluble extractives of the desired ingredients.

Medicated oils are mainly used topically, for example, in therapeutic massages and in certain cases, for oral administration.

4.4.4.1 Preparation of medicated oils

A fine paste of powdered herb or herbal material(s) together with a given media (if any, such as water, milk or fresh juices or decoctions of herbal materials) is mixed in a prescribed quantity of oil and macerated or boiled slowly with continuous stirring until complete removal of water or moisture (as the case may be). The oil is then decanted or strained while warm through muslin cloth and allowed to cool.

5. Technical issues supporting good herbal processing practices

In the formulation of a good practice protocol for herbal processing, a number of supporting technical measures must be considered and adopted. Since the primary objective is to produce quality processed herbal materials, herbal preparations and herbal dosage forms, many of the same technical issues associated with GACP, GMP and quality control (QC) methods are applicable to GHPP.

Therefore, these guidelines have been consulted for applicable good practice for adoption in GHPP. Moreover, the same technical issues relating to the post-harvest processing of cultivated and collected medicinal plant materials were addressed in section 4 of the *WHO guidelines on GACP for medicinal plants (1)*. Likewise, the same technical issues relating to the processing of herbal materials and herbal preparations were described in the WHO guidelines on GMP for herbal medicines (5, 6, 8). Thus, the applicable good practice guidelines have been adopted in whole or in part, or modified as appropriate for the present guidelines.

5.1 Processing facilities

The ideal design and construction of a “post-herbal processing” facility incorporating the most appropriate location, buildings, herbal material handling and processing areas, water supply, effluent and waste disposal, changing facilities and toilets, hand-washing facilities in processing areas, disinfection facilities, lighting, ventilation, dust and storage of waste and unusable materials, have already been fully described in sections 4.1.5 (pages 19–23) of the *WHO guidelines on GACP for medicinal plants (1)*. Therefore, they are adopted for the present guidelines and the descriptions are presented in Appendix 3 for easy reference.

Additionally, a facility for processing herbal preparations and herbal dosage forms would most appropriately be constructed following the principle of good manufacturing practice, as described in the *WHO guidelines on good manufacturing practice (GMP) for herbal medicines (5)*. The relevant descriptions of such a facility are provided in Appendix 4 for easy reference.

5.2 Packaging and labelling

Processed herbal materials, herbal preparations and herbal dosage forms should be packaged as quickly as possible to preserve their quality. Packaging should prevent deterioration of the herbal medicines and they should be protected against exposure to pest infestations and other sources of contamination. When

applicable, the maximal holding time of the unpacked herbal medicines should be established.

Continuous in-process QC measures should be implemented to eliminate substandard materials, contaminants and foreign matter prior to and during the final stages of packaging. Processed herbal materials, herbal preparations and herbal dosage forms should be packaged in clean, dry boxes, sacks, breathable bags or other containers in accordance with the SOP and should comply with national and/or regional regulations of the producer and the end-user countries. Materials used for packaging should be non-polluted, clean, dry and undamaged, and should conform to the quality requirements for the processed herbal materials, herbal preparations or herbal dosage forms concerned. Fragile herbal materials should be packaged in rigid containers. Wherever possible, the packaging used should be agreed upon between the supplier and the buyer.

A label affixed to the packaging should include, but is not limited to, the following:

- accepted scientific name of the herb(s);
- official common name of the herb(s), herbal material(s), herbal preparation(s) or herbal dosage form(s);
- brand name of the herbal medicines (herb(s), herbal material(s), herbal preparation(s) or herbal dosage form(s));
- date of the processing of the processed herb(s), herbal material(s), herbal preparation(s), or herbal dosage form(s) obtained;
- processing techniques used;
- names and addresses of the herbal materials or herbal preparations processor, herbal dosage forms (finished herbal products) manufacturer, importer and/or distributor (i.e. the entity responsible for receiving consumer complaints and conducting a recall should the need arise);
- potency or strength of the active ingredient, if applicable (for example, for an extract the drug extract ratio of herbal material to extract, or the concentration of active or marker substance(s) used for standardization);
- net amount in the immediate container in terms of weight, measure or unit number;
- in the case of a finished herbal dosage form, the quantity of each active ingredient or marker per dosage unit;
- list of excipients;
- recommended storage conditions;

- batch number; and
- expiry date.

The label should also contain information indicating quality approval and compliance with national and/or regional labelling requirements.

Finished herbal product labelling should comply with the national/regional regulation/requirements.

Records should be kept of batch packaging, and should include the product name, place of origin, batch number, weight, assignment number and date. The records should be retained for a period of three years or as required by national and/or regional authorities.

5.3 Storage and transportation

All processed herbal medicines should be properly stored and preserved before use. They must be protected from microbial and insect contamination, as well as rodents and other pests. Every effort should be made to use the type of packaging that provides the best protection against physical damage to the processed materials; and at the same time to keep them away, as far as possible, from exposure to moisture, light, heat, insect and animal attack.

Rejected samples should be kept in a separate designated quarantined area, clearly labelled and with a specified handling period.

Toxic or controlled herbal materials or preparations should be checked, labelled and stored according to the government's regulations.

Storage areas should be of sufficient capacity to allow orderly storage of the various types of processed herbal materials, herbal preparations or herbal dosage forms with proper separation and segregation. In particular, they should be clean, dry, sufficiently lit and maintained within acceptable temperature and humidity limits. They should be controlled, monitored and recorded where appropriate to ensure good storage conditions, and comply with the "first-in and first-out" principle.

Conveyances used for transporting processed herbal medicines from the place of processing to the storage location should be clean and, where appropriate, well ventilated to maintain an appropriate airflow and to prevent condensation.

Pest infestation control in conveyances and in storage areas should be carried out by licensed or trained personnel. Only registered chemical agents authorized by the regulatory authorities of the source country and the countries of intended end-use should be used. All fumigation, fumigation agents and dates of application should be documented. When freezing or saturated steam is used for pest control, the humidity of the stored herbal medicines should be checked after treatment.

5.4 Equipment

All equipment, including tools and utensils used in the herbal processing procedures should be made of materials that do not transmit toxic substances, odour or taste; are non-absorbent; are resistant to corrosion and are capable of withstanding repeated cleaning and disinfection. The use of wood and other materials that cannot be adequately cleaned and disinfected should be avoided, except when their use would clearly not be a source of contamination. The use of metals known to cause corrosion should be avoided.

All equipment and utensils should be designed and constructed so as to prevent hygiene hazards and permit easy and thorough cleaning and disinfection. Where practicable, they should be accessible for visual inspection. Stationary equipment should be installed in such a manner as to permit easy access and thorough cleaning.

Containers for unusable materials or waste should be leak-proof, constructed of metal or other suitable impervious materials, should be easy to clean or be disposable, and should close securely.

All refrigerated spaces should be equipped with temperature measurement and recording devices.

5.5 Quality assurance and quality control

A quality assurance system is essential to ensure that herbal processing practice is consistently executed and controlled. The system for verification of compliance may differ from country to country. In general, compliance with quality assurance measures should be verified through regular internal oversight personnel (quality assurance manager) and external auditing visits to processing facilities by expert representatives of buyers and other stakeholders, and through inspection by national and/or local regulatory authorities. No processed herbal medicine should be released until its quality complies with or conforms to standard specifications.

5.6 Documentation

The SOPs should be adopted and documented. All methods and procedures used in the herbal processing and the dates on which they are carried out should be documented.

The types of information that should be collected include the items described in sections 2.5 and 3.8. Additionally, documentation on post-processing transportation and storage of processed products should be prepared.

Where applicable, the results of inspection should be documented in an inspection report, which contains copies of all documents, QC analysis reports, and local, national and/or regional regulations, and which are stored in compliance with their requirements.

5.7 Personnel

5.7.1 General

All personnel should receive proper training in post-harvest handling and herbal processing. Furthermore, all personnel required to handle chemical solvents and adjuvants should receive adequate training and possess sufficient knowledge of the appropriate techniques to be employed for their safe handling and proper use. Training records should be signed by the trainer and trainee and documented.

Local, national and/or regional regulations governing labour should be respected in the employment of staff for all phases of herbal processing.

5.7.2 Health, hygiene and sanitation

All personnel involved in the pre-herbal processing and during herbal processing procedures should be properly trained and should perform tasks in compliance with local, national and/or regional regulations on safety, materials handling, sanitation and hygiene.

All personnel should be protected from contact with potentially toxic or allergenic herbs by means of adequate protective clothing, including gloves and masks.

Health status

All new staff should pass a medical examination. No personnel known or suspected to be suffering from or to be a carrier of a disease or illness likely to be transmitted, should be allowed to enter any processing area, and should immediately be reported to the management, and suspended from work as deemed medically appropriate.

Health conditions that should be reported to the management for consideration regarding medical examination and/or possible exclusion from handling of herbal medicines and herbal processing, processed herbal medicines and associated equipment include but are not limited to: jaundice, diarrhoea, vomiting, fever, sore throat with fever, visibly infected lesions (boils and cuts, among other conditions) and discharges from the ear, nose or eye. Any personnel who have cuts or wounds and are permitted to continue working should cover their injuries with suitable waterproof dressings.

Personal hygiene and behaviours

Personnel engaged in herbal processing and who handle processed herbal medicines should be trained to maintain a high degree of personal cleanliness, and, where appropriate, wear suitable protective clothing and gloves, including head/hair covering and footwear.

Personnel should always wash their hands at the start of handling activities, after using the toilet, and after handling herbal processing and herbal medicines, or any contaminated material.

Smoking, drinking and eating should not be permitted in herbal processing areas.

Visitors

Visitors to processing and handling areas should wear appropriate protective clothing and adhere to all of the personal hygiene provisions mentioned above (WHO, 2003a).

6. Other relevant issues

6.1 Ethical and legal considerations

All herbal processing must be carried out in accordance with applicable legal and environmental requirements and with the ethical codes or norms of the community and country in which the activities take place.

6.2 Research, research training and information sharing

Research to understand and gain knowledge on the mechanism and scientific basis of processing procedures, such as traditional or historical methods is needed. It is also necessary to conduct research to find alternative processing procedures to achieve the same therapeutic effect as traditional or historical methods. Additionally, research to determine the chemical conversion process and mechanism involved in the qualitative and quantitative alteration of the biologically active chemical constituents following processing is needed and encouraged.

Technical information resulting from research on processing methods is useful for promoting technical advancement, and should be shared through publication, conferences or otherwise conveyed to interested stakeholders.

As in all technical endeavours, education and research training are essential to preserve technical expertise and to promote innovation in development of new and better techniques and procedures in herbal processing.

Research to develop GHPP for individual herbs or herbal materials and to document each in a monograph is strongly encouraged.

6.3 Adoption of good herbal processing practices

Member States or nations that have not adopted GHPP for herbal medicines are encouraged to establish or adopt such practices as part of quality assurance and control measures, as well as a part of their regulatory requirements for herbal medicines.

6.4 Intellectual property rights and benefits-sharing

Agreements on intellectual property rights and the return of benefits and compensation for the use of source herbal materials or herbal preparations concluded in writing by the sourcing contractor, shall be acknowledged and followed by the processor as appropriate (for example “Aichi Protocol” under the framework of the United Nations Convention on Biodiversity).

6.5 Threatened and endangered species

When obtaining herbs or herbal materials that are protected by national and international laws, such as those listed in national “red” lists, for processing, the processor shall ascertain and obtain appropriate documentation from the sourcing contractor that said materials were acquired only by relevant permission according to national and/or international laws, and that the provisions of the Convention on International Trade in Endangered Species of Wild Fauna and Flora have been complied with.

6.6 Safety management of toxic herbs

Among the herbal medicines (and their source medicinal plants) being used in traditional medicine contexts in different parts of the world, some are known to contain toxic substances that may lead to severe side-effects or even death. In general, these toxic herbal materials and their preparations or dosage forms have narrow therapeutic windows between effective dose and lethal dose. Examples of such toxic/effective therapeutic agents are cardioactive herbal preparations such as *Powdered Digitalis* and *Digitalis Capsules*, which at the proper dosages, are excellent therapeutic cardiotonic agents, but are lethal when an overdose is taken.

In order to safeguard the use of these potentially toxic herbs, special attention and safety management measures are required, for example:

- they must go through proper processing procedures for the purpose of neutralizing the toxicity or reducing the side-effects prior to use.
- They must be used under stringent measures of control and supervision by qualified and/or trained personnel.
- When poisoning and/or accidents related to the use of these toxic herbs occur, proper medical treatment should be given immediately.
- Member States should promote and ensure the safe use of potentially toxic herbs and their preparations.
- Member States are encouraged to establish national policies to achieve effective control of herbal safety and to strengthen risk assessment and management.

- Member States are encouraged to develop their own standards and guidelines for the use of potentially toxic medicinal plants.

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Appendix 1

Example of a model format for a good herbal processing practices monograph/standard operating procedure protocol to produce a herbal material

TITLE of the monograph/protocol

Processing of (name of the plant) (*Scientific name of the medicinal plant; medicinal plant part*)

1. **Objective of the standard operating procedure (SOP) protocol**
2. **Scope**
3. **Procedures**
 - 3.1 **Sampling**

Sampling of herbal materials should follow applicable national or regional specifications. In absence of appropriate specifications, the following method may be considered: When a batch consists of five containers or packaging units, take a sample from each one. From a batch of 6–50 units, take a sample from five. In the case of batches of over 50 units, sample 10%, rounding up the number of units to the nearest multiple of 10 (WHO, 2011).

Quality testing of the raw material

Perform morphological identification/validation by macroscopic, microscopic or phytochemical and/or genomic identification/examinations and physicochemical tests by following the procedures set out in the national pharmacopoeia or other documents.

The following requirements must be fulfilled.

- Morphology: conform with the national pharmacopoeial or other relevant standards
- Identification (including macroscopic, microscopic examination, phytochemical and/or genomic identification/examinations, and/or chromatographic tests): conform with the pharmacopoeial standards
- Water content: \leq xxx %

- Total ash: \leq xxx %
- Acid-insoluble ash: \leq xxx %
- Extractive: \geq xxx %

3.2 Quality control assay

3.2.1 Marker compound(s)

Compound “Z” is used as the marker compound for plant X.y. for quality control purpose. Obtain analytical grade Compound Z (\geq 98% purity) from a reliable source to serve as chemical reference substance.

3.2.2 High-performance liquid chromatographic analysis

Set up the high-performance liquid chromatography (HPLC) system. Perform system suitability test to ensure suitability of the instrument and method.

Under the recommended HPLC conditions, establish calibration curves by injecting an appropriate amount of the chemical reference (marker) standard solution in a series of concentrations.

Obtain HPLC chromatogram of the herbal material. Identify the analyte signal in the chromatogram by comparing the retention time with that of the peak of the chemical reference substance obtained under same HPLC conditions.

Calculate the percentage content of the analyte in the sample using the calibration curve.

Determine the percentage content of the marker compound again after final drying of the processed herbal material (section 3.10 below).

The following requirement must be fulfilled.

- Content of Compound Z before processing: \geq xxx % calculated with reference to the dry weight of the starting material
- Content of Compound Z after processing: \geq xxx % calculated with reference to the dry weight of the processed material

3.3 Testing of the excipient*

(*This step is not required if excipient(s) are not employed in the processing protocol)

Perform tests by following the procedures set out in the SOP document. The following requirements must be fulfilled.

- Appearance: conform with internal standards
- Total excipient content: \geq xxx %

3.4 Initial sorting of herb for processing

The source herbs are manually sorted by trained personnel according to the requirements specified in the SOP. Impurities (for example, dirt and non-medicinal plant parts) should be removed, and any materials of non-uniformed sizes should be excluded.

The following requirements must be fulfilled.

- Impurity: \leq xxx %
- Size uniformity: \geq xxx %
- Total recovery: \geq xxx % (Recovery = Weight after sorting/Weight before sorting X 100%)

3.5 Washing

Washing should be performed by following the procedures set out in the SOP document. Pay attention to the quality of water used, the length of washing time, and any precautions applicable to the specific herb.

The following requirements must be fulfilled.

- Appearance after washing: in conformance with the SOP standard
- Recovery: xxx-xxx % (Recovery = Weight after washing/Weight before washing X 100%)

3.6 Steaming (or other treatment)

The procedures set out in the SOP document should be strictly followed. All equipment should be properly maintained, clean and performing at optimal and safe conditions.

The following requirements must be fulfilled.

- Appearance after steaming/treatment: in conformance with the SOP standard
- Recovery: \geq xxx % (Recovery = Weight after steaming/Weight before steaming X 100%)

3.7 Semi-drying

If required, dry the samples according to SOP guidelines, either by sunlight or by artificial heating.

The following requirements must be fulfilled.

- Appearance after semi-drying : in conformance with the SOP standard

- Recovery: xxx-xxx% (Recovery = Weight after drying/Weight before drying × 100%)

3.8 Cutting/sectioning/comminuting

The processed material should be comminuted into the required size and shape in conformance with the SOP.

The following requirements must be fulfilled.

- Non-conforming pieces: ≤ xxx %
- Powder fineness:
- Recovery: ≥ xxx % (Recovery = Weight after cutting/Weight before cutting × 100%)

3.9 Final drying of processed herbal material

The cut materials should be thoroughly dried according to the SOP requirement.

The following requirements must be fulfilled.

- Water content of the final product: xxx-xxx %
- Recovery: ≥ xxx % (Recovery = Weight after drying/Weight before drying × 100%)

3.10 Final sorting

The dried material should be carefully inspected by trained personnel, with impurities removed and sorted into specific grades in accordance with the pharmacopoeial or trading standard.

The following requirements must be fulfilled.

- Impurity: ≤ xxx %
- Grade-1 pieces: ≥ xxx%
- Grade-2 pieces: xxx –xxx%
- Recovery: ≥ xxx % (Recovery = Weight after sorting/Weight before sorting × 100%)

3.11 Packaging, labelling and storage

3.11.1 Packaging

Processed materials should be packaged quickly and appropriately in appropriate, non-corrosive containers, and protected from light to preserve quality, prevent deterioration and to protect against contamination.

3.11.2 Labelling

Labels affixed to each package should clearly indicate the scientific name of the medicinal plant, the plant part, the processing method, the date of processing, the batch number, quality specification and compliance, quantitative and other relevant information, in compliance with the national/regional requirements.

3.11.3 Storage

The packaged products must be stored in a clean, dry and well-ventilated area, at a temperature appropriate for the proper maintenance of the final product, and protected against microbial and other sources of contamination and free from insects and animal pest attacks.

Appendix 2

Example of a model format for a good herbal processing practices monograph/standard operating procedure protocol to produce a herbal preparation or herbal dosage form

TITLE of the monograph/protocol

Processing of (name of the plant) (*Scientific name of the medicinal plant; medicinal plant part*)

1. Objective of the standard operating procedure protocol

The objective of this protocol is to establish a procedure for preparation of the finished product.

2. Scope

This procedure applies to processes required in the preparation of the fluidextract of the herbal material from X...y...

3. Procedures

This protocol should be carried out in accordance with the standard operating procedures (SOP) for the processing of material X...y... as described in this document, the SOP for equipment operation and maintenance, as well as those for facility management and cleaning. Any other relevant requirements may also apply.

The protocol should be adhered to in conjunction with relevant internal standards of the processing facility.

After the completion of each processing step, the products should be inspected by qualified personnel. All inspection records should be properly filed and retained for a period of three years or as required by national and/or regional authorities.

4. Herbal material

The identity of the herbal material should be confirmed using morphological identification/validation by macroscopic and microscopic examinations, as well as by using phytochemical and/or genomic identification/examinations, and

physicochemical tests by following the procedures set out in the pharmacopoeia or other documents.

Specifications such as those below should be in place.

- **Origins of the herb (natural state/cultivation):** Describe appropriate origins of the herbal material
- **Plant part:** Describe the desired plant part (i.e. flower)
- **Harvest/collection time:** Describe the appropriate months for harvest/collection (for example during flowering (June-July))
- **Processing:** Describe the processing of the herbal material
- **Drying conditions:** Describe the process for drying, if applicable
- **Purification:** Describe the process for inspection and removal of impurities
- **Storage conditions:** Specify the storage conditions. In general, the herbal material should be stored in a clean, dry and well-ventilated area, at a constant, appropriate temperature, protected against microbial and other sources of contaminations, free from attack by insects and animal pests
- **Transportation conditions:** Commercial vehicles should be clean, dry, deprived of any foreign matter. Conditions should ensure protection against moisture and contamination. Baskets, chests and jute bags can be used as containers. Each container should be labelled with the name of the material, date of harvest/collection, harvesting/collection site, net and gross weight and the name of the supplier

5. Processing

Descriptions of the herbal processing facility requirements should be maintained, i.e. certification of the site as a good practice facility. Details are given here for the raw components to be used in the production of the final herbal preparation.

As an example, raw X...y... herbal material to be processed into X...y... juice are detailed in the table below. In this example, the herbal material is extracted using ethanol 95% (V/V) and water as needed. The drug extract ratio is 1:1.

Raw material components in the production of X...y...juice

Raw materials	Function	Amount per 100 kg	Standard
Fresh X...y... herb	Herbal material	100.0 kg	Standard specification
Ethanol 95%	Extraction solvent	xx litres	Pharmacopoeia .XYZ
Extraction water	Extraction solvent	<i>quantum satis</i>	Pharmacopoeia .XYZ

Raw materials accepted for processing must meet specifications for identity and quality. Specifications include appearance/description of the herbal material, water content, total ash, as well as appropriate chemical assays. These criteria may follow criteria detailed in pharmacopoeial monograph(s).

- The steps below describe the preparation of the juice of X.y...:
- Step 1. The fresh fragmented herbal material is stabilized with the vapours of boiling 95% ethanol in an autoclave. The duration, temperature and vapour pressure are specified in the SOP. When the process is completed, the fluid separates from the herbal material.
- Step 2. The stabilized herbal material is placed in a macerator with post-stabilization fluid and water. The maceration process lasts for a period of time (n days) specified. At the end of the extraction process, the extract is separated from the solid materials in a manner specified by the SOP. The ethanol content of the extract and density of the extract are specified.
- Step 3. The resulting extract is stored in a stainless steel container for a minimum time (days/weeks) specified. The process ensures sedimentation of inorganic residual waste.
- Step 4. The extract is filtered using a pressurized process. The filter size and input pressure are selected as specified by the manufacturer or manufacturer's catalogue of the filtering unit.

6. In-process controls

Controls for tests conducted during the process should be described. A description of the tests, their methods and the acceptance criteria should be given. These include appearance (i.e. colour), particle size (amount expected to pass through a specified sieve size), water or alcohol content, and/or relative density.

7. Herbal dosage form

The herbal dosage forms may include extracts, pills, spirits, infusions, decoctions, teabags, tinctures, aromatic waters and fluidextracts (see footnote¹).

8. Release specifications of final product

Identify criteria must be met for release of the final product. These criteria generally include appearance, organoleptic characteristics, relative density,

¹ A herbal preparation or a specific dosage form, as indicated above, can be prepared as per established pharmacopoeial methods.

chemical identity including specified quantities for chemical constituent(s), as well as limits for heavy metals, microbial contamination and residual matter.

- Chemical profile: i.e. TLC/HPLC fingerprint of chemical constituents
- Pharmacopoeial/standard quantitation of chemical markers, where applicable
- Heavy metals: limits defined
- Microbial: limits defined
- Residuals: limits for pesticides, fertilizers, foreign matter, solvent residue, mycotoxins, etc.

9. **Certificate of analysis**

A certificate of analysis should be generated following completion of quality control testing. This document should include the assay methods as well as the results obtained using those methods.

10. **Packaging**

The appropriate packaging of the containers should be described. Processed materials should be packaged quickly and appropriately in airtight, non-corrosive containers, and protected from light to preserve quality, prevent deterioration and to protect against contamination.

11. **Labelling**

Labels affixed to each package should clearly indicate the scientific name of the medicinal plant, the plant part, the herbal processing method, the date of processing, the batch number, quality specification and compliance, quantitative and other relevant information, in compliance with the national/regional requirements.

12. **Storage conditions**

The packaged products must be stored in a clean, dry and well-ventilated area, at a temperature appropriate for the proper maintenance of the final product, and protected against microbial and other sources of contaminations and free from insects and animal pest attacks.

13. **Stability**

Stability testing should be conducted to determine an appropriate shelf life.

14. **Retained samples**

Sufficient materials (raw material and finished goods) must be retained in proper storage conditions to allow for future verification of identity and quality.

Appendix 3

Processing facilities for post-harvest processing

The following is extracted from section 4.1.5 of the *WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants* (WHO, 2003) (pages 19–23).

Processing facilities

In constructing or designing a processing facility, the following elements should be considered that will allow the establishment of a quality assurance system adaptable to the different types and steps of processing to yield the desired end-products.

Location

Facilities should preferably be located in areas that are free from objectionable odours, smoke, dust or other contaminants and are not subject to flooding or other natural adverse conditions.

Buildings

Buildings should be of sound construction and maintained in good repair. Filthy areas must be isolated from clean processing areas. All construction materials should be such that they do not transmit any undesirable substance including toxic vapours to medicinal plant materials. Electrical supply, lighting and ventilation should be appropriately installed.

Buildings should be designed to:

- provide adequate working space and storage room to allow for satisfactory performance of all operations;
- facilitate efficient and hygienic operations by allowing a regulated flow in processing from the arrival of the raw medicinal plant materials at the premises to the dispatch of the processed medicinal plant materials;
- permit appropriate control of temperature and humidity;
- permit control of access to different sections, where appropriate;
- permit easy and adequate cleaning and facilitate proper supervision of hygiene;

- prevent the entry of environmental contaminants such as smoke, dust, the entrance and harbouring of pests, livestock and domesticated animals;
- where appropriate, prevent direct sunlight from entering a particular section.

Medicinal plant material handling and processing areas

The layout and design of the work area should be such as to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, and otherwise avoid any adverse effect on the quality of the processed product.

- Windows and other openings should be constructed so as to avoid accumulation of dirt, and where appropriate, those that open should be fitted with insect-proof screens. Screens should be easily removable for cleaning and kept in good repair. Internal window sills, if present, should be sloped to prevent use as shelves.
- Doors should have smooth, non-absorbent surfaces and, where appropriate, be self-closing and close-fitting.
- Overhead structures and fittings should be installed in such a manner as to avoid contamination of medicinal plant materials (both raw and processed) by condensation and drippings, and should be protected to prevent contamination in case of breakage. They should be insulated, where appropriate and be designed and finished so as to prevent the accumulation of dirt and to minimize condensation, mould development and flaking. They should be easy to clean.
- Food preparation and eating areas, changing facilities, toilets should be completely separated from and not open directly onto medicinal plant material processing areas.

Water supply

- An ample supply of potable water, under adequate pressure and at suitable temperature, used for processing medicinal plant materials, should be available with appropriate facilities for its storage, where necessary, and distribution with proper protection against contamination.
- Ice should be made from potable water; it should be manufactured, handled and stored so as to protect it against contamination.

- Unless there is a post-water filtration or treatment system, non-potable water used for steam production, refrigeration, fire control and other similar purposes not connected with processing should be carried in completely separate pipes, identifiable preferably by colour and with no cross-connection with or back siphonage into the system carrying potable water.

Effluent and waste disposal

Facilities should have an effective effluent and waste disposal system, which should at all times be maintained in good order and repair; and should be constructed so as to avoid contamination of potable water supplies.

Changing facilities and toilets

Adequate, suitable and conveniently located changing facilities and toilets should be provided. Hand-washing facilities with warm or hot and cold water, a suitable hand-cleaning preparation and hygienic means of drying should be provided adjacent to toilets and located so that employees have to pass them when returning to the processing area. Notices should be posted directing personnel to wash their hands after using the toilet.

Hand-washing facilities in processing areas

Adequate and conveniently located facilities for hand-washing and a hygienic means of drying should be provided whenever the process demands. Where appropriate, facilities for hand disinfection should also be provided.

Disinfection facilities

Where appropriate, adequate facilities for cleaning and disinfection of working implements and equipment should be provided. These facilities should be constructed of corrosion-resistant materials, should be easy to clean, and should be fitted with hot and cold water supplies.

Lighting

Adequate natural or artificial lighting should be fitted throughout the facility. Where appropriate, the lighting should not alter colours of the medicinal plants undergoing processing.

Ventilation

Adequate ventilation should be provided to prevent excessive heat, steam condensation and dust and to remove contaminated air from both the processing and storage areas/facilities.

Storage of waste and unusable materials

Facilities should be provided for the storage of waste and unusable materials prior to removal from the premises.

Appendix 4

Processing facilities for production of herbal preparations and herbal dosage forms

The following is extracted from section 12 of the WHO guidelines on good manufacturing practices (GMP) for herbal medicines (WHO, 2007a) (pages 41–44).

Premises

In principle, the premises must be located, designed, constructed, adapted and maintained for the suitable processing/production operations to be performed.

General

In general, the layout and design of the facility must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of the end-products.

- Where dust is generated (for example, during sampling, weighing, mixing and process operations, packaging of powders), measures should be taken to avoid cross-contamination and facilitate cleaning.
- The facility should be situated in an environment that, when considered together with measures to protect the processing/manufacturing process, presents minimum risk of causing any contamination of materials or products.
- The facility should be situated in an environment that, when considered together with measures to protect the processing/manufacturing process, presents minimum risk of causing any contamination of materials or products.
- The facility used for the processing of herbal preparations or manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.
- It should be carefully maintained, and be ensured that repair and maintenance operations do not present any hazard to the quality of products.
- It should be cleaned and, where applicable, disinfected according to written procedures, and records maintained.

- Electrical supply lighting, temperature, humidity and ventilation should be appropriate so that they do not adversely affect, directly or indirectly, the herbal products during their processing/manufacturing and storage, or the functioning equipment.
- It should be designed and equipped so as to afford maximum protection against the entry of insects, birds or other animals.
- It should be designed to ensure the logical flow of materials and personnel.

Ancillary areas

- Rest and refreshment rooms should be separated from processing/manufacturing and control areas.
- Facilities for changing and storage of clothes, for toilet and washing purposes should be accessible for users.
- Maintenance workshops should be separated, if possible, from production areas or tools kept in rooms or lockers.
- Animal houses should be well isolated from other areas, with separate entrance and air handling facilities.

Storage areas

- Storage areas should be of sufficient capacity to allow orderly storage of various categories of materials and products with proper separation and segregation: starting and packaging materials, intermediates, bulk and finished/processed products, products in quarantined and released, rejected, returned or recalled.
- Storage areas should be designed or adapted to ensure good storage conditions. They should be clean, dry, sufficiently lit and maintained within acceptable temperature limits. Where special conditions (for example, temperature and humidity) are required, they should be provided.
- Receiving and dispatch areas should be separated and protect materials and products from weather; and should be designed and equipped to allow containers to be cleaned if necessary.
- Where quarantine status is ensured by storage in separate areas, they must be clearly marked and access restricted to authorized personnel.
- Segregation should be provided for the storage of rejected, recalled or returned materials or products.

- Highly active and radioactive materials, narcotic and other dangerous materials presenting special risks, fire or explosion, should be stored in safe and secure areas.
- Printed packaging materials are considered critical to the conformity of the processed material/product to its labelling, and special attention should be paid to sampling and the safe and secure storage of these materials.
- There should be a separate sampling area for starting materials.

Weighing areas

- The weighing of starting materials and the estimation of yield by weighing should be carried out in separate areas designed for that use.

Production areas

- In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the processing or manufacture of particular herbal preparations/products, such as toxic and/or rare materials/products.
- Premises should be laid out as to allow the production to take place in such a way as to allow the processing/production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.
- The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different herbal preparations/products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any manufacturing or control steps.
- Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces of the facility should be smooth and free from cracks and open joints.
- Pipe work, light fittings ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean.
- Drains should be of adequate size and designed and equipped to prevent back-flow.

- Production areas should be effectively ventilated, with air control facilities appropriate to the herbal material/product handled, to the operations taken and to the environment. These areas should be regularly monitored during both processing/production and non-production/non-production periods to ensure compliance with their designed specifications.
- Premises for the packaging of processed/finished products should be specifically designed and laid out so as to avoid mix-ups or cross-contaminations.
- Production areas should be well lit, particularly where visual on-line controls are carried out.

Quality control areas

- Quality control laboratories should be separated from production areas.
- Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient spaces should be given to avoid mix-ups and cross-contaminations. There should be adequately suitable storage space for samples, reference standards (in appropriate storage facility), solvents, reagents and records.
- The design of the laboratories should take into consideration the suitability of construction materials, prevention of fumes and ventilation. There should be separate air supply to laboratories and processing/production areas.
- Instruments should be housed in a separate room to protect them against electrical interference, vibration, contact with moisture and other external factors, or where it is necessary to isolate the instruments.

Annex 2

Guidelines on good manufacturing practices for the manufacture of herbal medicines

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Introduction

In line with the publication of the revised World Health Organization (WHO) guidelines on *Good manufacturing practices for pharmaceutical products: main principles* (1), supporting and supplementary guidelines were developed to address specific issues connected with the manufacture of certain types of pharmaceutical product. As part of this series, the WHO *Supplementary guidelines for the manufacture of herbal medicinal products* (2) were issued in 1996. The guidelines were also reproduced in the second volume of the WHO compendium on *Quality assurance of pharmaceuticals* (3). Related WHO documents such as *Guidelines for the assessment of herbal medicines* (4), *General guidelines for methodologies on research and evaluation of traditional medicine* (5), *Quality control methods for medicinal plant materials* (6, 7), *Guidelines on good agricultural and collection practices for medicinal plants* (8), *WHO guidelines on assessing quality of herbal medicines with reference to contaminants and residues* (9), *WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines* (10) and *WHO guidelines on good herbal processing practices for herbal medicines* (11) were also issued.

WHO's *Good manufacturing practices: main principles for pharmaceutical products* were updated in 2003 (1, 12). Around the turn of the millennium, various product-specific good manufacturing practice (GMP) guidelines covering herbal medicines were developed by a number of WHO Member States, and by the European Union. They covered several issues relevant to the production and quality control of herbal medicines in more detail. For this reason, within the framework of the *WHO Traditional Medicine Strategy: 2000–2005*, revision of the existing supplementary guidelines was considered desirable; this was also endorsed by the WHO Expert Committee on Pharmaceutical Specifications at its meetings in 2002, 2003, 2004 and 2005. WHO's *Good manufacturing practices: main principles for pharmaceutical products* were further updated in 2013 (13).

These new guidelines are intended to complement those provided in *Good manufacturing practices for pharmaceutical products* (1, 13) and should be read in conjunction with the parent guide. The additional standards addressed by the present guidelines should therefore be considered supplementary to the general requirements (13). They relate specifically to the production and control of herbal medicines, in so far as they mainly focus on identifying the critical steps needed to ensure good quality. The emendation of the text was recommended by the Expert Committee on Specifications for Pharmaceutical Preparations at its fifty-second meeting in 2017 to ensure consistency with the current terminology used and to update the references cited.

The supplementary guidelines are intended to provide WHO Member States with general and minimum technical requirements for quality assurance

and control in the manufacture of herbal medicines. Each Member State should develop its own national GMP for manufacturing herbal medicines that are appropriate to its particular situation.

These guidelines deal exclusively with herbal medicines. They do not cover combination of herbal materials with animal materials, mineral materials, chemicals and other substances.

General considerations

Unlike conventional pharmaceutical products, which are usually produced from synthetic materials by means of reproducible manufacturing techniques and procedures, herbal medicines are prepared from materials of herbal origin, which are often obtained from varied geographical and/or commercial sources. As a result it may not always be possible to ascertain the conditions to which they may have been subjected. In addition, they may vary in composition and properties. Furthermore, the procedures and techniques used in the manufacture and quality control of herbal medicines are often substantially different from those employed for conventional pharmaceutical products.

Because of the inherent complexity of naturally grown medicinal plants and the often variable nature of cultivated ones, the instances of contamination with toxic medicinal plants and/or plant parts and the large numbers of active ingredients, few of which have been defined, the production and primary processing has a direct influence on the quality of herbal medicines. For this reason, application of GMPs in the manufacture of herbal medicines is an essential tool to assure their quality.

Glossary

Established terms such as batch, bulk, intermediate product, qualification, starting material and validation are used as defined in the *WHO Good manufacturing practices for pharmaceutical products* (1, 13).

The definitions given below apply to the terms as used in these guidelines. These terms and their definitions have been selected and adopted from other WHO documents and guidelines that are widely used by the WHO Member States (1, 2, 4–11). However, they may have different meanings in other contexts.

Note: As a consequence of the various types of “herbal medicines”, the same type of material may be classified, depending on the case, in different ways (for example, powdered plant material may be both *herbal material* and *herbal preparation* or, in a packed form, *herbal medicinal product*).

active ingredients. Constituents with known therapeutic activity, when they have been identified. When it is not possible to identify the active ingredients, the whole herbal medicine may be considered as an active ingredient.

blending. The process of combining materials or different batches to produce a homogeneous intermediate or finished product.

constituents with known therapeutic activity. Substances or groups of substances that are chemically defined and known to contribute to the therapeutic activity of a herbal material or of a preparation.

herbal medicines. These include *herbs* and/or *herbal materials* and/or *herbal preparations* and/or *finished herbal products* in a form suitable for administration to patients (10).

Note: In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (for example, animal and mineral materials, fungi, algae, lichens, etc.).

Herbs

Herbs include crude plant materials such as leaves, flowers, fruits, seeds, stem wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered (5).

*Herbal materials*¹

Herbal materials include, in addition to herbs: fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir-baking with honey, alcoholic beverages or other plant materials (5).

Herbal preparations

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration, or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials (5).

Finished herbal products

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations

¹ The participants of the third WHO consultation on quality control, held in Hong Kong SAR, China from 4 to 6 September 2017, recommended that latex and exudates can be included.

made of the same plant as well as herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”) (10).

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be “herbal”.

markers (marker substances). Reference substances that are chemically defined constituents of a herbal material. They may or may not contribute to their therapeutic activity. However, even when they contribute to the therapeutic activity, evidence that they are solely responsible for the material’s clinical efficacy may not be available (10).

medicinal plant. Plants (wild or cultivated) used for medicinal purposes.

medicinal plant materials see **herbal materials**

therapeutic activity. Successful prevention, diagnosis and treatment of physical and mental illnesses, improvement of symptoms of illnesses, as well as beneficial alteration or regulation of the physical and mental status of the body and development of a sense of general well-being.

1. Quality assurance in the manufacture of herbal medicines

In addition to the use of modern analytical techniques (especially high-performance thin-layer chromatography (HPTLC), gas chromatography, high-performance liquid chromatography (HPLC), capillary electrophoresis, mass spectrometry (MS) and atomic absorption) to characterize herbal medicines, quality assurance requires the control of starting materials as well as of storage and processing. For this reason, an appropriate quality assurance system should be applied to the manufacture of herbal medicines.

Note: The methods of choice may depend on the country’s infrastructure.

2. Good manufacturing practice for herbal medicines

2.1 The general principles of GMP are set out in the parent guidelines (13). Cultivation and collection of medicinal plants, as the starting materials for herbal medicines, as well as processing of herbal medicines are covered by other guidelines (8, 11). The first critical step of their production, where

the application of GMP starts, should be clearly designated (see subsection 16.1). This is of particular importance for those products that consist solely of comminuted or powdered herbal materials.

3. Sanitation and hygiene

- 3.1 Because of their origin, herbal materials may contain microbiological contaminants. Furthermore, during the course of harvesting and processing, herbal products that may be especially prone to microbiological contamination are produced. To avoid alterations and to reduce contamination in general, a high level of sanitation and hygiene is necessary during manufacture (for guidelines on personal hygiene see section 11, and for those on sanitation see section 12).
- 3.2 Water supply to the manufacturing unit should be monitored, and, if necessary treated appropriately to ensure consistency of quality.
- 3.3 Waste from the manufacturing unit should be disposed of regularly so as to maintain a high standard of hygiene in the manufacturing area. Clearly marked waste bins should be available, emptied and cleaned as needed, but at least daily.

4. Qualification and validation

- 4.1 Qualification of critical equipment, process validation and change control are particularly important in the production of herbal medicines with unknown therapeutically active constituents. In this case, the reproducibility of the production process is the main means for ensuring consistency of quality, efficacy and safety between batches.
- 4.2 The written procedure should specify critical process steps and factors (such as extraction time, temperature and solvent purity) and acceptance criteria, as well as the type of validation to be conducted (for example, retrospective, prospective or concurrent) and the number of process runs.
- 4.3 A formal change control system should be established to evaluate the potential effects of any changes on the quality of the herbal medicines, particularly content of the active ingredients. Scientific judgement should be used to determine which additional testing and validation studies are appropriate to justify a change in a validated process.

5. Complaints

- 5.1 The person responsible for handling complaints and deciding on the measures to be taken to deal with them should have appropriate training and/or experience in the specific features of the quality control of herbal medicines.
- 5.2 There are two types of complaint, product quality complaints and complaints about adverse reactions or events.
- 5.3 Product quality complaints may be caused by problems such as faulty manufacture, product defects or deterioration as well as, particular to herbal medicines, adulteration of the herbal material. These complaints should be recorded in detail and the causes thoroughly investigated (for example, by comparison with the reference samples kept from the same batch). There should also be written procedures to describe the action to be taken.
- 5.4 To address the second type of complaint, reports of any adverse reaction or event should be entered in a separate register in accordance with national and international requirements. An investigation should be conducted to find out whether the adverse reaction or event is caused by a quality problem and whether such a reaction or event has already been reported in the literature or whether it is a new observation. In either case, complaint records should be reviewed regularly to detect any specific or recurring problems requiring special attention and possible recall of marketed products. The *WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems* deal with specific issues relating to adverse reactions and adverse events following treatment with herbal medicines (14).
- 5.5 The licensing authority should be kept informed of any complaints leading to a recall or restriction on supply and the records should be available for inspection.

6. Product recalls

- 6.1 The product recall procedure depends very much on the national regulations. There should be a standard operating procedure for storage of recalled herbal medicines in a secure segregated area, complying with the requirements specified under subsection 12.1 (Storage areas) while their fate is decided.

7. Contract production and analysis

- 7.1 The contract partner should have adequate premises and equipment for the production of herbal medicines according to GMP. Validated methods should be applied for cleaning the equipment and premises carefully before using them to produce different herbal medicinal, food or cosmetic products. In the case of raw materials used for producing food, it is recommended to require manufacturing departments to be separated from those where the plant raw material will be cut or powdered for use in the preparation of medicines.
- 7.2 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable on the specific characteristics of herbal medicines, including their production and quality control testing.

8. Self-inspection

- 8.1 At least one member of the self-inspection team should possess a thorough knowledge of herbal medicines.

9. Personnel

- 9.1 General guidance in relation to personnel involved in the manufacture of medicinal products is given in the parent guide (13).
- 9.2 The release of herbal medicines should be authorized by a person who has been trained in the specific features of the processing and quality control of herbal materials, herbal preparations and finished herbal products.
- 9.3 Personnel dealing with the production and quality control of herbal medicines should have adequate training on the specific issues relevant to herbal medicines.

10. Training

- 10.1 The personnel should have adequate training in appropriate fields such as pharmaceutical technology, taxonomic botany, phytochemistry, pharmacognosy, hygiene, microbiology and related subjects (such as traditional use of herbal medicines).
- 10.2 Training records should be maintained and periodic assessments of the effectiveness of training programmes should be made.

11. Personal hygiene

- 11.1 Personnel entrusted with the handling of herbal materials, herbal preparations and finished herbal products should be required to have a high degree of personal hygiene and to have received adequate training in maintaining appropriate standards of hygiene. Personnel with infectious diseases or skin diseases should not work. Written procedures listing the basic hygiene requirements should be made available.
- 11.2 Personnel must be protected from contact with toxic irritants and potentially allergenic plant materials by means of adequate protective clothing. They should wear suitable gloves, caps, masks, work suits and shoes throughout the whole procedure from plant processing to product manufacture.

12. Premises

- 12.1 Premises should be designed, located, constructed, adapted and maintained to suit the operations to be carried out according to GMP (13).
- 12.2 Because of their potential for degradation and infestation with certain pests as well as their sensitivity to microbiological contamination, production, and particularly storage, of herbal materials and herbal preparations assume special importance.

Storage areas

- 12.3 Storage areas should be well organized and tidy. Special attention should be paid to cleanliness and good maintenance. Any accidental spillage should be cleaned up immediately using methods that minimize the risk of cross-contamination of other materials, and should be reported.
- 12.4 The set-up of storage areas depends on the type of materials stored. The areas should be well labelled and materials stored in a such a way as to avoid any risk of cross-contamination. An area should be identified for the quarantine of all incoming herbal materials.
- 12.5 Storage areas should be laid out to permit effective and orderly segregation of the various categories of materials stored, and to allow rotation of stock. Different herbal materials should be stored in separate areas.
- 12.6 To protect the stored material, and reduce the risk of pest attacks, the duration of storage of any herbal material in unpacked form should be kept to a minimum.

- 12.7 Incoming fresh herbal materials should be processed, unless specified otherwise, as soon as possible. If appropriate, they should be stored between 2 °C and 8 °C, whereas frozen materials should be stored below –18 °C.
- 12.8 Where materials are stored in bulk, to reduce the risk of mould formation or fermentation, it is advisable to store them in aerated rooms or containers using natural or mechanical aeration and ventilation. These areas should also be equipped in such a way as to protect against the entry of insects or animals, especially rodents. Effective measures should be taken to limit the spread of animals and microorganisms brought in with the plant material and to prevent cross-contamination.
- 12.9 Herbal materials, even when stored in fibre drums, bags or boxes, should be stored off the floor and suitably spaced to permit cleaning and inspection.
- 12.10 The storage of plants, extracts, tinctures and other preparations may require special conditions of humidity and temperature or protection from light. Appropriate steps should be taken to ensure that these conditions are provided, maintained, monitored and recorded.
- 12.11 Herbal materials, including raw herbal materials, should be kept in a dry area protected from moisture and processed following the principle of “first in, first out” (FIFO).

Production areas

- 12.12 Production areas should comply with the general requirements of GMP (13). As a rule, campaign work in their processing is necessary. However, if feasible, the use of dedicated premises is encouraged. Moreover, the special nature of the production of herbal medicines requires that particular attention be given to processing products that generate dust. When heating or boiling of the materials is necessary, a suitable air exhaust mechanism should be employed to prevent accumulation of fumes and vapours.
- 12.13 To facilitate cleaning and to avoid cross-contamination, adequate precautions should be taken during the sampling, weighing, mixing and processing of medicinal plants, for example, by use of dust extraction and air-handling systems to achieve the desired differential pressure and net airflow.

13. Equipment

- 13.1 Processing of herbal materials may generate dust or material that is susceptible to pest-infestation or microbiological contamination and cross-contamination. Effective cleaning of the equipment is therefore particularly important.
- 13.2 Vacuum or wet-cleaning methods are preferred. If wet-cleaning is done, the equipment should be dried immediately after cleaning to prevent the growth of microorganisms. Cleaning with compressed air and brushes should be avoided if possible and, if used, should be done with care, as these methods increase the risk of product contamination.
- 13.3 Non-wooden equipment should be used unless tradition demands wooden material. Where it is necessary to use traditional equipment (such as wooden implements, clay pots, pallets or hoppers), this should be dedicated, unless otherwise justified. Such equipment should not come into direct contact with chemicals or contaminated material. If the use of wooden equipment is unavoidable, special consideration must be given to its cleaning as wooden materials may retain odours, be easily discoloured and are easily contaminated.

14. Materials

- 14.1 All incoming herbal materials should be quarantined and stored under appropriate conditions that take into account the degradability of herbal materials and herbal preparations.
- 14.2 Only permitted substances should be used for fumigation, and allowable limits for their residues together with specifications for the apparatus used should be set according to the national regulations.

Reference samples and standards

- 14.3 The reference standard for a herbal medicine may be a botanical sample of the herbal material; a sample of the herbal preparation, for example, extract; or a chemically defined substance, for example, a known active constituent, a marker substance or a known impurity. The reference standard should be of a quality appropriate to its purpose. If the herbal medicine is not described in a recognized pharmacopoeia, a herbarium sample of the flowering or fruiting top of the whole medicinal plant or part of the

medicinal plant (for example, if the whole medicinal plant is a tree) should be available. All reference standards should be stored under appropriate conditions to prevent degradation. Their expiry and/or revalidation date should be determined and indicated.

15. Documentation

15.1 The general principles for documentation are set out in the parent guidelines (13).

Specifications

15.2 The specifications for herbal starting materials, for herbal preparations and finished herbal products are primarily intended to define the quality rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring safety and efficacy. Consistent quality for herbal medicines (finished herbal products) can only be assured if the starting herbal materials are defined in a rigorous and detailed manner. In some cases more detailed information may be needed on aspects of collection or agricultural production. For instance, the selection of seeds, conditions of cultivation and harvesting are important in producing herbal medicines of a reproducible quality (8). Their characterization (which also includes a detailed evaluation of the botanical and phytochemical aspects of the medicinal plant, manufacture of the herbal preparation and the finished herbal product) is therefore essential to allow the establishment of specifications that are both comprehensive and relevant.

15.3 For this reason, in addition to the data called for (13), the specifications for herbal materials should as far as possible include, as a minimum, the following information:

15.4 Herbal materials

- The family and botanical name of the plant used according to the binomial system (genus, species, variety and the authority, i.e. the reference to the originator of the classification, for example, Linnaeus). It may also be appropriate to add the vernacular name and the therapeutic use in the country or region of origin of the plant.
- Details of the source of the plant, such as country and/or region of origin (also state and province, if applicable), whether it was cultivated or collected from the wild and, where applicable, method of cultivation, dates and conditions of harvesting (for example, whether there was

extreme weather), collection procedures, collection area, and brand, quantity and date of pesticide application, as required by the *WHO Guidelines on good agricultural and collection practices* (8).

- Whether the whole plant or only a part is used. In the latter case, which part of the plant is used and its state, for example, whole or reduced. For dried plant material, the drying system should be specified, if applicable.
 - A description of the plant material based on visual (macroscopic) and/or microscopic examination.
 - Suitable identity tests including, where appropriate, identification tests (such as thin-layer chromatography (TLC) or other chromatographic fingerprint) for known active ingredients or markers. A reference sample should be available for identification purposes.
 - Details of the assay, where appropriate, of active constituents or markers.
 - Limit tests such as dry residue of liquids, ash value (total ash, and ash insoluble in hydrochloric acid), water-soluble extractives, moisture/water content and loss on drying (taking into account the presence of essential oils if any).
 - Suitable methods for the determination of possible pesticide contamination and the acceptable limits for such contamination in herbal materials or herbal preparations used in the manufacture of herbal medicines.
 - Tests for toxic metals and for likely contaminants, foreign materials and adulterants.
 - Tests for fungal and/or microbiological contamination, fumigant residues (if applicable), mycotoxins, pest infestations, radioactivity and their acceptable limits.
 - Other appropriate tests (for example, particle size, swelling index and residual solvents in herbal preparations and biological fingerprints such as induced fluorescent markers).
- 15.5 Specifications for starting materials (and also of primary or printed packaging materials) should include, if applicable, reference to a pharmacopoeial monograph.
- 15.6 If the herbal material for processing does not comply with its quality specifications, the rules that apply for its rejection, and to storage and disposal of the rejected herbal material, should be included.

- 15.7 Starting materials derived from or comprising genetically modified organisms should comply with existing national or international regulations and the label should include this information. Chemical protection of herbal materials should be in accordance with national and/or international regulations (8).
- 15.8 Qualitative and quantitative information on the active ingredients or constituents with known therapeutic activity in herbal materials and herbal preparations should be given as described in subsection 17.5 (Labelling).

15.9 Finished herbal products

- Tests for microbiological contamination and tests for other toxicants.
 - Uniformity of weight (for example, for tablets, single-dose powders, suppositories, capsules and herbal tea in sachets), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, for uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (for tablets or capsules), if applicable.
 - Physical appearance such as colour, odour, form, shape, size and texture.
 - Loss on drying, or water content.
 - Identity tests, qualitative determination of relevant constituents of the plants (for example, fingerprint chromatograms).
 - Quantification of relevant active ingredients, if they have been identified, and the analytical methods that are available.
 - Limit tests for residual solvents.
- 15.10 The control tests and specifications for the finished herbal product should be such as to allow the qualitative and quantitative determination of the main active constituents. If the therapeutic activity of constituents is known, these constituents should be indicated in the documentation. If the therapeutic activity of the individual substances is not known (for example, because they are part of a complex mixture), the constituents useful for assessing the quality should be identified as markers. In both cases, the assay (i.e. quantitative determination) specifications should be defined. When the therapeutic activity of the constituents cannot be determined quantitatively, specifications should be based on the determination of markers.
- 15.11 If either the final product or the herbal preparation contains several herbal materials and a quantitative determination of each active ingredient is

not feasible, the mixture of several active ingredients may be determined. The need for such a procedure should be justified.

- 15.12 The concept of different acceptance criteria for release versus shelf-life specifications applies only to finished herbal medicines and not to herbal materials and herbal preparations. Adequate retest periods should be established for the latter. Examples where this may be applicable include assay and impurity (degradation product) levels.

15.13 Herbal preparations

The specifications of herbal preparations consist, depending on the preparation in question, of the relevant items of the specifications for herbal materials or for finished herbal products as outlined above

Processing instructions

- 15.14 The processing instructions should describe the operations to be performed on the plant material, such as drying, crushing, milling and sifting. They should also include the duration and, if applicable, temperatures required for the drying process, and the methods to be used to control fragment or particle size. Instructions on removing foreign matter and other unwanted materials should also be given.
- 15.15 The drying conditions chosen should be appropriate to the type of plant material processed. These depend on both the character of the active ingredients (for example, essential oils) and the type of plant part collected (for example, root, leaf or flower). Drying by direct exposure to sunlight, if not specifically contraindicated is possible, but drying on the ground should be avoided. If the plant should be processed fresh, without drying, the reasons and criteria determining the use of fresh material should be stated.
- 15.16 The instructions for the production of processed extracts should specify details of any vehicle or solvent that may be used, the durations and temperatures needed for extraction, and any concentration stages and methods that may be required.
- 15.17 The permissible environmental conditions, for example, temperature, humidity and standard of cleanliness, should be stated.
- 15.18 Any treatment, such as fumigation, used to reduce fungal or microbiological contamination or other infestation, together with methods of determining the extent of such contamination and potential residues, should be

documented. Instructions for carrying out these procedures should be available and should include details of the process, tests and allowable limits for residues together with specifications for apparatus used.

- 15.19 Steps in the processes of blending and adjustment to reach defined contents of pharmacologically active constituents should be clearly documented.
- 15.20 Rules on the disposal of spent herbal material after processing should also be drawn up.

16. Good practices in production

- 16.1 To ensure not only the quality, but also the safety and efficacy of complex products of biological origin such as herbal medicines, it is essential that the steps in their production are clearly defined.

Selection of the first production step covered by these guidelines

- 16.2 For medicinal plants – which are either cultivated or collected from the wild, and which may be used in crude form or subjected to simple processing techniques (such as cutting or comminuting) – the first critical step of their production, i.e. where the application of these guidelines starts, should be clearly designated. The rationale for this designation should be stated and documented. Guidance is provided below. However, for processes such as extraction, fermentation and purification, this rationale should be established on a case-by-case basis.

- Collection/cultivation and/or harvesting of medicinal plants should follow other relevant guidance such as the *WHO Guidelines on good agriculture and collection practices (GACP) for medicinal plants (8)* or national guidelines.
- Generally, post-harvest processing including primary cutting is (or should be) covered by GACP. If further comminuting is carried out during the manufacturing process, it should be covered by GMP, or by these supplementary guidelines. If cutting and comminuting considerably reduce the probability of detection of adulteration or mix-up of herbal materials, application of these supplementary guidelines may be extended to encompass these steps.
- When the active ingredient, as defined in the Glossary, consists exclusively of comminuted or powdered herbs, application of these

guidelines starts at the physical processing following primary cutting and comminuting, and includes packaging.

- When herbal extracts are used, the principles of these guidelines should apply to any production step following post-harvest processing.
- In the case of finished herbal products manufactured by fermentation, application of GMP should cover any production step following primary cutting and comminuting. Particular attention should be given to the introduction of cells from a cell bank into the fermentation process.

General considerations

- 16.3 Materials should be handled in a way that is not detrimental to the product. On arrival at the processing facility, the herbal material should be promptly unloaded and unpacked. During this operation, the herbal material should not come into direct contact with the soil. Moreover, it should not be exposed directly to the sun (except where this is a specific requirement, for example, for sun-drying) and it should be protected from rain and microbiological contamination.
- 16.4 Attention should be paid to “classification” of clean area requirements taking into account the possible high degree of initial microbial contamination of herbal materials. Classification of premises as applied to sites for the production of other pharmaceutical substances may not be applicable to sites for the processing of herbal materials. Specific and detailed requirements should be developed to cover microbial contamination of equipment, air, surfaces and personnel, and also for rest rooms, utilities, ancillary and supporting systems (for example, water and compressed air).
- 16.5 Care should be taken to choose cleaning methods appropriate to the characteristics of the herbal materials being processed. Washing dried herbal materials with water is generally inappropriate. When it is necessary to clean them, an air duster or air shower should be used. Where immersion of herbal materials in water or other appropriate agents (such as disinfectants) for cleaning is unavoidable (for example, to eliminate suspected coliform bacteria), it should be kept to a minimum.
- 16.6 The presence of plant materials from different species and varieties, or different plant parts should be controlled throughout the entire production process to avoid contamination, unless it is assured that these materials are equivalent.

- 16.7 If time limits are specified in the master production instructions, these limits should not be exceeded, to ensure the quality of intermediates and finished products. The less is known about the constituents responsible for the therapeutic activity, the more strictly this rule should be obeyed. Such time limits, however, may be inappropriate when processing to achieve a target value (for example, drying to a predetermined specification) because completion of processing steps is determined by in-process sampling and testing.

Mixing of batches and blending

- 16.8 Herbal medicines with constituents of known therapeutic activity are often standardized (i.e. adjusted to a defined content of such constituents). The methods used to achieve such standardization should be documented. If another substance is added for these purposes, it is necessary to specify, as a range, the quantity that may be added. Blending different batches of a specific herbal material (for example, before extraction) or mixing different lots of similar herbal preparations may also be acceptable. Records should be maintained to ensure traceability. The blending process should be adequately controlled and documented and the blended batch should be tested for conformity with established specifications where appropriate.
- 16.9 Batches should be mixed only if homogeneity of the mixture can be guaranteed. Such processes should be well documented.
- 16.10 Out-of-specification batches of herbal medicines should not be blended with other batches for the purpose of meeting specifications, except for standardization of the content of constituents with known pharmaceutical therapeutic effect. Every batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.
- 16.11 Where particular physical attributes of the material are critical, blending operations should be validated to show uniformity of the combined batch. Validation should include testing of critical attributes (for example, particle size distribution, bulk density and tapped density) that may be affected by the blending process.
- 16.12 The expiry date of the blended batch should be chosen according to the date of manufacture of the oldest batch in the blend.

17. Good practices in quality control

17.1 General

- 17.1.1 The personnel of quality control units should have the necessary expertise in herbal medicines to enable them to carry out identification tests and recognize adulteration, the presence of fungal growth or infestations and lack of uniformity in a consignment of herbal materials.
- 17.1.2 The quality control of the herbal material, herbal preparations and finished herbal products should establish their quality but this does not imply the control of every single constituent.

17.2 Sampling

- 17.2.1 Because herbal materials are an aggregate of individual plants and/or different parts of the same plant and thus have an element of heterogeneity, sampling should be carried out with special care by personnel with the necessary expertise.
- 17.2.2 Further advice on sampling and visual inspection is given in the WHO document *Quality control methods for herbal materials* (7).

17.3 Testing

- 17.3.1 The identity and quality of herbal material, herbal preparations and of finished herbal products should be tested as described in the *Quality control methods for herbal materials* (7). The minimum requirement for the technical equipment is for instruments to perform the tests described (7). Moreover, each country should develop this basic requirement for technical equipment further, according to the country's needs.
- 17.3.2 Herbal material, herbal preparations (including extracts) and finished herbal products can be categorized as follows:
- the active constituents are identified, and may be quantified as such;
 - the main group of components that contribute to the activity (i.e. the constituents with known therapeutic activity) are known and can be quantified as a total (for example, essential oils) or calculated using a representative substance belonging to the group (for example, flavonoids);
 - the former are not identified and/or are not quantifiable, but marker substances are;

- d. others, where quantification (i.e. specification for a certain quantity of a constituent) is not applicable or feasible.

17.3.3 Identification methods may be based on:

- physical and, if applicable, macroscopic (organoleptic) and microscopic tests;
- chromatographic procedures (TLC, HPLC, HPTLC or gas–liquid chromatography (GLC)), spectrometric techniques (ultraviolet-visible (UV-VIS), IR, nuclear magnetic resonance (NMR), MS); and/or;
- chemical reactions.

17.3.4 The identification test methods should be specific for the herbal material, herbal preparation or finished herbal product and ideally should be capable of discriminating between the required herbal material and likely potential substitutes or adulterants. The identification methods used for groups a and b should be capable of detecting the said active ingredients and at least the main ingredients should be stated on the label. For group c, the analytical procedure should be based on characteristic constituents, if any.

17.3.5 Reference samples of herbal materials should be made available for use in comparative tests, for example, visual and microscopic examination and chromatography.

17.3.6 Quantitative determination of known active components for members of groups a and b and of markers for members of group c is necessary.

17.3.7 The development and execution of quality control methods for herbal materials, herbal preparations and the finished herbal products should be in line with subsection 15.1 (Specifications). Tests and quality requirements that are characteristic of the given analyte should be selected.

17.3.8 Particularly for herbal materials in group d and for finished herbal products containing such materials, characteristic chromatograms (and/or fingerprint chromatograms) may be applicable. Use of these methods may ensure that the main constituents can be easily tracked throughout the production process. Caution is necessary, however, for every delivery of herbal materials and every batch of herbal preparations (including extracts) will have slightly different chromatograms/fingerprints resulting from differences in chemical compositions caused by intrinsic or extrinsic factors.

17.4 Stability studies

- 17.4.1 If the expiry date for a herbal material or herbal preparation is given, some stability data to support the proposed shelf life under the specified storage conditions should be available. Stability data are always required to support the shelf life proposed for the finished herbal products.
- 17.4.2 Finished herbal products may contain several herbal materials or herbal preparations, and it is often not feasible to determine the stability of each active ingredient. Moreover, because the herbal material, in its entirety, is regarded as the active ingredient, a mere determination of the stability of the constituents with known therapeutic activity will not usually be sufficient. Chromatography allows tracing of changes that may occur during storage of a complex mixture of biologically active substances contained in herbal materials. It should be shown, as far as possible, for example, by comparisons of appropriate characteristic/fingerprint chromatograms, that the identified active ingredient (if any) and other substances present in the herbal material or finished herbal product are likewise stable and that their content as a proportion of the whole remains within the defined limits.
- 17.4.3 The fingerprint methods used for the stability studies should be as similar as possible to those used for quality control purposes.
- 17.4.4 For identified active ingredients, constituents with known therapeutic activity and markers, widely used general methods of assay, and physical and sensory or other appropriate tests may be applied.
- 17.4.5 To determine the shelf life of finished herbal products, strong emphasis should also be placed on other tests mentioned in subsection 15.1 (Specifications), such as moisture content, microbial contamination and general dosage form control tests.
- 17.4.6 The stability of preservatives and stabilizers should be monitored. When these are not used, alternative tests should be done to ensure that the product is self-preserving throughout its shelf life.
- 17.4.7 Samples used for stability studies should be stored in the containers intended for marketing.
- 17.4.8 Normally the first three commercial production batches should be included in the stability-monitoring programme to confirm the expiry date. However, where data from previous studies, including pilot batches, show that the product is expected to remain stable for at least two years,

fewer than three batches can be used. The testing frequency depends on the characteristics of the herbal medicinal products and should be determined on a case-by-case basis.

- 17.4.9 The protocol for ongoing stability studies should be documented. This would normally involve one batch per year being included in a stability-monitoring programme.

17.5 Packaging materials and labelling

- 17.5.1 All packaging materials, such as bottles, should be stored properly. Controls on the issue and use of these packaging materials should be adequate to ensure that incorrect labels and cartons are not used.

- 17.5.2 All containers and closures should be thoroughly cleaned and dried before being used to pack the products.

- 17.5.3 There should be adequate information on the label (or the package insert) to inform the users of the composition of the product (in addition to the brand name, if any), indications or actions, directions for use, cautions and adverse reactions, if any, and the expiry date.

- 17.5.4 Finished herbal products may contain several herbal materials and/or herbal preparations. Unless otherwise fully justified, the full quantitative composition of the herbal ingredients should be stated on the product label. If this is not possible, at least the main ingredients should be stated on the label while the full qualitative composition could appear on the package insert.

- 17.5.5 The qualitative and quantitative characteristics of the active ingredients in herbal materials and herbal preparations should be expressed in the following ways:

- for herbal materials and herbal preparations consisting of comminuted or powdered herbal materials:
 - a. the quantity of the herbal material must be stated or, if constituents with known therapeutic activity have not been identified, the quantity of the herbal material or herbal preparation should be stated; or
 - b. the quantity of the herbal material or herbal preparation should be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see examples).

Examples:

(a)

Name of the active ingredient or active plant material(s)	Quantity of constituent
<i>Valerianae radix</i>	900 mg

(b)

Name of the active ingredient or active herbal material(s)	Quantity of constituent
<i>Sennae folium</i>	415–500 mg, corresponding to 12.5 mg of hydroxyanthracene glycosides, calculated as sennoside B

- For herbal preparations produced by steps, which go beyond comminution, the nature and concentration of the solvent and the physical state of the extract should be given. Furthermore, the following should be indicated:
 - a. the equivalent quantity or the ratio of a herbal material to herbal preparation must be stated if therapeutic activity of the constituents is unknown (this does not apply to fatty or essential oils); or
 - b. if the therapeutic activity of the constituents is known, the quantity of the herbal preparation may be given as a range, corresponding to a defined quantity of the constituents with known therapeutic activity (see examples).

Examples:

(a)

Name of the active substance or active herbal material(s)	Quantity of constituent
<i>Valerianae radix</i>	25 mg dry ethanolic (96% v/v) extract (8:1) or 125 mg ethanolic (96% v/v) extract, equivalent to 1000 mg of <i>Valerianae radix</i>
other ingredient	
dextrin	20–50 mg

(b)

Name of the active substance or active herbal material(s)	Quantity of constituent
<i>Sennae folium</i>	100–130 mg dry ethanolic (96% v/v) extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B
other ingredient	
dextrin	20–50 mg

17.5.6 The composition of any solvent or solvent mixture used and the physical state of the extract should be identified.

17.5.7 If any other substance is added during the manufacture of the herbal preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) should be described as such or as “other ingredients” and the genuine extract as the “active ingredient”. However, where different batches of the same extract are used to adjust constituents with known therapeutic activity to a defined content or for any other purpose, the final mixture should be regarded as the genuine extract and listed as the “active ingredient” in the unit formula.

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Annex 3

Considerations for requesting analysis of medicines samples

An earlier version of this guidance was published as *Considerations for requesting analysis of drug samples* in 2002.¹

Medicines quality control testing independent of manufacturers is an important tool of medicines regulation. However, it demands considerable resources and the need for analysis should therefore always be thoroughly considered. Independent quality control testing should be performed if it adds value to the evaluation performed, when viewed from a public health perspective, and it should not cause unnecessary delays in access to medicines.

Testing should focus on medicines most likely to pose a risk to patients, for example, medicines:

- produced by manufacturers for which poor evidence of compliance with the principles of good manufacturing practices (GMP) (1) is available, or where the origin is uncertain;
- suspected of being falsified;
- suspected of being substandard because of incorrect distribution or storage conditions, or their instability;
- suspected of causing adverse reactions due to a quality defect;
- for which analytical testing results are needed as evidence in litigation (requires the implementation of a rigorous chain of custody – see World Health Organization (WHO) guidelines) (2).

The risk of poor quality should be assessed before deciding to request analysis of a particular product. For example, if the manufacturing site has been found to comply with GMP principles, the manufacturer is under regular supervision of an authority applying international standards, and there is no specific reason for testing of the product (such as a quality complaint or a suspicion of quality deterioration during distribution or storage), the manufacturer's batch certificate may be relied upon to indicate the quality of the product. Such a certificate should be issued in accordance with the criteria applicable to the WHO Model Certificate of good manufacturing practices (3) or WHO Certification Scheme (4).

¹ This guidance was previously published as Annex 4 in the WHO Technical Report Series, No. 902, 2002.



Independent post-production testing may be performed by regulators for different reasons and in various regulatory phases of the medicine's life. The following should be borne in mind when considering testing approaches:

- pre-registration testing of samples submitted for registration
 - As the sample is selected by the manufacturer, it may not provide a true picture of product quality. Testing at this stage may be useful to assess functionality of analytical methods in local conditions in certain rare cases when data reviewers have some doubts.
- Official batch release of some biological products by the national medicines regulatory authority (NMRA)
 - This is usually requested to fulfil national regulations for specified products and described in guidelines.
- Pre-marketing testing of all or of selected batches
 - Often samples of imported medicines are collected at points of entry into a country. It would be reasonable to subject them to screening and select for testing only those that show physical signs of instability or deterioration (5), other indications of inferior quality, or those whose origin is suspicious. Routine testing of each imported batch is not considered reasonable as the quality of medicines should in principle be assured through the registration process. Batch-to-batch testing may be worthwhile in specific situations, for example, when proper registration assessment and verification of compliance with good practices in production and/or product development is not feasible. Again the risk of poor quality should be assessed before deciding on the testing of a particular product.
- Post-marketing testing as risk-based sampling and surveillance/monitoring projects
 - The advantage of this approach is the selection of samples that are in the distribution chain and are intended for administration to patients. Detailed advice is provided in WHO *Guidelines on the conduct of surveys of the quality of medicines* (6).

1. Selection of tests and specifications

Tests to be performed and applicable specifications depend on the reasons for testing a particular sample. Full-scale testing is expensive and it may be reasonable to limit the tests chosen to those that can provide the answers sought. However, tests should always be considered in terms of logical combinations: for example, a

dissolution test or a test for impurities without assay/potency, would not provide sufficient information.

Selection of specifications (methods and limits) for testing again depends on the reasons for testing a particular sample. If the compliance of a product with registered specifications is to be verified, specifications approved by the NMRA as part of the registration process should be used.

If products containing the same active pharmaceutical ingredients in the same dosage form produced by different manufacturers are to be compared, pharmacopoeial specifications should be used. However, noncompliance with pharmacopoeial specifications may not necessarily imply noncompliance of the test product with the registered specifications. Also, in spite of efforts to harmonize pharmacopoeias, there are still many differences between them. When a monograph for a particular medicine is available in more than one pharmacopoeia the ability of the respective specifications to reveal quality problems should be considered and the monograph selected accordingly. In particular, when impurities are evaluated, the suitability of the pharmacopoeial monograph tests for the detection of impurities should be evaluated, especially if the product is from a new source, which may cause it to have a different impurity profile.

If samples suspected of being falsified are to be tested, manufacturers' or pharmacopoeial methods may not be sufficient and further examination should be conducted (for guidance on such investigation see WHO guidelines (2)).

If necessary, advice on selection of tests and specifications should be sought from an experienced laboratory.

2. Selection of laboratory and communication before samples are submitted

Once it has been decided to test a medicine, a laboratory, which produces reliable testing results and is capable of and competent to perform the tests required, should be selected. This can be a local national laboratory or a contracted laboratory in the same or in another country.

In general, to demonstrate that testing results are reliable, a laboratory should work in compliance with internationally recognized standards such as *WHO good practices for pharmaceutical quality control laboratories* (7) or ISO 17025 (8). Compliance with the relevant standard should be verified, for example, the laboratory should be WHO-prequalified,² or ISO 17025 accredited by an internationally recognized accreditation body. Assurance that the laboratory

² The list of WHO-prequalified laboratories can be found at www.who.int/prequal.

works in a reliable manner can also be obtained by organizing an audit by competent auditors or using the audit report from an independent third party, if available.

Before submitting samples to a laboratory, an understanding of its capability to carry out the requested tests and an agreement on performance of the analysis should be reached. The following information, as a minimum, should be provided to the laboratory:

- the reason(s) for the request and the purpose of the analysis;
- the composition of the product(s) (using International Nonproprietary Names (INNs), where possible), concentration or strength and pharmaceutical dosage form;
- a reference to specifications, including (if needed) analytical methods that should be used;
- the expiry date(s) of the sample(s), required storage conditions and duration of the storage of retention samples;
- the number of samples of each product to be tested;
- the date by which testing results are expected;
- the proposed mode of payment for the analysis;
- the preferred language and format of the report containing the results, and the method to be used to transmit the results.

The laboratory that has been contacted should indicate, as quickly as possible, whether or not it is able and willing to undertake the analysis. Any laboratory has the right to decline a request for analysis without furnishing any explanation.

If the laboratory agrees to undertake the analysis, the following should be communicated to the requesting party and mutually agreed:

- the size of the sample (minimum number of dosage units) required for each product (if possible, the number should be sufficient for conducting the tests; investigation and confirmatory testing for those found to be out of specification; and retention of samples to be used in case of dispute);
- any additional tests that may be required or recommended;
- the cost and the mode of payment;
- a tentative estimate of how long the analysis will take.

It is recommended that an appropriate arrangement between the requesting party and the laboratory that will perform the tests should be formalized. The arrangement should, in addition to the points above, settle issues such as liability, confidentiality, acceptance of a possible audit of the laboratory, deadlines, retention period for samples and records, and access to records and retained

samples. The arrangement should also specify when the testing results need to be communicated rapidly (such as when defects that can endanger patients' health are identified). The responsibilities of the two parties should be defined.

An example of an analysis request form is shown in Appendix 1.

3. Submission of samples

Upon reaching agreement with a laboratory, the sample(s) should be dispatched by the requesting party. If samples are not delivered to the laboratory directly by the requesting party, they should be transported using a courier service to avoid any delays and deterioration of the quality. Unless there are special circumstances, the sample(s) must be kept in the original packaging and suitably packaged and labelled to avoid breakage and contamination during transport (9). Freezing should be avoided during air transport and, where required, the cold chain should be maintained. When transporting temperature-sensitive medicines, temperature data loggers may be included within shipments to document that appropriate temperatures have been maintained during prolonged transit.

When sending samples to another country, delays in customs clearance should be prevented. The accompanying documents should state that the samples are being sent for laboratory testing purposes only, will not be used on humans or animals, have no commercial value and will not be placed on the market. In the case of products that are subject to legal controls on exportation, appropriate arrangements must be made by the requesting party to ensure due compliance with customs requirements. The laboratory may be able to advise on further precautions. If the country where the laboratory is located requires permission for importation of samples, the laboratory may assist in applying for permission, to avoid long clearance procedures. The laboratory should be informed of the dispatch of the shipment, including the tracking number as provided by the courier service, to enable it to follow the shipment and arrange for prompt collection.

If the product to be tested contains a controlled substance (a substance regulated under the international drug control conventions³) the requirements of the relevant national legislation (for example, secure storage, documentation, etc.), are to be implemented.

As soon as the sample has been received by the laboratory, the requesting party should be notified of the delivery and condition of the sample. This information can assist any investigations at a later stage.

³ http://www.incb.org/incb/en/narcotic-drugs/1961_Convention.html;
http://www.incb.org/incb/en/psychotropic-substances/1971_convention.html;
http://www.incb.org/incb/en/precursors/precursors/legislation_and_control/legislation_and_control.html.

4. Analytical results

All analyses undertaken by a laboratory should be performed in accordance with the specifications mentioned in the request for analysis, or as subsequently agreed, and conducted in compliance with *WHO good practices for pharmaceutical quality control laboratories* (7). All individual results (all test data), with acceptance criteria should be reported (7). The results should be compiled in the agreed language in the form of an analytical test report or certificates of analysis in line with WHO guidelines (7, 10) and transmitted by the agreed method.

References

1. WHO good manufacturing practices for pharmaceutical products. Geneva, World Health Organization, http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/ accessed 30 October 2017).
2. WHO guidance on testing of “suspect” falsified medicines In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 5 (WHO Technical Report Series, No. 1010).
3. WHO Model Certificate of good manufacturing practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 5 (WHO Technical Report Series, No. 908).
4. Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fourth report. Geneva: World Health Organization; 1996: Annex 10 (WHO Technical Report Series, No. 863).
5. The International Pharmacopoeia, sixth edition. Quality specifications for pharmaceutical substances and dosage forms together with supporting general methods for analysis. Geneva: World Health Organization; 2016 (<http://who.who.int/phint/>).
6. Guidelines on the conduct of surveys of the quality of medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 7 (WHO Technical Report Series, No. 996).
7. Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).
8. General requirements for the competence of testing and calibration laboratories. Geneva: International Organization for Standardization; 2005 (ISO/IEC 17025).
9. WHO guidelines for sampling of pharmaceutical products and related materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 4 (WHO Technical Report Series, No. 929).
10. Model certificate of analysis. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 4 (WHO Technical Report Series, No. 1010).

Appendix 1

Example of an analysis request form

Requesting party	
Name, address	
Contact person: name, phone no., email	
Product to be tested ^a	
Name, dosage form	
INN(s), strength	
Package size, type and material of the container	
Name and address of the manufacturer	
Number of samples to be tested	
Batch number/s	
Date/s of manufacture	
Date/s of expiry	
Required storage conditions	
Sample/s source	
Sample size: number of dosage units/packages per sample ^b	
Testing	
Reason/s for the request and purpose of the analysis	
Reference to specifications (pharmacopoeial monograph or methods and specifications attached to the request)	

Table *continued*

Tests requested – tick ✓ requested tests			
Identity		Specific optical rotation	
Assay		Melting range/point	
Related substances/impurities		Conductivity	
Dissolution		Refractive index	
Disintegration		Microbial enumeration tests	
Friability		Tests for specified microorganisms	
Fineness of dispersion		Sterility	
Uniformity of dosage units		Bacterial endotoxins	
Water content		Other tests (please specify):	
pH value			
Relative density			
Viscosity			
Date by which testing results are expected			
Period for which retention samples should be kept			
Preferred language and format for reporting results			
Method to be used for transmission of the results			

^a Section to be repeated for each product tested.

^b To be agreed with the laboratory.

Signature of the person representing the requesting party
Name, function

Date

Annex 4

Model certificate of analysis

It has been recommended in various forums that the World Health Organization (WHO) should establish a model certificate of analysis (CoA) for use by quality control laboratories (QCLs) and in trade in starting materials and finished pharmaceutical products (FPPs). The model for such a certificate was first published in 2002 (1) and the current model is shown in Appendix 1. The items included are based on *WHO good practices for pharmaceutical quality control laboratories* (2) and *WHO good manufacturing practices for pharmaceutical products* (3). In addition, requirements of the International Standard ISO/IEC 17025 (4) and recommendations of the International Pharmaceutical Excipients Council (5) have been taken into account. Any specific legal requirements existing in the country of issue or importation should also be considered when issuing the certificate. This guidance is essentially designed for QCLs not related to manufacturers since the QCLs of manufacturers may have some of the information listed below in other quality system documents and therefore not necessarily included in the CoA.

The format and organization of the information on the CoA is at the issuing laboratory's discretion. The CoA can be printed on letterhead with the logo of the issuing laboratory.

According to *WHO good practices for pharmaceutical quality control laboratories* (2) the CoA lists tests performed on a particular sample with the results obtained and the acceptance criteria applied, followed by an indication of whether or not the sample complies with the specification. A CoA is usually prepared for each batch of a substance or product and should include the following information:

- the name and address of the laboratory issuing the CoA;
- the identification number of the CoA and on each page an identification, the page number and the total number of pages to ensure that every page is recognized as a part of the certificate;
- the name, address and contact person representing the originator of the request for analysis;
- the number assigned to the sample by the laboratory during registration upon receipt;
- the date on which the sample was received in the laboratory and the quantity of sample (number of units or packages);

- the name, description (for example, active ingredient, dosage form, strength, package size in the case of FPPs; grade in the case of starting materials; type and material of the primary packaging), batch number (used by the original manufacturer and repacker or trader) of the sample for which the certificate is issued, the expiry date (or retest date, where applicable) and date of manufacture (if available);
- the name and address of the original manufacturer; in addition, if supplied by repackers or traders, the certificate should show the name and address of the repacker or trader;
- specifications for testing and a reference to the test procedure(s) used, including the acceptance criteria (limits);
- the results of all tests performed on the sample for which the certificate is issued (in numerical form, where applicable) and a comparison with the established acceptance criteria (limits); results of tests performed by subcontractors should be identified as such;
- any comments, observations or information on specific test conditions, where these are necessary for the interpretation of the results;
- a conclusion as to whether or not the sample was found to be within the limits of the specification;
- the date and signature of the head of the laboratory or other authorized person approving the certificate.

If the sampling plan and procedures used by the laboratory or other bodies are relevant to the validity or interpretation of the results, they should be referenced in the CoA.

Where relevant to the validity or application of the results, or if required by a customer, a statement on the estimated uncertainty of measurement should be included. However, it should be borne in mind that pharmacopoeial content limits are set taking into account the uncertainty of measurement and the production capability, and acceptance criteria for an analytical result should be predefined. Under currently applicable rules, neither the pharmacopoeias nor the medicines regulatory authorities require the value found to be expressed with its associated expanded uncertainty for compliance testing.

In the case of testing under contract, a customer may also request other information to be specified in the CoA.

If appropriate, the CoA may include a photograph(s) of the packaging and/or product tested.

If new certificates are issued by or on behalf of repackers or traders, these certificates should show the name and address of the laboratory that performed

the tests and the name and address of the original manufacturer. A copy of the CoA generated by the original manufacturer should be attached.

When the certificate is used in trade it may also include a statement of the expected conditions for shipping, packaging, storage and distribution, deviation from which would invalidate the certificate.

QCLs with accreditation to the International Standard ISO/IEC 17025 should include in the CoA a reference to the accreditation, if related to the specific analysis.

References

1. Model certificate of analysis. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-sixth report. Geneva: World Health Organization; 2002: Annex 10 (WHO Technical Report Series, No. 902).
2. Good practices for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).
3. WHO good manufacturing practices for pharmaceutical products. Geneva: World Health Organization (http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/, accessed 29 December 2017).
4. General requirements for the competence of testing and calibration laboratories. Geneva: International Organization for Standardization; 2005 (ISO/IEC 17025:2005).
5. Certificate of analysis guide for pharmaceutical excipients. Brussels: International Pharmaceutical Excipients Council; 2013 (<http://ipeceurope.org/UPLOADS/CoA-guide-2013.pdf>, accessed 29 December 2017).

Appendix 1

Model certificate of analysis for starting materials and finished pharmaceutical products

This model is intended to serve as an example and not to be prescriptive.

Header:

Logo of the laboratory or company issuing the certificate (if applicable)

Identification no. of the CoA

page X of Y

Name and address of the laboratory

issuing the CoA: _____

Identification no. of the CoA: _____

Name, address and contact person representing the originator

of the request for analysis: _____

Registration no. of the sample: _____

Date received: _____ Quantity received: _____

Name of the product (International Nonproprietary

Name (INN), brand name, etc.): _____

Dosage form, strength, package size (if applicable): _____

Type and material of the primary packaging: _____

Batch number: _____

Date of manufacture (if available): _____

Expiry date/retest date: _____

Name and address of the original manufacturer: _____

Phone: _____ Email: _____

Name and address of the repacker and/or trader (if applicable): _____

Phone: _____ Email: _____

Specifications for testing: _____

Test	Method reference ¹	Acceptance criteria	Result ^{2,3}	Compliance statement

Additional information, if requested by the customer:

Comments:

Conclusion on compliance of the sample with the specifications:

Name of the head of laboratory or person authorized to approve the certificate:

Phone: _____ Email: _____

Signature:

Date:

¹ Reference to a pharmacopoeia or technique.

² Results in numerical form, whenever applicable.

³ Results of tests performed by subcontractors should be identified as such.

Annex 5

WHO guidance on testing of “suspect” falsified medicines

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1. Introduction

1.1 “Suspect” medicines

“Suspect” medicines can be divided into three main categories of products as follows:¹

(a) substandard medicines

Also called “out of specification”, these are authorized medicines that fail to meet either their quality standards or their specifications, or both.²

(b) unregistered/unlicensed medicines

Medicines that have not undergone evaluation and/or approval by the national regulatory authority (NRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.

These medicines may or may not have obtained the relevant authorization from the NRA of their geographical origin.

(c) falsified medicines

Medicines that deliberately/fraudulently misrepresent their identity, composition or source.

Any consideration related to intellectual property rights does not fall within this definition.

Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized medicine or the manufacture of a medicine that is not an authorized product.

This document deals specifically with products that are suspected to belong to the third category, i.e. “falsified” medical products.

1.2 Responsibility of regulatory authorities

NRAs should establish rules and instruments that control the production, distribution and commercialization of medical products in order to ensure their quality through rigorous regulatory oversight, including postmarketing surveillance, in line with national legislation and regulations on pharmaceutical products. Rigorous regulatory oversight of medical products throughout their

¹ Based on World Health Assembly (WHA) A70/23 and WHA70(21) for “medical products”.

² When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to misrepresentation of identity, composition or source, then the product should be considered “falsified”.

life cycle is necessary to recognize and remove unauthorized and/or falsified products and to protect the supply chain against infiltration of such products.

Falsified medical products can originate from inside or outside the legal supply chain. It is important that NRAs secure the supply chain and raise awareness among health workers and patients of risks associated with medicines from illegal sources.

A legal definition of falsified medicines and specific legal provisions to penalize acts related to falsification of medicines will empower NRAs to take actions against this problem. In implementing and enforcing legal provisions on falsified medicines, NRAs should collaborate with customs, police, legislature, industry experts, judiciary, prosecutors and enforcement agencies at the national and international level as appropriate.

1.3 The role of the World Health Organization

The World Health Organization (WHO), through its Expert Committee on Specifications for Pharmaceutical Preparations, sets technical standards on quality assurance of pharmaceutical products, including guidance on registration, good manufacturing practices (GMP), good distribution practices (GDP) and quality control (QC) testing of medicines, and on other topics that are relevant to the regulatory oversight of medicines.

A survey conducted among regulatory authorities of WHO Member States (1) indicated the need for specific technical guidance on laboratory testing of suspect falsified products. The present document was developed in response to the survey findings and complements the Committee's guidelines on sampling and market surveillance (2).

The Member State Mechanism on substandard and falsified medical products, created in 2012, makes recommendations to support regulatory authorities to prevent, detect and respond to activities and behaviours that result in falsified medical products (3). This document is intended to complement the Member State Mechanism's recommendations in accordance with the sixty-seventh World Health Assembly resolution WHA67.20 on Regulatory system strengthening for medical products (4).

2. Scope

This document provides technical guidance on laboratory testing of samples of suspect deliberately falsified medical products detected on the markets of WHO Member States and related aspects of sampling and reporting. This guidance should be read in conjunction with the guidelines on sampling and market surveillance (2).

3. Glossary

The definitions given below apply specifically to the terms used in this document. They may have different meanings in other contexts.

authorized product. A product in compliance with national and regional regulations and legislation. National or regional regulatory authorities can, according to national or regional regulations and legislation, permit the marketing or distribution of medical products with or without registration and/or licence.

chain of custody. A chronological and continuous record of the seizure and custody of the suspect product and the subsequent transfer of a sample of the suspect product to the laboratory as well as the handling of the sample within the laboratory.

falsified product. For the purposes of this document, a product that has been deliberately and/or fraudulently misrepresented as to its identity, composition or source, and which therefore requires testing beyond the routine quality control testing. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized product or the manufacture of a product that is not an authorized product.

“Identity” shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized product. “Composition” shall refer to any ingredient or component of the product in accordance with applicable specifications authorized/recognized by the NRA. “Source” shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable.³

forensic. Related to analysis for law enforcement purposes.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that authorizes the marketing or free distribution of a pharmaceutical product in the respective country after evaluation for safety, efficacy and quality. In terms of quality it establishes inter alia the detailed composition and formulation of the pharmaceutical product and the quality requirements for the product and its ingredients. It also includes details of packaging, labelling, storage conditions, shelf life and approved conditions of use.

³ Member State mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products. Report by the Director-General; 2017 (A70/23; http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_23-en.pdf, accessed 27 February 2018).

medical product⁴ refers to medicines, vaccines and in vitro diagnostics (and in the future may include medical devices).

quality control. Embraces all measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other pharmaceutical characteristics.

quality management. A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use.

screening technologies. The qualitative and/or semiquantitative technologies that can rapidly acquire the information or analytical data for preliminary identification of suspect medical products in the field.

standard operating procedure. An authorized written procedure giving instructions for performing standardized operations both general and specific.

4. Detection of suspect falsified products

4.1 Entry points for detection

Regulatory authorities are responsible, in collaboration with relevant national and international stakeholders, for establishing mechanisms to detect falsified products circulating in their territories and for removing them from the market.⁵

Suspect falsified products can be detected using a range of approaches, including routine inspections performed by national or regional authorities and enforcement agencies, targeted risk-based surveys (1), investigation of complaints, follow-up of reports on any suspicious observations in the supply chain (for example, inconsistent documentation or unexpected stock levels), discrepancy during verification and investigation of unexpected adverse events reported to have occurred with a specific product. It is important to evaluate any information on suspect falsified products reported by customs, medicines inspectorates and other authorities, procurement agencies, wholesalers and importers, pharmacies, health-care institutions, patients and other stakeholders.

⁴ Working Group of the Member State Mechanism (http://apps.who.int/gb/sf/pdf_files/A_SFFFC_WG2_2-en.pdf).

⁵ See also reference (3), Paragraph II.1. Quality monitoring and control.

4.2 Detection methods⁶

Falsified medical products may be identified by their packaging characteristics and/or by identity verification, physical and chemical testing. This may require confirmation, where appropriate, by the stated manufacturer, that the product was not manufactured by them (for example, written confirmation that packaging and other elements do not correspond to the genuine manufacturer's records).

When available, the packaging and patient information leaflets of suspect falsified medicines should always be examined visually and compared with samples or photographic images of genuine registered products if available.⁷ Product protection features may also be utilized to screen and/or authenticate suspect packaging components. Attention should be paid to any irregularities or inconsistencies, such as spelling mistakes, unusual batch numbers, unusual printing of batch number and shelf life, verification of serialization data when appropriate, unexpected or modified manufacturing or expiry dates, signs of repacking, for example, to circumvent inspection activities, or instructions in a language that does not match the area of their distribution. Microscopy and other analytical techniques (including but not limited to optical techniques) may be utilized for package examination. The purpose of these technologies is to rapidly provide evidence that the sample comes from a falsified product.

An extensive list of analytical techniques that can be used to screen the market for falsified products is provided in Appendix 1. More detailed descriptions of available technologies can be found in published literature and online guidance (5, 6, 7).

The result of a screening test is only indicative (preliminary or presumptive adverse analytical result) and other analytical techniques must be applied to confirm unequivocally that a falsified medical product has been detected.

Some of the methods shown in Appendix 1 rely on a comparison with suitable reference materials or data available in a library or a reference database. Sharing of reference values and screening results through access-controlled information technology interfaces can provide strong support for the application of rapid screening technologies.

⁶ Further guidance on screening technologies is provided by the Working Group of the WHO Member State Mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit medical products (3) through its prioritized activities 2014–2015, specifically Activity C, aiming to establish and convene a working group comprising Member States' experts to assess and report on: (a) existing "track and trace" technologies in use by Member States; and (b) existing field detection devices in use or available to Member States.

⁷ The manufacturer or marketing authorization holder should inform the relevant NRA of any changes to the artwork or packaging of its registered products. Details of analysis/observation of authentication features displayed on the product packaging, or embedded within the product itself, should also be included in the registration dossier. This will help the NRA to assess the authenticity of a given suspect product when conducting visual inspections.

4.3 Selection of analytical techniques

Appendix 1 provides an overview of the analytical techniques available at the time these guidelines were developed. The choice of analytical technology to be applied should be based on the information required. The regulatory authority should obtain advice about available analytical techniques including, for example, from the manufacturer and the analytical testing laboratory, before deciding which analytical technique to use, taking into account:

- the expected benefits of each technology (scientifically based), given its applicability and performance characteristics;
- opportunities for efficient use within existing postmarketing surveillance activities, such as inspections for compliance with licensing requirements, GMP or GDP;
- the availability of adequately trained local operators and cost of training;
- the expected cost of equipment, including its periodic calibration and qualification;
- recurring costs and availability of consumables, reference materials, libraries and maintenance;
- any other factors that may influence the use of analytical techniques in the national context.

5. Sampling and documentation

5.1 Sampling

Sampling of suspect falsified products is typically performed by inspectors or enforcement officers (such as police or customs officers) or other competent personnel, for example, laboratory personnel. Suspect medical products can also be detected during the complaint process. Care should be taken to ensure that the sample taken or seized is representative of the suspect medical product. A sufficient number of dosage units should be taken to enable thorough analytical testing. Guidance and advice should be sought from a suitably qualified analytical testing laboratory (1). However, if the requisite amount is not available all units should be collected.

5.2 Documentation of information on suspect falsified medical products

An information collection form, which is to be completed by the inspector or enforcement officer, should be comprehensive and include, but not be limited to:

- the point of detection in the supply chain (manufacturer, wholesaler, pharmacy, hospital or patient);
- the quantity of suspect product found;
- a visual description of its packaging;
- product name as marketed (if any);
- name of active substance (if known);
- the dosage units;
- the batch number;
- photographs;
- any signs of irregularities;
- the supply history of the product including the name, address of parties involved, date of transfer, etc.;
- a description of the circumstances leading to its detection (for example, adverse effects and any other relevant information).

This document should accompany the sample from the time it is taken until it is delivered to the testing laboratory. An example of an information collection form is presented in Appendix 2.

5.3 Chain of custody considerations⁸

From the time of collection or seizure of the suspect falsified medical product until its ultimate fate is decided, a rigorous chain of custody should be maintained to ensure that the integrity of the sample and its accompanying documentation is preserved. Secure packing, labelling, appropriate transport and storage conditions for the sample must be provided and documented. In addition, adequate security arrangements must be in place to prevent any theft, tampering, substitution or unauthorized disclosure of information.

The chain of custody of a sample consists of two parts. The first starts at the location where the suspect falsified medical product was seized or purchased by the inspector, or when a suspect falsified medical product has been detected by a manufacturer or any other stakeholder and includes all stages of the process of delivering the sample to the analytical testing laboratory. The second part relates to the laboratory, where all transfers of the sample must be recorded so that the analytical report generated by the laboratory can be unequivocally linked to the source of the sample.

⁸ See also reference (3), Paragraph IV.1.1.30.

The inspectors or enforcement officers should document details of the suspect falsified product including (but not limited to):

- location of detection (name or title and address);
- at what point in the supply chain detection occurred (manufacturer, wholesaler, pharmacy, hospital, patient, etc.);
- pharmaceutical product type, pharmaceutical dosage form (tablet, capsule, injection, etc.);
- quantity and/or volume;
- date and time of seizure or purchase;
- names and signatures of the inspector or enforcement officer and the owner of the suspect falsified medicine at the location;
- the amount collected;
- description of packaging;
- location to which the sample is sent;
- other relevant information (international nonproprietary name (INN), brand name, batch number, shelf life, dosage, strength, etc.).

The inspector or enforcement officer is responsible for securing the sample appropriately and arranging transport to the testing laboratory. Whenever possible, samples that cannot be transported immediately are to be stored according to the storage conditions defined by the manufacturer, in a secure place. Otherwise, whenever possible, samples are to be stored in a secure, cool environment.

The inspector or enforcement officer should include a copy of the appropriate documentation (see section 5.2) in each transport bag or container holding the samples, to ensure that the laboratory can verify the contents upon delivery.

Samples may be taken directly to the analytical testing laboratory by the inspector or enforcement officer or handed over to a qualified and approved courier for transportation.

If an approved courier company is used to transport the samples, this should be documented in the chain of custody of the samples and the inspector or enforcement officer should record the waybill and tracking numbers of the shipment. The recipient of the sample should be informed of the expected delivery date and the storage and transportation conditions.

Within the laboratory, samples are considered to be in custody when they are:

- in the physical possession of authorized staff;
- visible to authorized staff after being in his/her physical possession;

- stored in a secure location.

The laboratory chain of custody should be reflected in all the documentation generated by the laboratory, which may include logbooks, worksheets, photographs and analytical reports where the custody of the samples during analysis and storage is recorded with the signature of the staff member concerned and the date and time of the action(s). The laboratory chain of custody shall be a continuous record of authorized staff with custody of the samples at all stages of the process from receipt to disposal. At each stage, the authorized staff involved must sign and date the entry for the action performed (for details see WHO *Guidance on good data and record management practices* (8)).

It is essential to ensure traceability throughout the process – from the seizure or purchase of the suspect falsified medical product to the conclusion of the investigation.

6. Regulatory actions upon detection of suspect falsified medical products

6.1 Risk assessment

When a suspect falsified medical product has been found, the relevant NRA is to be informed (for details see section 8). The NRA should then perform a risk assessment to determine what further action is required to protect public health.⁹ This assessment should be done in communication and collaboration with the marketing authorization, licence or registration holder, and if applicable with the manufacturer of the genuine product, and an analytical testing laboratory with experience in testing suspect falsified medical products. WHO and other regulatory authorities should also be informed as appropriate.

Further action may include confirmatory laboratory testing of the suspect samples.

6.2 Questions to be answered by analytical testing

If laboratory analysis is to be conducted, NRAs should send the samples to a laboratory with adequate capacity to perform the testing as described in this document. If no such laboratory is available in the country concerned, the NRA should identify a competent and suitably equipped laboratory in its region or elsewhere that can advise on designing a testing plan and/or perform some or all of the testing. The manufacturer of the genuine product may also be requested to

⁹ See reference (3), Section III. Assessment of alerts, reports and notifications received.

provide information or methods (including reference substances and a sample of the genuine product), which may be used for the testing of suspect samples and/or may be requested to analyse the samples.

Upon receipt of a suspect falsified medical product, the regulatory authority, enforcement agencies and other relevant stakeholders need to clarify the purpose and aims of testing. Some examples of questions that laboratories may be requested to answer (with the assistance of the regulatory authority, enforcement agencies and other relevant stakeholders) are listed below.

- Does the sampled product fall under the national legislation for pharmaceutical products?
- Does the sample meet specifications defined as part of the stated product's marketing authorization?
- What specific substances should the testing be designed to detect? (Examples include specific unexpected active ingredients or groups of active ingredients, specific impurities and any substances that are consistent with reported adverse effects.)
- What additional parameters should be tested to assess the health impact of the ingredients? (Examples include content, dissolution or disintegration properties and sterility.)
- Is there a forensic relationship between different falsified products? If yes, in what aspects?
- Are there any market authorization specifications and methods of analysis available for the suspect samples? *Note:* Check if there is a product monograph in *The International Pharmacopoeia*, or any national or regional pharmacopoeia.

What are the expected excipients (if any) in the suspect samples?

Note: As it is often not possible to answer that question, the testing should be arranged in such a way that there is no (negative) interference of the excipients in the identification and quantification of the substance that is expected to be contained in the sample.

6.3 Communication

Care should be taken by the NRA to convey clear and appropriate messages when communicating information about suspect or confirmed falsified medical products to the stakeholders. Dissemination of information should be well planned, to reach all relevant stakeholders while ensuring confidentiality as appropriate. NRAs should keep a record of the date, recipients and content of information disseminated. WHO and other regulatory authorities should also be informed as appropriate.

Patients who might be affected by falsified medical products should be advised to consult their health professional. Health professionals and procurement agencies, wholesalers and importers should be instructed on the action(s) to be taken to enable a continued supply and treatment while ensuring patient safety. In all communications the manufacturer whose name is printed on the packaging of the products should be described as the “*Stated* manufacturer”, making it clear that the falsified medical product may not have originated from the stated manufacturer. Miscommunication can amount to falsely accusing the legitimate manufacturer of falsifying a product, which would be grounds for legal action by that manufacturer.

7. Confirmatory analytical testing

NRAs should refer samples to a laboratory with adequate capacity to perform the testing as described in this document. The manufacturer of the genuine product may also be requested to provide information or methods (including reference substances and a sample of the genuine product) that may be used for the testing of suspect samples or may provide technical support. Any information and/or materials provided by the marketing authorization holder to a government laboratory in support of an investigation of a suspect falsified medical product must be handled as confidential. Where necessary, material transfer agreements or confidentiality agreements are to be invoked.

7.1 Laboratory capacity

Best practices for QC laboratories and the minimum requirements for equipment are described in WHO guidance (6). That guidance focuses on QC laboratories using compendial or manufacturers’ methods, as described in dossiers submitted for marketing authorization, to ensure compliance with the requirements of compendial monographs or manufacturer’s specifications. However, these methods are designed to detect problems that may arise during the approved manufacturing process and subsequent storage and distribution and may not necessarily be appropriate to detect all possible issues that could arise with medical products that have been deliberately falsified. Methods used to authenticate suspect medical products must be suitable for their intended use.

Laboratories, normally national medicines testing laboratories, that test suspect falsified medical products should preferably be ISO/IEC 17025 accredited by a recognized accreditation body (affiliated, for example, to the International Laboratory Accreditation Cooperation, etc.) to perform the appropriate analytical procedures that are listed in their scope of accreditation. Alternatively, a WHO-prequalified laboratory with the capability to test suspect falsified medical products, an appropriate array of analytical techniques and

sufficient expertise, may be chosen. Furthermore, the laboratories should be able to perform, interpret and document the testing according to rigorous procedures to ensure that the results can withstand legal scrutiny.

Beyond the requirements of good practices, described in general WHO guidance (6) and ISO/IEC 17025, some additional skills and capacity, as outlined below, are required for the analytical testing of suspect falsified medical products.

7.1.1 Expertise

- **Critical thinking.** Laboratory staff should have the ability to critically appraise all that is known about each case of a suspect falsified product and not simply rely on pre-existing standard testing procedures. This skill can be strengthened through discussions with peers on specific cases and by learning from senior experts in the field.
- **Experience.** Laboratories should have access to staff with experience in designing and implementing science-based, tailor-made testing plans for suspect falsified medical products. Where this is not the case, they should cooperate with other institutions and/or refer the testing request to an institution where the required experience is available.
- **Knowledge.** Laboratory staff should have up-to-date scientific expertise enabling them to fully understand the scientific methods used in testing falsified medical products, to apply them correctly and to interpret the results adequately.

7.1.2 Equipment

Laboratories should ensure that technical equipment for testing of suspect falsified medical products about which they have adequate knowledge and experience is appropriately qualified and maintained in good condition. Investments should be planned so as to enable the basic functioning of the laboratory for all its intended purposes and to maximize the benefits of any additional specialized equipment purchased. The cost of the equipment should be considered together with that of accessory products such as consumables, reagents, standards, databases and libraries, as well as the costs of and access to installation, maintenance and training. Sharing of equipment in accordance with regional cooperation agreements can be considered to minimize the costs while maximizing the benefits.

Laboratories also need secure and adequate storage facilities for the suspect falsified samples, when not being tested, to ensure the chain of custody.

7.2 Standard operating procedure

Laboratories should develop, implement and maintain a standard operating procedure (SOP) for testing of suspect falsified medical products. Such an SOP cannot define each step in the testing, since this will be determined on a case-by-case basis. Rather, it should ensure that the laboratory follows good practice and internal quality management systems in planning, implementing and documenting its actions with regard to each request for testing. *WHO guidelines for sampling of pharmaceutical products and related materials* (7) and *Good practices for pharmaceutical quality control laboratories* (6) should be followed, as applicable.

Measures should be taken to minimize bias. Sampling should be separate from testing. Staff performing each analysis on the testing plan should be blinded to the results of the other analyses as far as possible.

The laboratory should ensure full traceability of samples and results as described in relevant WHO guidelines (1, 6, 7), and should follow rigorous procedures to preserve the integrity of samples and documentation, with a chain of custody that will stand up to scrutiny in case of legal action.

An example of an SOP for testing of suspect falsified products is provided in Appendix 3.

7.3 Testing plan and test procedures

All the available information about the samples should be provided to the laboratory in the form of a request for analysis that clearly indicates what is expected from experimental testing. The inspector or enforcement officer who collected the sample should inform the laboratory as comprehensively as possible and necessary for efficient running of the testing.

A suitable analytical testing programme should be prepared to detect the suspect substances. An initial study should then be undertaken, keeping in mind the number of sampling units available, to determine the substances to expect in the sample and parameters to be tested, and to design a science-based testing plan identifying the most efficient combination of methods to provide the required answers.

A wide range of methods may be considered for inclusion in the testing plan, which includes simple visual checks as well as the technologies listed in Appendix 1, and other forensic analyses that may assist in determining likely sources of suspect falsified medical products. Each technique should be appraised to determine its most appropriate use in order to achieve the best possible performance in the given context.

More detail on combining technologies to identify falsified medical products can be found in the literature (e.g. (5)). Various examples of flowcharts describing how to proceed with testing are reproduced in Appendix 4 for

illustrative purposes (with the kind permission of the authors, the European Network of Official Medicines Control Laboratories).

7.4 Interpretation and reporting of results

General good practices in interpreting laboratory testing results are described in WHO guidance (6). Specific points to document for testing of suspect falsified medical products include:

- reasons for selecting the particular methods used in the testing plan;
- measures taken to avoid bias in analysis and reporting;
- traceability of the measurements, with links to all physical material and to the original sample on which the test was done;
- limitations of the selected methods as used in the testing plan, together with an estimate of the measurement of uncertainty of a quantitative result, if performed, and the conclusions.

8. Reporting and regulatory action on confirmed falsified medical products

A legal framework for reporting of falsified products should be in place at national level (9).

The confirmed testing results should be reported to the regulatory authority of the country where the falsified product was found. It is the responsibility of the NRA, under the given circumstances, to decide how the findings should be translated into appropriate action in accordance with national legislation and in cooperation with enforcement agencies and other stakeholders.¹⁰ The marketing authorization holder should be kept informed of the results of testing. Other regulatory authorities should be informed as appropriate. A report should be submitted to the WHO Global Surveillance and Monitoring system for Substandard and Falsified Medical Products (10).

9. Archiving of samples and reports

The testing laboratory should store the samples appropriately and archive the related documentation in separate secure locations for future reference as required by legislation, documenting that the integrity of samples and results have been preserved.¹¹

¹⁰ <http://www.who.int/medicines/regulation/ssffc/surveillance/en/>.

¹¹ See also reference (3), Paragraph IV.1.1. 30.

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Appendix 1

Examples of analytical techniques that may be used for package identification, screening and testing of suspect falsified medical products

The list in Table 1 provides examples of analytical techniques that may be considered. These include compendial methods as well as specific advanced techniques. Each technique should be appraised to determine its most appropriate use in order to achieve the best possible performance in the given context. Laboratories may decide to outsource some of the analyses necessitating specific advanced techniques to other suitably qualified laboratories.

Note: The list should not be considered to be complete or exhaustive. It is intended to provide illustrative examples of commonly available technologies. Moreover, not all techniques are required for a laboratory that undertakes such testing.

Table 1
Illustrative examples of commonly available techniques

Main use	Technique	Full name	Remark
Identification	ATR/FTIR spectroscopy	Attenuated total reflectance/Fourier transform infrared spectroscopy	–
Identification	Melting point	–	–
Identification	XRPD	X-ray powder diffractometry	–
Identity	RI	Refractive index	–
Identification assay	Spectrophotometry (colorimetry)	–	–
Identification assay impurities	TLC	Thin-layer chromatography	–
Assay identification impurities	GC/FID	Gas chromatography with flame ionization detection	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Forensics identification assay impurities	GC/MS	Gas chromatography with mass spectrometric detection	–
Assay identification impurities	LC/UV	Liquid chromatography with ultraviolet detection	–
Residual solvents impurities	HS-GC/FID	Headspace gas chromatography with flame ionization detection	–
Forensics residual solvents impurities	HS-GC/MS	Headspace gas chromatography with mass spectrometric detection	–
Inorganic impurities	ICP/OES	Inductively coupled plasma with optical emission spectroscopy	–
Inorganic impurities	ICP/MS	Inductively coupled plasma with mass spectrometric detection	–
Elemental and chemical analysis	XRF	X-ray fluorescence	–
Finished pharmaceutical product testing	Dissolution testing	–	Indication on bioavailability of the active pharmaceutical ingredient (API)
Finished pharmaceutical product testing	Disintegration testing	–	Indication of bioavailability of API
Specific testing	Sterility	–	–
Specific testing	BET	Bacterial endotoxins test	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Specific testing	Osmolarity and osmolality	–	Characterization of injections and infusions
Finished pharmaceutical product testing forensics	Light microscopy	–	Particle characterization (size distribution, size, particulate impurities)
Identification	Raman spectroscopy	–	Characterization of material
Forensics	Photo scan/overlay	–	Documentation, comparison (e.g. packaging, leaflets)
Forensic	FTIR/Raman imaging spectroscopy	–	Characterization of material composition (distribution, particulate impurities)
Forensics	TEM	Transmission electron microscopy	Characterization of material morphology (tablet, particles)
Forensics	SEM-EDX	Scanning electron microscopy with energy dispersive X-ray spectroscopy	Characterization of material (surface, distribution in mixtures, particulate impurities)
Forensics; identification of impurities	LC-HRMS	Liquid chromatography with high resolution mass spectrometric detection	Characterization of unknowns down to trace levels
Forensics; identification assay impurities	LC/MS	Liquid chromatography with mass spectrometric detection	–

Table 1 *continued*

Main use	Technique	Full name	Remark
Forensics; impurities	TDS-GC/MS	Thermodesorption gas chromatography with mass spectrometric detection	Qualitative analysis of volatiles and semi-volatiles in solid samples (direct analysis/ without sample preparation)
Forensics	LC/ELSD	Liquid chromatography with evaporative light scattering detection	–
Forensics; identification assay impurities	NMR, qNMR	Nuclear magnetic resonance, quantitative nuclear magnetic resonance	Characterization of unknown compounds and mixtures – qualitative and quantitative

Appendix 2

Example of an information collection form

RECEIPT OF SUSPECT FALSIFIED PRODUCT		
Date on which the suspect product was received:		
Suspect product received by:		
Signature of the inspector/ enforcement officer and that of the owner of the product collected or seized		
Suspect product:		
Supply history of the product		
Source of the suspect product:		
Contact details of source of suspect product:	Name and surname:	
	Physical address:	
	Email:	
	Telephone number(s):	
	Other:	

INFORMATION ON SUSPECT FALSIFIED PRODUCT

1. Suspect product name(s):			
2. Type of product (select the most appropriate box):			
Innovator product	<input type="checkbox"/>	Generic product	<input type="checkbox"/>
Vaccine	<input type="checkbox"/>	Blood product	<input type="checkbox"/>
Other biological product	<input type="checkbox"/>		
Diagnostic	<input type="checkbox"/>	Herbal medicine	<input type="checkbox"/>
Traditional medicine	<input type="checkbox"/>	Other, please specify	<input type="checkbox"/>
Additional comments (if applicable):			
3. API(s) present in the product and declared strengths:			
4. Description of the dosage form:			
5. Description of product packaging (primary and secondary):			

Table continued

INFORMATION ON SUSPECT FALSIFIED PRODUCT		
6. Does the packaging contain any holographic security features or short message service (SMS) verifiable coding?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Provide description (if applicable):		
7. Is there a patient information leaflet available with the product?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
8. Batch number/lot number (if available):		
9. Date of manufacture (if available):		
10. Expiry date (if available):		
11. Does this product fall under the national legislation for pharmaceutical products?	Yes <input type="checkbox"/>	No <input type="checkbox"/>
12. Market authorization holder (if applicable):		
13. Manufacturer(s) details as given on the suspect product packaging:		
14. Quantity of suspect product received:		

Table continued

INFORMATION ON SUSPECT FALSIFIED PRODUCT	
15. Does the suspect product meet specifications defined as part of the stated product's marketing authorization?	Yes <input type="checkbox"/> No <input type="checkbox"/>
Provide full data content by scanning the code (if applicable):	
Additional information:	
16. Any other information applicable:	

TESTING REQUIREMENTS

1. Has the product been subjected to any preliminary testing?

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If "Yes" provide a summary of results

2. What specific substances should the testing be designed to detect?

3. What tests or parameters should be considered to assess the product?

4. Is this sample physically and/or chemically similar to other samples (either specified or in general)?

5. Are the market authorization specifications available?	Yes	No
	<input type="checkbox"/>	<input type="checkbox"/>
6. Are official testing methods available?	Yes	No
	<input type="checkbox"/>	<input type="checkbox"/>

Description of methods available:

7. Any specific testing requests:

IMPACT ON PUBLIC HEALTH			
Have any adverse reactions been reported?	Yes	<input type="checkbox"/>	No <input type="checkbox"/>
If "Yes" provide more information:			
Estimated number of patients adversely affected?			
Estimated number of patients at risk?			
Any other related information:			

Appendix 3

Example of the content of a standard operating procedure for testing suspect falsified tablets

1. Purpose

The standard operating procedure (SOP) describes the workflow and the required test procedures for the testing of suspect falsified tablets.

2. Scope

The SOP is only valid for the good laboratory practices/good manufacturing practices test facility of _____ .

3. Sample receipt, documentation and storage

a. Sample receipt

Upon receipt of a shipment of suspect falsified tablets for analysis, the receiving laboratory should:

- record the
 - name and signature of the person delivering the sample or courier company waybill;
 - date and time of receipt of the sample in the laboratory with signature of the staff member;
 - presence of accompanying documentation in the shipment;
- check integrity (e.g. damage, broken sealing) of shipment packaging;
- check completeness of shipment against shipping documents;
- read out and check data logger (e.g. temperature control) – if applicable;
- check and sign shipment documentation – if applicable;
- archive all documents in the corresponding project files as per the corresponding SOP xxx.xxx.xxx.

b. Sample documentation

After sample receipt and unpacking:

- document packaging that contains the suspect falsified tablets as received as photographic image(s);

- document package insert or patient information leaflet as photographic image(s);
- check contents using shipping documents and previously received information from sending party;
- document each sample: secondary packaging and primary packaging (e.g. blister) including labels as photographic image(s);
- archive all documents and photographic images in the appropriate project files as per the corresponding SOP xxx.xxx.xxx;
- store samples under appropriate storage conditions according to SOP xxx.xxx.xxx until testing, record storage location;
- prior to testing let samples equilibrate to ambient temperature.

c. Checklists and records of observations

- All the above observations should be recorded on a checklist and signed and dated upon completion by the staff member responsible for these duties.
- The time and date of storage should be verified and recorded, with the signature of the person responsible.
- The time and date of sample removal from storage for equilibration to room temperature should be recorded, with the signature of the person responsible

d. Remarks

- When using photographic images for documentation purposes, check image quality (e.g. readability of text elements, colour correctness) before proceeding.
- Ideally, sample documentation should include dimensions (e.g. primary and secondary packaging, thickness and diameter of tablets).
- The sending party should be informed of receipt of the sample – if applicable.

e. Observations

Any observations such as damaged packaging, missing or additional samples should be documented and communicated to the sending party in order to decide how to proceed.

4. Sampling and samples

- Split each sample set into three subsets.
- Subset 1 for packaging inspection and documentation and Subset 2 for analytical testing as described in the following sections.
- Keep Subset 3 as a retained sample for any further investigation.

5. Overall aspect

Inspect known product protection features (i.e. holograms, colour-shift inks, etc.)

a. Packaging

- Use Subset 1 (see section 4).
- Visually inspect the secondary and primary packaging, use authentic comparators whenever possible.
- Report observations of the external appearance of the packaging materials (including labels and printing) such as visible damage, holes, discoloration and stains, spelling mistakes and unusual typography.
- Document observations as photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

b. Samples

- Use Subset 2 (see section 4).
- Visually inspect the tablets.
- Report observations of the external appearance of the tablets, such as visible fissures, holes, inclusions, discoloration or stains, presence or absence of score lines, and presence or absence of film or sugar coating.
- Document observations as photographic images and archive them together with corresponding notes in the project files as per the SOP xxx.xxx.xxx.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

6. Analytical testing

a. Packaging testing

- Use Subset 1 (see section 4).
- Record Fourier transform infrared spectroscopy (FTIR) or Raman spectra according to the SOP xxx.xxx.xxx in order to confirm or elucidate the identity of the primary packaging.
- Report results.
- A reporting form should be signed and dated on completion by the staff member responsible.

b. Solid medicine (tablet) testing

i. Active pharmaceutical ingredient (API)

- Use Subset 2 (see section 4).
- Homogenize at least one of the tablets of Subset 2 by mechanical grinding and use the homogenized material for the next steps.
- Confirm identity and concentration of the expected API in the suspect sample using the reference standard and corresponding compendial method. Alternatively, an in-house method can be used as long as the suspect tablet is tested against a suitable reference sample. The suitability of the in-house method for its intended use should be proven by means of validation reports and should be a stability indicative method.
- Report results.

A reporting form should be signed and dated on completion by the staff member responsible.

ii. Excipients

- Use Subset 2 (see Chapter 4).
- Record FTIR or Raman spectra of a reference sample (i.e. certified medicine reference sample) according to the SOP xxx.xxx.xxx.
- Record FTIR or Raman spectra according to the SOP xxx.xxx.xxx of the tablet, which was homogenized by mechanical grinding and compare against a reference sample in order to confirm presence and relative concentration of expected excipients.
- If differences from the data of the reference sample are observed perform in-depth analysis of experimental data (e.g. presence of unexpected substances or lack of expected substances).

- Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

iii. Additional tests

If tests as described in sections i. and ii. do not deliver unambiguous results additional screening tests can be performed on Subset 2. These screening tests can include:

- elemental analysis screening using inductively coupled plasma with optical emission spectroscopy (ICP-OES) or ICP/mass spectrometry (MS) as per SOP xxx.xxx.xxx;
- screening for volatiles and semi-volatiles using thermodesorption gas chromatography (TDS-GC)/MS as per SOP xxx.xxx.xxx;
- screening for volatiles and semi-volatiles via GC/MS as per SOP xxx.xxx.xxx;
- screening for non-volatile, polar compounds via high pressure liquid chromatography mass spectrometry (HPLC)/MS as per SOP xxx.xxx.xxx.

7. Dissolution and disintegration testing

- Use Subset 2.
- Perform dissolution testing in comparison to suitable reference sample.
- Report results.

There should be a reporting form to be signed and dated on completion by the staff member responsible.

8. Abbreviations

GC/MS	gas chromatography/mass spectrometry
HPLC/MS	high-pressure liquid chromatography/mass spectrometry
ICP/OES	inductively coupled plasma/optical emission spectrometry
ICP/MS	inductively coupled plasma/optical mass spectrometry
SOP	standard operating procedure

Appendix 4

Examples of flowcharts for testing of suspect falsified medicines

Explanatory note to the Appendix

This Appendix includes the examples from an “*Aide-Memoire for the Testing of Suspected Illegal and Counterfeit Medicines*” prepared by the European Official Medicines Control Laboratory (OMCL) Network (*Reference: PA/PH/OMCL (06) 81 R6, Strasbourg, July 2016*) which has been reproduced with the kind permission from the Network members. Terminology may therefore differ from WHO style.

“The original version of this document was produced in response to many presentations given at a number of Annual General Meetings of the OMCL Network (GEON).

The paper provides some practical and theoretical advice to OMCLs on the development of protocols for the confirmation or determination of counterfeit medicinal products and was adopted by the Network in 2007.

Subsequently, the testing of potentially illegal and counterfeit medicines throughout the Network has expanded and many laboratories now have established processes and expertise.

At the GEON annual meeting in June 2015, it was agreed that the “aide-memoire” document should be revised and updated to provide an overview of the overall approaches that should be taken for OMCLs analysing suspected illegal/counterfeit medicines.

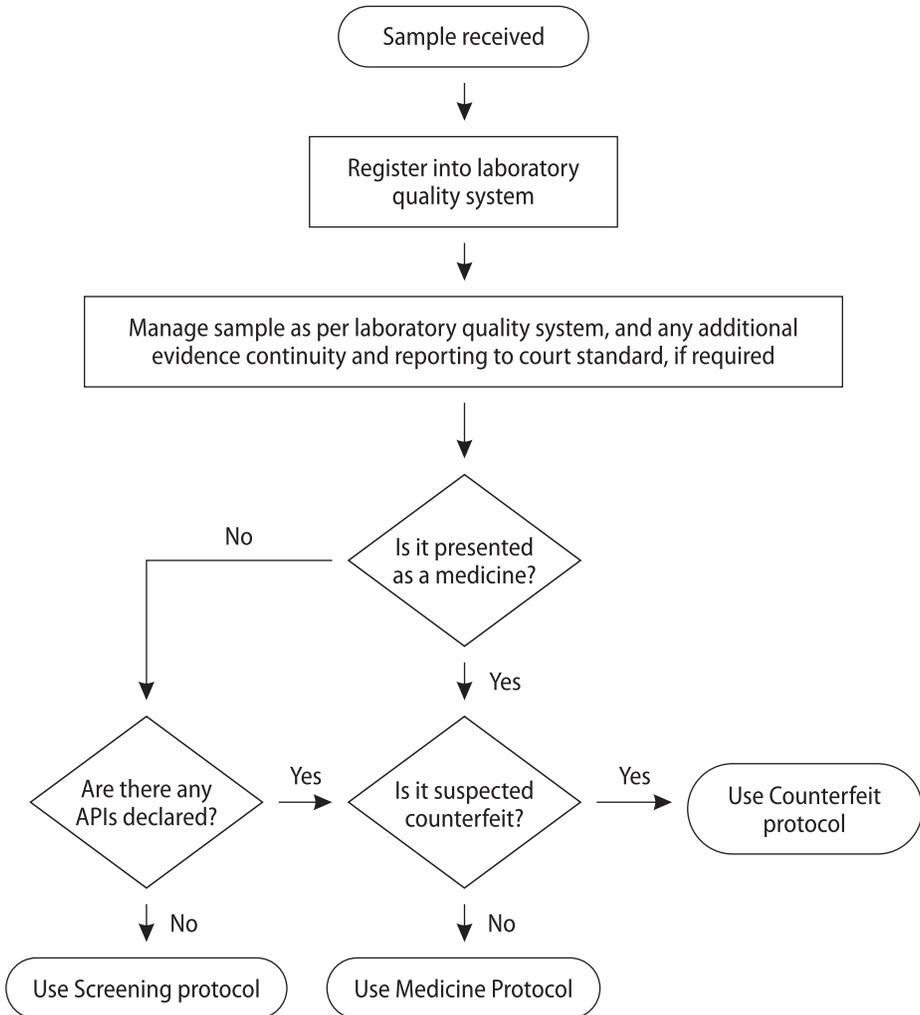
This document has been prepared to include example high-level process flows/decision trees to assist OMCLs and promote a harmonised approach across the Network. It is recognised that OMCLs will have existing processes in place and this document does not supersede existing systems. This document is intended as an “aide memoire” only and OMCLs are not expected to be audited for compliance with the document.

The techniques listed in this document are examples only and should not be seen as exclusive or even preferred techniques. OMCLs should choose and use appropriate equipment to meet their testing needs.

The individual OMCLs' choice of specific analytical techniques and detailed testing SOPs are outside the scope of this document and should be decided locally in accordance with local legislation or policies (for example, some OMCLs may routinely quantify APIs found but others may not – either approach is acceptable), equipment availability and staff expertise/preferences.

The final decision on what techniques to use and equipment to purchase and exactly what testing to apply is left to individual OMCLs.”

Example 1. Decision tree to determine testing requirements



Note:

Where no APIs are declared, often the name or marketing of the item can indicate what APIs may be present (for example, products may be marketed as weight loss or sexual potency enhancers, or have suggestive pictures/branding that implies the product's intended effect).

Also Internet searches using the product or producer name of the item can often provide information on APIs, use and/or indication.

Further details of the protocols that may be applied are given in the following sections.

Example 2. Screening protocol (testing for “medicines in disguise”)

Samples may be presented as a food supplement, health tonic, “nutraceutical” or naturally derived or herbal product. Usually there will be either no mention of API(s) in the product or even a more positive statement such as “100% natural extracts” or similar. Alternatively samples may be presented in foreign language variants, or even unlabelled.

In these circumstances the priority of the testing is to establish whether there are any APIs/potential pharmacologically active substances present and, if there is, at what level if required.

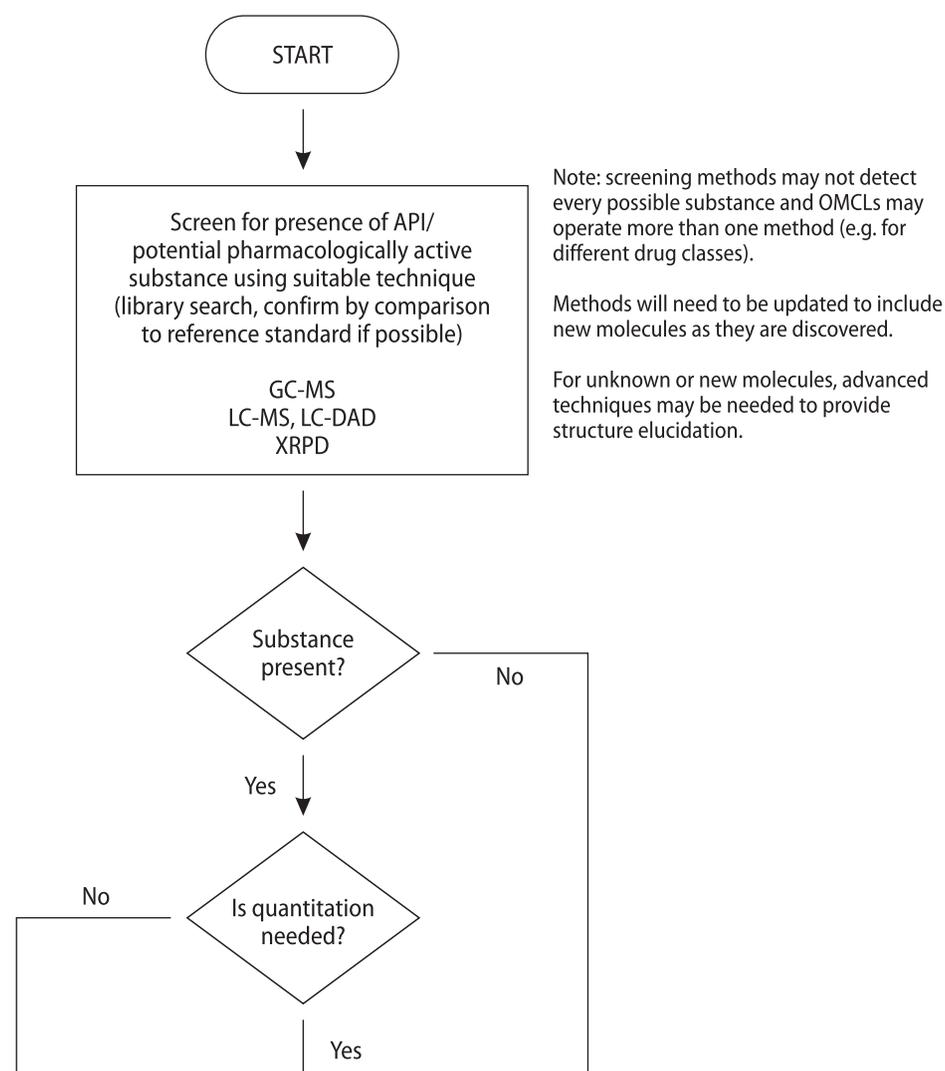
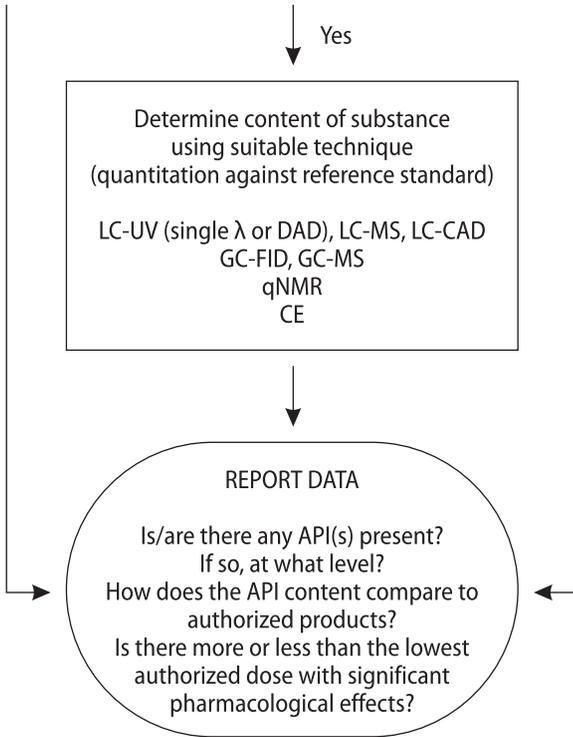


Figure continued



Example 3. Medicine protocol (testing of “unapproved products”)

Samples may be legal, licensed medicines in other countries, but not necessarily in the country where they have been found, or they may be legal medicines sold outside of the correct, legal supply chain. They might also contain drug substances that are not licensed or legally authorized for sale or treatment. Usually the API(s) in the product will be listed on the label and the product will be packaged and presented as a medicine. In some cases, the samples may be presented in foreign language variants, so the API(s) present may be unclear.

The priority of the testing is to establish that the labelled API is present, and (if required) at what level.

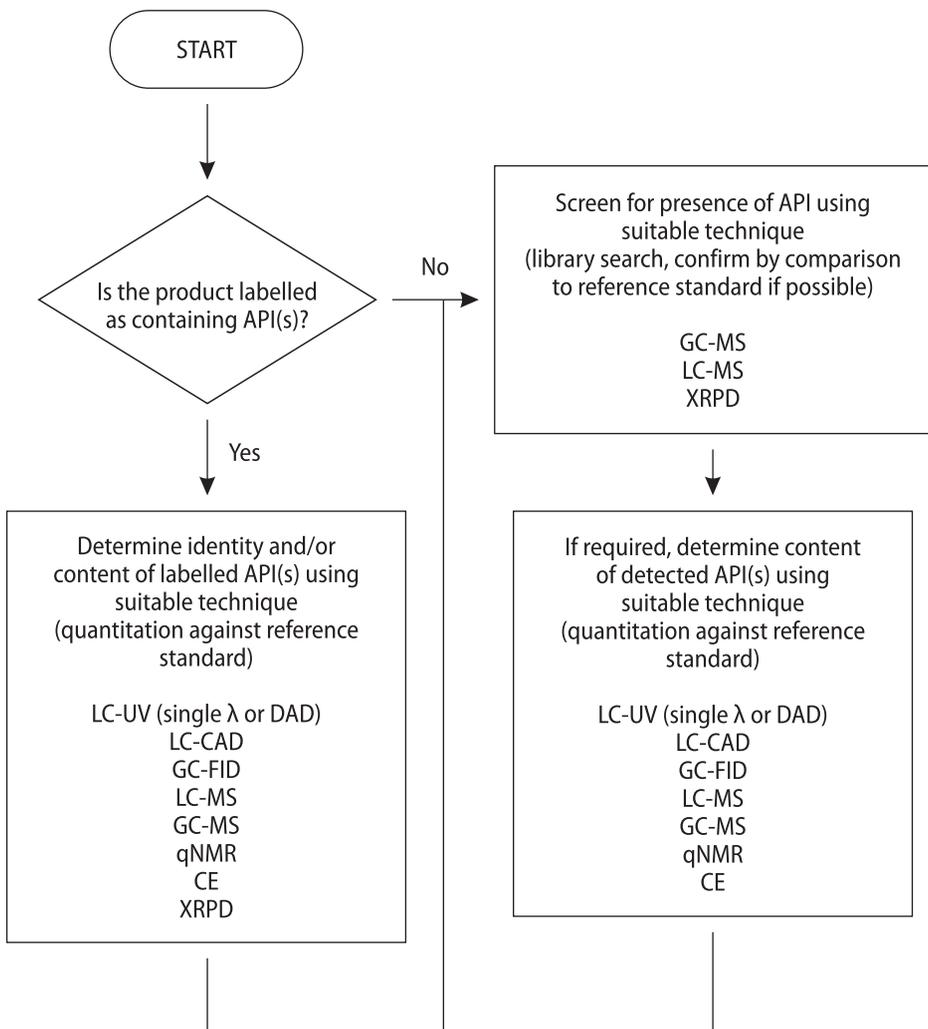
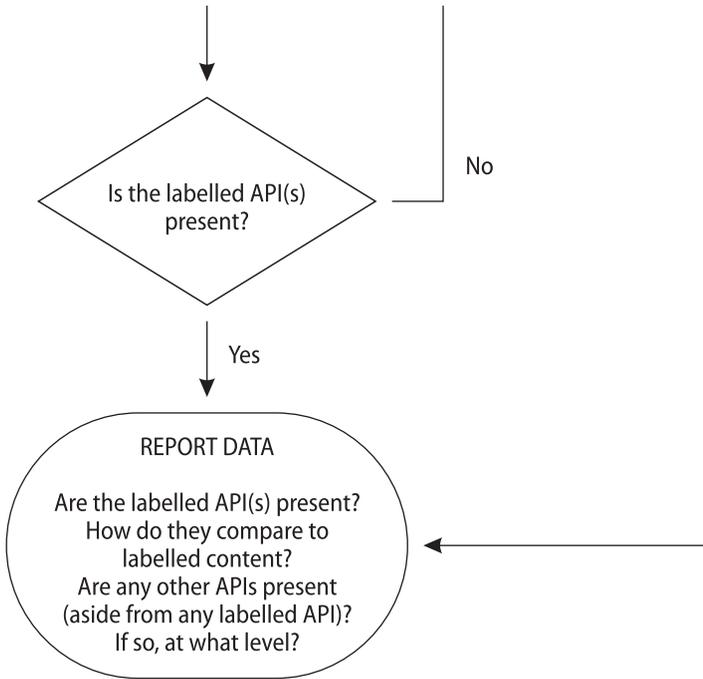
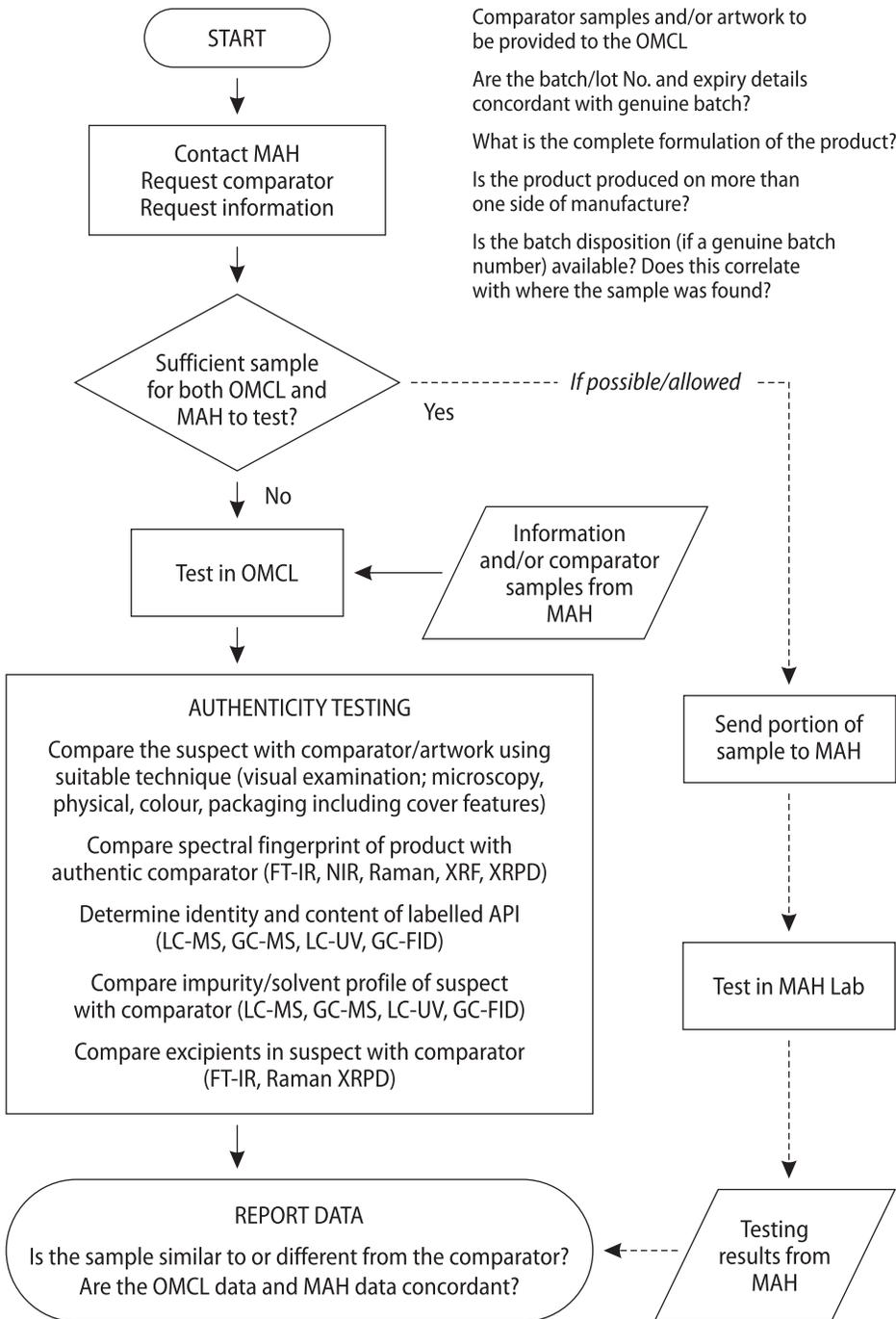


Figure continued



Example 4. Counterfeit protocol

For samples that are presented as licensed medicines but are suspected of being falsified, or counterfeit, it is essential that the OMCL is able to make contact with the market authorization holder of the genuine product. This may either be directly or through the competent authority, inspectorate or enforcement group. Genuine comparator batches (ideally three batches including the suspicious lot) should be obtained. If the product is manufactured at a variety of production sites samples should be obtained from each. It is not usually possible for a laboratory to determine conclusively that a sample of product is counterfeit based on testing alone. The priority of the testing can only be to say whether the suspect sample is consistent with the genuine product or not.



Note: when a suspect sample is found not to contain labelled API, the OMCL may wish to apply the screening protocol to determine what, if anything is present

Annex 6

Good pharmacopoeial practices: Chapter on monographs for compounded preparations

Background

Following the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidance on good pharmacopoeial practices (GPhP) was published as Annex 1 to the report.¹ The primary objective of the GPhP is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization. In line with this objective, this guidance on monographs for compounded preparations has been developed outlining the structure and contents of such monographs.

1. Introduction

Compounded preparations² involve the preparation, mixing, assembling, altering, packaging and labelling of a medicine or drug-delivery device, in accordance with a licensed practitioner's prescription, medication order or initiative based on the relationship between the practitioner, patient, pharmacist and compounder in the course of professional practice.

This section of the GPhP helps define good practices for developing pharmacopoeial monographs for compounded preparations, which will help ensure the quality of these preparations.

2. Monograph development

Pharmacopoeial monographs for compounded preparations are generally developed by a pharmacopoeia and its expert committees rather than by donation from a manufacturer. Monographs for compounded preparations may include a stability-indicating assay and acceptable limits for the active pharmaceutical ingredient(s) (API(s)). Where required, a beyond-use date (BUD) or assigned

¹ Good pharmacopoeial practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

² The term "compounded preparations" is used throughout this document. This term encompasses medicines that are (i) prepared extemporaneously, under the supervision of a pharmacist, for a specific patient and (ii) those that are prepared in advance in appropriate facilities (also known as stock preparations).

shelf life³ is included, based on suitable stability studies. Typical sources of pharmacopoeial monographs for compounded preparations include:

- laboratory-conducted method development, validation and stability studies;
- peer-reviewed literature, evaluated based on stringent criteria;
- donated scientific data.

3. Quality of ingredients

Ingredients specified in the definition and/or used in the formula in pharmacopoeial monographs for compounded preparations comply with relevant monographs for pharmaceutical substances and general monographs, if available.

4. Monograph title

The titles of monographs for compounded preparations will follow national naming conventions, but should include the name of the pharmaceutical substance and the dosage form. Some pharmacopoeias may use the following naming convention for compounded preparations that are used for both humans and animals:

- [medicine name] dosage form;
- [medicine name] compounded [route] [dosage form];
- [medicine name] compounded [route] [dosage form], veterinary (for animals only).

5. Sections of the compounded preparation monograph

Compounded preparation monographs may include the following sections:

- Definition and content
- Assay
- Compounding procedures
- Identification tests
- Specific tests
- Additional information
- Stability information and BUD

³ The term “beyond-use date” (BUD) is used throughout this document synonymously with “assigned shelf life”.

5.1 Definition and content

Assay limits provide the acceptable range of the labelled amount of the API(s). The assay limits should take into account the precision and accuracy of the method, the strength of the preparation and the stability of the pharmaceutical substance in the specific preparation. Assay limits are normally expressed with reference to the active moiety or the label claim, in accordance with national and regional requirements.

5.2 Assay

The assay quantifies the amount of API in the compounded preparation. It may also quantify certain excipients, such as preservatives, depending on national and regional legislation. In certain cases more than one assay method may be necessary, for example, where the preparation contains more than one API.

Where required, the compounded preparation should be tested for strength and potency. The purpose of strength or potency testing is to establish or verify the concentration of the pharmaceutical substance(s) in the compounded preparation.

Where possible, a validated stability-indicating assay method is described. Methods used generally include high-performance liquid chromatography or gas chromatography, among others. Other methods include titration and microbiological assays, which are sometimes used to test antibiotics.

The routine testing of each batch may not be feasible.

5.3 Compounding procedures

The monograph may contain a formula for the preparation which lists all of the ingredients and their quantities. Compounding procedures may include all of the steps necessary to accurately and reproducibly prepare the preparation.

5.4 Identification tests

The tests given in the identification section are not designed to give a full confirmation of the chemical structure or composition of the API(s) in the compounded preparation. They are intended to give confirmation, with an acceptable degree of assurance, that the API(s) in the compounded preparation is/are the one(s) stated on the label.

5.5 Specific tests

In addition, specific tests may be included, as appropriate. Examples are included in the following list, which is neither exhaustive nor comprehensive:

- pH;
- sterility;

- bacterial endotoxins;
- uniformity of dosage units;
- particulate matter;
- antimicrobial effectiveness;
- impurities or related substances;
- other tests, as appropriate.

5.6 Additional information

▪ *Packaging and storage information*

For containers and container-closure system materials it is preferable to reference pharmacopoeial monographs, if available. The container system is chosen to prevent contamination and minimize degradation.

Storage conditions, which are necessary to assure the quality of the product until the BUD, should be included.

▪ *Labelling information*

Pharmacopoeial labelling requirements are not comprehensive, and only those statements that are necessary to demonstrate compliance with the monograph are mandatory. National and international requirements for licensed products may not apply to compounded preparations and specific guidance on compounded preparations should be available.

5.7 Stability information and beyond-use dating for compounded preparations

Where specified in a monograph, BUDs should be assigned conservatively, taking note of the following:

- the nature of the medicine and its degradation mechanism;
- the dosage form and its components;
- the method of sterilization, if applicable;
- the potential for microbial proliferation in the preparation;
- the container in which it is packaged;
- the expected storage conditions;
- the intended duration of therapy.

When an authorized or licensed product is used as the source of the API for a compounded preparation, the compounder should refer to the manufacturer for stability information and to the literature for information on stability,

compatibility and degradation of ingredients as well as using his or her compounding education and experience.

Compounded preparations should be stored under conditions that prevent contamination and minimize degradation. The chemical, physical and microbiological stability until the BUD should be assured.

■ *Additional considerations*

For compounded preparations it is preferable to include a BUD based on laboratory-derived stability data in the pharmacopoeial monograph.

Susceptible preparations should contain suitable antimicrobial agents to protect against bacteria, yeast and mould contamination inadvertently introduced during or after the compounding process. When antimicrobial preservatives are contraindicated in susceptible compounded preparations intended for multiple use, storage of the preparation in a refrigerator is necessary and this should be stated in the monograph. Appropriate patient instruction and consultation is essential to ensure proper storage and handling of such compounded preparations by the patient or caregiver.

For sterile compounded preparations, it is preferable to include laboratory-derived stability and sterility information in pharmacopoeial monographs for such preparations. The laboratory-derived sterility information should evaluate the suitability of the sterilization method (for example, filtration, steam or dry heat) and container-closure integrity.

Annex 7

Good pharmacopoeial practices: Chapter on monographs on herbal medicines

Background

Following the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, the guidance on good pharmacopoeial practices (GPhP) was published as Annex 1 to the report.¹ The primary objective of the GPhP is to define approaches and policies in establishing pharmacopoeial standards with the ultimate goal of harmonization. In line with this objective, this guidance for monographs on herbal medicines has been developed outlining the structure and contents of a herbal medicine monograph.

1. Introduction

Pharmacopoeial monographs for herbal medicines should contain information in the definition that is consistent with the monograph title, followed by specifications for quality including identity, purity and content. Individual monographs describe test procedures, together with the corresponding specifications. The monograph may include:

- an official title;
- a definition;
- a production section;
- an identification section;
- a test section covering, for example, physicochemical tests and, where appropriate, tests on contaminants;
- an assay section on determining constituents with known therapeutic activity, active or analytical markers.

Further sections providing information on labelling and storage may also be provided.

¹ Good pharmacopoeial practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 1 (WHO Technical Report Series, No. 996).

2. General chapter

The general testing methods and other specifications that are common for herbal medicines may be described in a General chapter.

3. Individual monographs on herbal medicines

3.1 Monograph title

The title of the monograph may include the Latin name, or the well-established common local name and English common name. This may be followed by the name of relevant plant part(s) or plant material (e.g. resin, gum-resin) and, where applicable, its state and the type of herbal preparation (e.g. liquid extract, dry extract) and its dosage form (e.g. tablet, capsule or other form). Individual pharmacopoeias may apply their own nomenclature policies that meet regulatory needs and reflect the common names in commerce, as appropriate.

3.2 Definition

The definition provides details about the subject of the monograph and includes: the Latin binomial name and the taxonomic authority (abbreviations, if used, should be according to internationally accepted rules); the plant family name, if required by national legislation; the well-established common local name and English common name may be provided in addition to the scientific name, together with well-recognized synonyms. This section also provides details about the plant part(s) (i.e. aerial parts, root, leaves, flowers, rhizome, etc.), plant material (e.g. resin, gum-resin) and, where applicable, its state and the type of herbal preparation (e.g. liquid extract, dry extract) and its dosage form (tablet, capsule, etc.). When necessary, as dictated and supported by data, the definition also states the season or period in which plant material should be harvested according to *Good agricultural and collection practices (GACP) for medicinal plants*.² If more than one species is covered by the monograph, the definition should include, for each of the species, the requirements listed above. The definition should include the names and molecular formulae of relevant known constituents for which there is a specified range or minimum content, in percentages, usually calculated on the basis of the dry weight of the herbal medicine. Where a monograph applies to the herbal medicine in different states or stages of processing, this is stated in the definition.

² WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva: World Health Organization; 2003.

3.3 Identification

The purpose of the Identification section is to ensure that the herbal medicine under examination is the one stated on the label. It is only necessary to include those techniques that are applicable for the identification of specific herbal medicines. Macroscopic and microscopic descriptions may be supported by illustrations. Identification tests should be specific for the herbal medicine under examination. Typically, several identification tests, using independent approaches, are required in order to confirm the identity. The tests given in the Identification section are not designed to give a full confirmation of the chemical structure or composition of the herbal medicine. They are intended to give confirmation, with an acceptable degree of assurance, that it is the one stated on the label.

Test methods should be able to detect substitutes or adulterants that are likely to be found.

3.3.1 Macroscopic characteristics

The important macroscopic botanical characteristics of the herbal materials are specified to enable a clear identification. Where two or more species of a genus or subspecies are included in the definition, the differences, if any, between them should be indicated.

3.3.2 Microscopic characteristics

The microscopic examination of herbal materials is useful in determining their identity. Histological characteristics, such as microscopic characteristics of a transverse or longitudinal section may support the identification. For herbal materials for which macroscopic identification cannot be performed (for example, powdered herbal materials), the microscopic characteristics are important to determine their identity.

3.3.3 Chemical tests

Chemical tests can also be useful in determining the presence of substitution, adulteration or other foreign matter. Nonspecific chemical tests should be avoided. Phytochemical screening tests that recognize general classes of compounds such as alkaloids, flavonoids, terpenes, steroids, saponins and tannins, among others, should be avoided unless they provide a means of identifying potential adulteration due to species substitution or adulteration.

3.3.4 Fingerprinting

Chromatographic or spectroscopic patterns, often referred to as “fingerprints”, may be used for identification. The fingerprints should ideally be able to

distinguish the herbal material under examination from other species that constitute both intentional and unintentional adulterants.

Fingerprints may be obtained, for example, by thin-layer chromatography (TLC), high-performance thin-layer chromatography (HPTLC), high-performance liquid chromatography, ultra-high-performance liquid chromatography, capillary electrophoresis or gas chromatography methods. The methods should include all of the information required to perform the test, for example, preparation of sample and reference solutions, nature of plates or columns, testing conditions, mobile phase preparation, flow rate, and method of detection/detectors.

The results of such testing should contain a description of the critical features of the fingerprint chromatograms, such as the presence of specific peaks, bands or spots, retention time or relative retention values, retardation or retention factor (RF or Rf), their order of elution and, where applicable, their relative abundance. A colour image of a typical reproducible TLC fingerprint and/or table presentation may be provided as a guide for users. Pharmacopoeias may consider providing reference standards (RS) to be used for fingerprint testing.

3.3.5 DNA-based tests

DNA-based tests, such as polymerase chain reaction and DNA sequencing, can be useful in identifying specific herbal materials or detecting adulteration with either related or unrelated species that are difficult to detect using other methods.

3.4 Tests for contaminants/impurities

3.4.1 General

Tests for the following may be included and limits specified, as appropriate:

- foreign matter;
- elemental contaminants or impurities (for example, toxic metals such as lead, cadmium, mercury and arsenic);
- microbiological quality: individual pharmacopoeias may consider specifying requirements for total aerobic microbial count and total combined yeast/moulds count as well as for specified microorganisms, for example, bile-tolerant Gram-negative bacteria, *Escherichia coli* and *Salmonella*;
- mycotoxins;
- toxic and harmful substances (such as pesticide residues, radioactive contaminants and natural toxins);
- residual solvents.

3.4.2 Specific

An individual herbal medicine may require specifications that are peculiar to that item, especially when patient safety is an issue. Limits should be set for certain constituents of the herbal medicines that may be considered undesirable “negative markers”, negative botanical characteristics or histological parameters.

For some individual herbal medicines, there could be a risk of adulteration by herbal medicines that have a related morphological appearance or are marketed under similar common names. In such cases, additional tests may be specified, as appropriate, to detect and determine such adulterants. Where appropriate, tests for compounds that may affect the safety of the herbal medicines (such as alkaloids or cardiotoxic steroids, among others) may be included in the monograph.

3.5 Assay

Where the constituent(s) responsible for the therapeutic activity of the herbal medicine is/are known, its/their quantitative determination should be included. Where the chemical constituent(s) responsible for the known therapeutic activity is/are not known, the pharmacopoeia may include testing for determination of the chemical constituent(s) that act as analytical or active marker(s).

Where an assay of one or more chemical constituents is carried out, assay limits are specified for each constituent either as a minimum content or as a percentage content range. Where the herbal medicine contains constituents that are known to degrade (e.g. due to improper drying, storage under high temperatures or extended storage), those constituents may be used as analytical markers to control the quality of the herbal medicine.

Stability-indicating chromatographic procedures that are validated for routine quality control work should be used, where possible. Pharmacopoeial procedures should be validated in accordance with accepted scientific practice and current recommendations on analytical validation. Assay methods developed through a collaborative process involving several laboratories, or using other suitable approaches, may be adopted.

3.6 Physicochemical tests

Physicochemical tests can serve as a valuable source of information and provide appropriate characterization standards to establish the quality of herbal medicines. Such evaluations may include:

- water and/or alcohol extractable matter;
- total ash content;
- water-soluble ash;

- alcohol-soluble ash;
- acid-insoluble ash;
- loss on drying;
- water content;
- volatile oils, etc.

3.7 Other tests

The following tests may be included, as appropriate:

- swelling index;
- bitterness values;
- particle size;
- any other test(s) specific to the particular herbal medicine.

Reference to taste and/or odour in the definition or the test procedures may be inappropriate due to safety reasons and should be avoided.

3.8 Additional information

3.8.1 Packaging, labelling and storage

Labelling requirements consistent with applicable national or regional legislation may be provided. Storage conditions may be provided when considered necessary to prevent contamination and/or to minimize possible deterioration. Guidance statements specifying the packaging may be included, where applicable, for example, in monographs for oils or oleoresins or distilled oils.

3.8.2 Reference standards

Pharmacopoeias may describe the use of RS in the analysis of individual herbal medicines. RS may be pure substances or extracts of herbal materials or powdered herbal materials used for comparison. The RS established by individual pharmacopoeias are suitable for their intended purpose.

Glossary

To comply with national and regional legislation, the definitions given in the individual pharmacopoeias may deviate from those provided below.

Adulterant is herbal material, a herbal constituent or other substance that is either deliberately or non-intentionally (through cross-contamination or contamination) added to a herbal material, herbal preparation or finished herbal product.

Herbal dosage forms are the physical form (liquid, solid, semi-solid) of herbal products produced from herbs, with or without excipients, in a particular formulation (such as decoctions, tablets and ointments). They are produced either from herbal materials (such as dried roots or fresh juices) or herbal preparations (such as extracts).

Herbal medicines include herbs and/or herbal materials and/or herbal preparations and/or finished herbal products in a form suitable for administration to patients.

Note: In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g. animal and mineral materials, fungi, algae or lichens).

Herbs include crude plant materials such as leaves, flowers, fruit, seed, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.

Herbal materials³ include, in addition to herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries these materials may be processed by various local procedures, such as steaming, roasting or stir-baking with honey, alcoholic beverages or other plant materials.

Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials. They are produced by extraction, fractionation, purification, concentration or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey or in other materials.

Finished herbal products consist of one or more herbal preparations made from one or more herbs (i.e. from different herbal preparations made from the same plant as well as herbal preparations from different plants. Products containing different plant materials are called “mixture herbal products”).

Finished herbal products and mixture herbal products may contain excipients in addition to the active ingredients. However, finished products or mixture herbal products to which chemically defined active

³ The participants of the third WHO consultation on quality control, held in Hong Kong SAR, China, from 4 to 6 September 2017, recommended that latex and exudates can be included.

substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be “herbal”.

Medicinal plant materials: see Herbal materials

Medicinal plants are plants (wild or cultivated) used for medicinal purposes.

State of the herbal material means whole, fragmented, peeled, cut, fresh or dried.

Annex 8

Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

Background

The World Health Organization (WHO) published the first edition of the *WHO Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* in 2006 (1). After a revision, the second edition of the document was published in 2011 (2). Consideration of various comments and questions related to good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems led to the proposal to revise the document. After wide public consultation, and taking into account comments received, the document and comments were discussed during an informal consultation in Geneva in April 2017.

During this informal consultation the proposed changes based on comments received as well as additional suggestions made during the consultation, were discussed. It was agreed that the guidelines be amended to comprise two documents: one that would consist of guidelines containing recommendations for GMP for HVAC systems for non-sterile products and a second document that would contain examples and drawings that would clarify some of the recommendations made in the first document.

Therefore, the previous version of the *WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* as published in 2011 (2) should be amended according to these new guidelines.

Summary of main changes

In accordance with the recommendation made during the informal consultation in April 2017, the guidelines have been rewritten in two parts. The present document is the first part and contains the recommendations that are to be considered as good practices in design, management, control and qualification over the life cycle of HVAC systems.

The second part will contain non-binding examples, clarifications and drawings in support of the guidelines in the present document and is currently being drafted.

No summary of changes is provided here, as the content of the previous guidelines has been reorganized taking into account all the comments received during the last comment period.

The illustrative guidance and explanations (second part) will be published separately.

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1. Introduction

Heating, ventilation and air-conditioning (HVAC) play an important role in ensuring the manufacture of quality pharmaceutical products. The good manufacturing practice (GMP) requirements for the prevention of contamination and cross-contamination are an essential design consideration of an HVAC system. A well-designed HVAC system also provides for protection of the environment and the operators as well as comfortable working conditions.

These guidelines mainly focus on recommendations for HVAC systems used in facilities for the manufacture of non-sterile dosage forms, which include tablets, capsules, powders, liquids, creams and ointments. The general HVAC system design principles contained in these guidelines may, however, also be applied to other dosage forms.

HVAC system design influences architectural building design and layout, for example, with regard to airlock positions, doorways and lobbies. These in turn have an effect on room pressure, pressure differentials, pressure cascades, contamination and cross-contamination control. Therefore, the design of the HVAC system should be considered at the initial design stage of a pharmaceutical manufacturing plant.

Temperature, relative humidity and ventilation should be appropriate and should not adversely affect the quality of pharmaceutical products during their manufacture and storage, or the accurate functioning of equipment and instruments.

A comprehensive science- and risk-based approach should be followed throughout the life-cycle of an HVAC system, including its design, qualification and maintenance. Risk assessment is, however, not a substitute for GMP (3).

2. Scope

These guidelines focus primarily on GMP for the design, qualification, management and maintenance of HVAC systems in facilities for the manufacture of non-sterile dosage forms. They are intended to complement the guidelines on GMP for pharmaceutical products and should be read in conjunction with the parent guide. The additional standards addressed in these guidelines should therefore be considered supplementary to the general requirements set out in the main principles guide (4).

Most of the system principles described in these guidelines may also be considered in facilities manufacturing other dosage forms and products, and finishing processing steps for active pharmaceutical ingredients (APIs). Additional, specific requirements may apply for air-handling systems for pharmaceutical products containing hazardous substances, sterile products and

biological products. These are covered in separate WHO guidelines (3, 5) and working document WHO/BS/2015.2253, intended to replace (6), respectively.

3. Glossary

The definitions given below apply to terms used in this document. They may have different meanings in other contexts.

acceptance criteria. Numerical limits, ranges or other suitable measures for acceptance of test results.

action limit. The action limit is reached when the acceptance criteria of a critical parameter have been exceeded. Results outside these limits will require specified action and investigation.

air changes per hour. The flow rate of air supplied to a room, in m³/hour, divided by the room volume, in m³.

air-handling unit (AHU). The AHU serves to condition the air and provide the required airflow within a facility.

airflow protection booth. A booth or chamber, typically for purposes of carrying out sampling or weighing, in order to provide product containment and operator protection.

airlock. An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for and used by either people or goods (personnel airlock (PAL); material airlock (MAL)).

alert limit. The alert limit is reached when the normal operating range of a critical parameter has been exceeded, indicating that corrective measures may need to be taken to prevent the action limit being reached.

as-built. Condition where the installation is complete, with all services connected and functioning but with no production equipment, materials or personnel present.

at-rest. Condition where the installation is complete, with equipment installed and operating in a manner agreed upon by the customer and supplier, but with no personnel present.

central air-conditioning unit (see air-handling unit).

change control. A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state.

clean area (cleanroom). An area (or room or zone) with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation and retention of contaminants within the area.

clean-up (see **recovery**).

closed system. A system where the product or material is not exposed to the manufacturing environment.

commissioning. Commissioning is the documented process of verifying that the equipment and systems are installed according to specifications, placing the equipment into active service and verifying its proper action. Commissioning takes place at various stages during project construction but prior to validation.

containment. A process or device to contain product, dust or contaminants in one zone, preventing it from escaping to another zone.

contamination. The undesired introduction of impurities of a chemical or microbial nature, or of foreign matter, into or on to a starting material or intermediate, during production, sampling, packaging or repackaging, storage or transport.

controlled area (classified area). An area within the facility in which specific procedures and environmental parameters, including viable and non-viable particles, are defined, controlled and monitored to prevent degradation, contamination or cross-contamination of the product.

controlled not classified. An area where some environmental conditions or other attributes (such as temperature) are controlled, but the area has no cleanroom classification.

critical parameter or component. A processing parameter (such as temperature or relative humidity) that affects the quality of a product, or a component that may have a direct impact on the quality of the product.

critical quality attribute. A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or product during production.

cross-over bench. Cross-over or step-over bench in the changing room to demarcate the barrier between different garment change procedures.

design condition. Design condition relates to the specified range or accuracy of a controlled variable used by the designer as a basis for determining the performance requirements of an engineered system.

design qualification. The documented check of planning documents and technical specifications for design conformity with the process, manufacturing, good manufacturing practices and regulatory requirements.

differential pressure. The difference in pressure between two points, such as the pressure difference between an enclosed space and an independent reference point, or the pressure difference between two enclosed spaces.

direct impact system. A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with good engineering practice and, in addition, are subject to qualification practices.

exfiltration. The egress of air from a controlled area to an external zone.

extract air. Air leaving a space, which could be either return air or exhaust air. Return air refers to air that is returned to the air-handling unit and exhaust air is air that is vented to the atmosphere.

facility. The built environment within which the clean area installation and associated controlled environments operate together with their supporting infrastructure.

good engineering practice. Established engineering methods and standards that are applied throughout the project life cycle to deliver appropriate, cost-effective solutions.

hazardous substance or product. A product or substance that may present a substantial risk of injury to health or to the environment.

HEPA filter. High-efficiency particulate air filter.

HVAC. Heating, ventilation and air-conditioning. Also referred to as “environmental control systems”.

indirect impact system. A system that is not expected to have a direct impact on product quality, but typically will support a direct impact system. These systems are designed and commissioned according to good engineering practice only.

infiltration. Infiltration is the ingress of air from an external zone into a controlled area.

installation qualification. Documented verification that the premises, HVAC system, supporting utilities and equipment have been built and installed in compliance with their approved design specification.

ISO 14644. The International Standards Organization (ISO) has developed a set of standards for the classification and testing of cleanrooms. Where ISO 14644 is referenced it implies the latest revision and all its separate parts.

no-impact system. A system that will not have any impact, either directly or indirectly, on product quality. These systems are designed and commissioned according to good engineering practice only.

noncritical parameter or component. A processing parameter or component within a system whose operation, contact, data control, alarm or failure will have an indirect impact or no impact on the quality of the product.

normal operating range. The range that the manufacturer selects as the acceptable values for a parameter during normal operations. This range must be within the operating range.

operating limits. The minimum and/or maximum values that will ensure that product and safety requirements are met.

operating range. The range of validated critical parameters within which acceptable products can be manufactured.

operational condition. This condition relates to carrying out room classification tests with the normal production process with equipment in operation and the normal staff present in the specific room.

operational qualification. This is the documentary evidence to verify that the equipment operates in accordance with its design specifications within its normal operating range and performs as intended throughout all anticipated operating ranges.

oral solid dosage form. Usually refers to solid dosage forms of medicinal products such as tablets, capsules and powders to be taken orally.

pass-through hatch or pass box. A cabinet with two or more doors for passing equipment, material or product while maintaining the pressure cascade and segregation between two controlled zones. A passive pass-through hatch (PTH) has no air supply or air extraction. A dynamic PTH has an air supply into the chamber.

performance qualification. The documented verification that the process and/or the total process related to the system performs as intended throughout all anticipated operating ranges.

point extraction. Air extraction point located so that it effectively captures dust near its source.

pressure cascade. A process whereby air flows from one area, which is maintained at a higher pressure, to another area maintained at a lower pressure.

qualification. The planning, carrying out and recording of tests on equipment and a system, which forms part of the validated process, to demonstrate that it will perform as intended.

quality critical process parameter. A process parameter that could have an impact on the critical quality attribute.

recovery. Room recovery or clean-up tests are performed to determine whether the installation is capable of returning to a specified cleanliness level within a finite time, after being exposed briefly to a source of airborne particulate challenge.

relative humidity. The ratio of the actual water vapour pressure of the air to the saturated water vapour pressure of the air at the same temperature expressed as a percentage. More simply put, it is the ratio of the mass of moisture in the air, relative to the mass at 100% moisture saturation, at a given temperature.

standard operating procedure. An authorized written procedure, giving instructions for performing operations, not necessarily specific to a given product or material, but of a more general nature (for example operation of equipment, maintenance and cleaning, validation, cleaning of premises and environmental control, sampling and inspection). Certain standard operating procedures may be used to supplement product-specific master and batch production documentation.

turbulent air flow. Turbulent flow, or non-unidirectional airflow, is air distribution that is introduced into the controlled space and then mixes with room air by means of induction.

unidirectional airflow. A rectified airflow over the entire cross-sectional area of a clean zone with a steady velocity and approximately parallel streamlines (see also **turbulent air flow**). (Modern standards no longer refer to laminar flow, but have adopted the term unidirectional airflow.)

validation. The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results.

validation master plan. A high-level document that establishes an umbrella validation plan for the entire project and is used as guidance by the project team for resource and technical planning (also referred to as a master qualification plan).

4. Premises

- 4.1 The manufacture of non-sterile pharmaceutical products should take place in a controlled environment, as defined by the manufacturer.
- 4.2 The design of the HVAC system should be closely coordinated with the architectural design of the building.
- 4.3 Infiltration of unfiltered air into a manufacturing facility should be prevented as this can be a source of contamination.
- 4.4 Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to prevent the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the outside, special precautions should be taken to mitigate any risks (see (3)).
- 4.5 Areas for the manufacture of products, especially where materials and products are exposed to the environment, should be of an appropriate level of cleanliness. The level of air cleanliness for different areas should be determined according to, but not limited to, the products manufactured, the process used and the products' susceptibility to degradation.

Where a clean room classification is specified, the manufacturer should state whether the classification is rated for the “as-built”, “at-rest” or “operational” condition.

- 4.6 HVAC systems should ensure that the specified room conditions are attained, for example through heating, cooling, air filtration, air distribution, airflow rates and air exchange rates.

- 4.7 Any area where pharmaceutical starting materials, products, primary packing materials, utensils and equipment are exposed to the environment should have the same level of cleanliness or classification as the area in which the products are produced.
- 4.8 Appropriate design and controls for the premises and HVAC systems should be in place to achieve containment, cleanliness and the appropriate levels of protection of the product, personnel and the environment.

Note: For facilities where the highest level of containment is a requirement, refer to the guidance in *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (3).

- 4.9 Containment, cleanliness and protection may be facilitated through, for example:
- correct building layout;
 - building finishes;
 - the use of airlocks such as personnel airlocks (PAL) and/or material airlocks (MAL);
 - pass-through hatches (PTH);
 - change rooms and passages;
 - sufficient pressure differentials.
- 4.10 Detailed schematic diagrams should be maintained, indicating, for example, air supply and air return, room pressure differentials and airflow directions.
- 4.11 Where possible, personnel and materials should not move from a higher cleanliness zone to a lower cleanliness zone and back to a higher cleanliness zone. Where this is unavoidable, risks should be identified and controlled.
- 4.12 The final change room should be at the same cleanliness level (at rest) as the area into which it leads.
- 4.13 Where appropriate, such as where the simultaneous opening of airlock doors might lead to a cross-contamination risk, airlock doors should not be opened at the same time. In such cases, controls such as interlocking systems, warning systems and procedures should be implemented.
- 4.14 Swing doors should normally open to the high-pressure side and be provided with self-closers. Exceptions to the door swing direction should be justified and may include for fire escapes or other health and safety measures. In these cases, door closer mechanisms should be carefully controlled and other controls should be in place to prevent any risk.

- 4.15 Sampling, weighing and dispensing areas should be appropriately designed to provide the required levels of containment, operator protection and product protection.
- 4.16 Sampling, weighing and dispensing should be performed under the same environmental conditions as specified in the areas for the next stage of processing of the product.
- 4.17 Factors such as airflow should not disrupt the accuracy of balances.
- 4.18 The position of the operator, equipment and containers should not obstruct airflow patterns and result in risks.
- 4.19 Once an area is qualified with a specific layout for operators, equipment and processes, this configuration should be ensured during routine activity.
- 4.20 Return and exhaust filters and grilles selected and installed should be appropriate and their design should facilitate cleaning and maintenance.
- 4.21 The impact and risk to the HVAC system should be considered when changes are planned to an existing facility. This includes upgrades and retrofitting of facilities.

5. Design of HVAC systems and components

HVAC systems should be appropriately designed and managed throughout their life cycle. Documentation such as schematic drawings should be maintained to reflect the current situation.

- 5.1 Risk management principles should be applied for HVAC systems. This includes, but is not limited to, appropriate design, operation and monitoring, control of the climatic conditions and the prevention of contamination and cross-contamination.
- 5.2 The HVAC system capacity should be sufficient to ensure that the required performance is maintained during normal use by taking into consideration, for example, room leakage, duct leakage and filter conditions.
- 5.3 Materials for constructing the components of an HVAC system should not become a source of contamination.
- 5.4 Where possible, ducting, piping, fittings, sensors and other components should be clearly marked or labelled for ease of identification, indicating location and direction of flow as appropriate.

- 5.5 Air intake and exhaust air terminals should be positioned in a manner in relation to one another that assists in preventing cross-contamination.
- 5.6 Air-handling units (AHUs) should be provided with adequately designed drains to remove any condensate that may form in them.
- 5.7 Conditions and limits for parameters such as temperature, relative humidity and air cleanliness should be specified and achieved, as needed, for the materials and products handled, as well as for process risk.
- 5.8 Where appropriate, recovery rates should be specified and achieved to demonstrate that the HVAC system is capable of returning an area to a specified level of cleanliness or classification, temperature, relative humidity, room pressure and microbial limits within the specified time.
- 5.9 Failure mode and effect of critical components should be analysed. The analysis should include possible room pressure changes due to fan failure and possible impact of partial system shutdown on ease of opening doors for escape purposes.
- 5.10 The air distribution and airflow patterns should be appropriate and effective.
- 5.11 Air supply and extract grilles should be appropriately located to provide effective room flushing and to prevent zones of stagnant air.
- 5.12 The performance of HVAC systems should be controlled and monitored to ensure continuous compliance with defined parameters, and records should be maintained. Limits defined should be justified.
- 5.13 Where automated monitoring systems are used, these should be capable of indicating any out-of-limit condition by means of an alarm or similar system. Where these systems are identified as GXP systems, they should be appropriately validated.
- 5.14 Appropriate alarm systems should be in place to alert personnel in case of failure of a critical component of the system, for example, a fan.
- 5.15 The effect of fan failure on building and HVAC components should be assessed. Where appropriate, provision should be made for a fan interlock failure matrix.
- 5.16 Periodic switching off of AHUs, for example, overnight or at weekends, or reducing supply air volumes during non-production hours, should be avoided so that material or product quality is not compromised. Where

AHUs are switched off, there should be appropriate justification and no risk to materials or products. The procedure and its acceptability should be proven and documented.

- 5.17 Procedures should be in place and records maintained for the startup and shutdown sequence of AHUs.

6. Full fresh air systems and recirculation systems

- 6.1 Full fresh air or recirculation type HVAC systems may be used. Fresh air should be adequately filtered to remove contaminants. Where recirculation systems are used, there should be no risk of contamination or cross-contamination.
- 6.2 HEPA filters may be installed (in the supply air stream or return air stream) to remove contaminants and thus prevent cross-contamination. The HEPA filters in such an application should have an EN 1822 classification of at least H13 or equivalent.
- 6.3 HEPA filters may not be required to control cross-contamination where evidence that cross-contamination would not be possible has been obtained by other robust technical means, or where the air-handling system is serving a single product facility.
- 6.4 The amount of fresh air intake required should be determined. As a minimum, the following criteria should be considered:
- sufficient volume of fresh air to compensate for leakage from the facility and loss through exhaust air systems;
 - operator occupancy;
 - regional or national legislation.
- 6.5 Air that might be contaminated with organic solvents or highly hazardous materials should normally not be recirculated.
- 6.6 The need for and the degree of filtration of the exhaust air should be considered based on risk, exhaust air contaminants and local environmental regulations.
- 6.7 Where energy-recovery wheels are used in multiproduct facilities, controls should be in place to ensure that these do not become a source of cross-contamination.

7. Air filtration, airflow direction and pressure differentials

- 7.1 Where different products are manufactured at the same time, i.e. in different areas or rooms in a multiproduct manufacturing site, measures should be taken to ensure that dust cannot move from one room to another. Facility design and layout, appropriate levels of filtration, airflow direction and pressure differentials can assist in preventing cross-contamination.
- 7.2 Filters selected should be appropriate for their intended use and classified according to the current international classification system (see Table A8.1).
- 7.3 Airflow directions should be appropriate, taking operator and equipment locations into consideration.
- 7.4 The pressure differential between areas in a facility should be individually assessed according to the products handled and level of protection required. The pressure differential and the direction of airflow should be appropriate to the product and processing method used, and should also provide protection for the operator and the environment.
- 7.5 The pressure differential should be designed so that the direction of airflow is from the clean area, resulting in dust containment, for example, from the corridor to the cubicle.
- 7.6 The limits for the pressure differential between adjacent areas should be such that there is no risk of overlap in the defined dynamic operating ranges.
- 7.7 Normally, for rooms where dust is liberated, the corridor should be maintained at a higher pressure than the rooms and the rooms at a higher pressure than atmospheric pressure. (For negative pressure facilities refer to *WHO good practices for pharmaceutical products containing hazardous substances* (3), for guidelines and design conditions.)

Room pressure differential indication should be provided. This may be by pressure gauges or suitable electronic systems such as EMS or BMS. Where pressure indication gauges are provided, these should have a range and graduation scale that enables them to be read to an appropriate accuracy. The normal operating range, alert and action limits should be defined and displayed at the point of indication or EMS/BMS.

Room pressure should be traced back to representative ambient pressure (by summation of the room pressure differentials), in order to determine the actual absolute pressure in the room.

- 7.8 The pressure control and monitoring devices used should be calibrated. Compliance with specifications should be regularly verified and the results recorded.
- 7.9 Pressure control devices should be linked to an alarm system which is set according to the levels determined by a risk analysis and justified dead times.
- 7.10 Zero setting of gauges should be tamper proof. Zero setting should be checked at regular intervals.
- 7.11 Where airlocks are used, the pressure differentials selected should be appropriate. When selecting room pressure differentials, transient variations, such as machine extract systems and their impact, should be taken into consideration.

Table A8.1
Comparison of filter test standards – approximate equivalencies^a

Eurovent 4/5 rating	ASHRAE 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Average dust spot efficiency Em (%) (superseded)	EN 779 & EN 1822		ISO 29463
					MPPS integral overall efficiency (%)	EN rating	
(superseded)	Merv rating	Average arrestance Am (%) (superseded)	Average dust spot efficiency Em (%) (superseded)		99.999995	U17	75E
					99.999995	U16	65E
EU 14					99.9995	U15	55E
EU 13					99.995	H14	45E
EU 12					99.95	H13	35E
EU 11					99.5	E12	25E
EU 10					95	E11	15E
EU 9	Merv 16		>95		85	E10	
EU 9	Merv 15		95			F9	
EU 8	Merv 14		90			F8	
	Merv 13	>98	85			F7	
EU 7		>98	80				

Table A8.1 continued

Eurovent 4/5 rating (superseded)	ASHRAE 52.2 Merv rating	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1 Average airresistance Am (%) (superseded)	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1 Average dust spot efficiency Em (%) (superseded)	EN 779 & EN 1822		ISO 29463
				MPPS integral overall efficiency (%)	EN rating	
EU 6	Merv 12	>95	75		M6	EN 779: 2012
		>95	70			
	Merv 11	>95	65			
EU 5	Merv 10	>95	60		M5	EN 779: 2012
		>95	55			
	Merv 9	>95	50			
EU 4	Merv 8	>95	45		G4	EN 779: 2012
		>95	40			
	Merv 7	>90	35			
EU 3	Merv 6	>90	30		G3	EN 779: 2012
		90	25			
	Merv 5	85	20			
		80	<20			

Table A8.1 continued

Eurovent 4/5 rating (superseded)	ASHRAE 52.2	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	Eurovent 4/5 ASHRAE 52.1 BS6540 Part 1	EN 779 & EN 1822		ISO 29463	
				MPPS integral overall efficiency (%)	EN rating		
	Merv rating	Average arrestance Am (%) (superseded)	Average dust spot efficiency Em (%) (superseded)				
	Merv 4	75			EN 779: 2012		
EU 2	Merv 3	70				G2	
	Merv 2	65					
EU 1	Merv 1	<65			G1		

^a Ensure that the classification is current.

MPPS: most penetrating particle size.

Note: The filter classifications referred to above relate to the EN 1822:2009 and EN 779: 2012 test standards (EN 779 relates to filter classes G1 to F9 and EN 1822 relates to filter classes E10 to U17).

8. Temperature and relative humidity

- 8.1 Where appropriate, temperature and relative humidity should be controlled, monitored and recorded to ensure that the conditions are maintained pertinent to the materials and products as required, and provide a comfortable environment for the operators.
- 8.2 Limits for minimum and maximum room temperatures and relative humidity should be appropriate taking into consideration, for example, materials and products.
- 8.3 Where steam or humidity is present, controls should be in place to ensure that the HVAC system will remain effective. Precautions should be taken to prevent moisture migration that may increase an uncontrolled load on the HVAC system.

Where humidification or dehumidification is required, this should be achieved by appropriate means that will not become a source of contamination.
- 8.4 Dehumidification and cooling systems should be well drained. Condensate should not accumulate in air-handling systems and should not become a source of contamination.

9. Dust, vapour and fume control

The discharge location of dust, vapours and fumes should be carefully considered to prevent contamination and cross-contamination.

- 9.1 Dust, vapours and fumes could be sources of contamination and should be appropriately controlled. Wherever possible, they should be removed at source. The HVAC system should not normally serve as the primary mechanism of dust control.
- 9.2 Dust extraction systems should be appropriately designed and installed. Dust should not be able to flow back in the opposite direction, for example, in the event of component failure or airflow failure. The transfer velocity should be sufficient to ensure that dust is carried away and does not settle in the ducting.
- 9.3 The dust extraction points should be positioned in such a way as to prevent dust and powders dropping down from the extract point causing contamination or cross-contamination.

- 9.4 Air should not flow through the dust extraction ducting or return air ducting from the room with the higher pressure to the room with the lower pressure.
- 9.5 Periodic checks should be performed to ensure that there is no build-up of dust in the ducting.
- 9.6 Dust extraction systems should be interlocked, where appropriate, to the relevant AHU to avoid any risk or any impact on pressure cascade imbalances.

10. Protection of the environment

Where exhaust air from equipment such as fluid bed driers, dust extraction systems and facilities carries dust loads, adequate filtration or other control technology should be in place to prevent contamination of the ambient air.

- 10.1 Waste from dust extraction and collection systems should be disposed of in an appropriate manner.
- 10.2 Dust-slurry should be removed by suitable means, for example, a drainage system or waste removal contractor.

11. Commissioning

Note: Commissioning is a precursor to system qualification and validation, and is normally associated with good engineering practice (GEP).

12. Qualification

Note: For general notes on qualification and validation, see *WHO guidelines on validation* (7).

- 12.1 HVAC systems, including recirculation and full fresh air systems, should be qualified to ensure continued performance in accordance with specifications and achievement of the conditions as specified.
- 12.2 The scope and extent of qualification should be determined based on risk management principles.
- 12.3 The qualification of the HVAC system should be described in a master plan. The master plan should define the nature and extent of testing, the test procedures and protocols to be followed.

- 12.4 Where relevant, the procedures followed for conducting the tests should be in accordance with the appropriate parts of the standard as mentioned in ISO 14644 (8) and relevant WHO guidelines.
- 12.5 The design condition, operating ranges, alert and action limits should be defined. Alert limits should be based on system capability.
- 12.6 Performance parameters to be included in qualification of the HVAC system should be determined by means of a risk assessment.
- 12.7 Acceptable tolerances for system parameters, where appropriate, should be specified before commencing the physical installation.
- 12.8 There should be standard operating procedures describing the action to be taken when alert and action limits are reached. This may include, where relevant:
- temperature;
 - relative humidity;
 - supply air quantities;
 - return air or exhaust air quantities;
 - room air-change rates;
 - room pressures and pressure differentials;
 - airflow pattern tests;
 - unidirectional airflow velocities;
 - containment system velocities;
 - HEPA filter penetration tests;
 - room particle count tests;
 - duct leakage tests;
 - materials of construction;
 - microbiological counts;
 - de-dusting and dust extraction systems.
- 12.9 Where routine or periodic revalidation is done, the frequency should be established based on, for example, risk, the type of facility, the level of product protection necessary, performance of the system and the extent of routine ongoing monitoring activities.
- 12.10 Any change to the HVAC system should be handled according to a change control procedure. The extent of qualification or requalification should be decided based on the scope and impact of the change.

13. Maintenance

- 13.1 Operation and maintenance (O&M) manuals, procedures and records should be available and kept up to date with details of any system revisions made.
- 13.2 O&M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.
- 13.3 The O&M manuals may typically contain the following information:
 - system description;
 - operating instructions;
 - troubleshooting;
 - commissioning data;
 - maintenance instructions;
 - list of equipment suppliers;
 - spare parts list;
 - equipment data/capacity schedules;
 - supplier's literature;
 - control system description;
 - electrical drawings;
 - as-built drawings.
- 13.4 There should be a planned preventive maintenance programme for the HVAC system. The details of this programme should be commensurate with the criticality of the system and components.
- 13.5 Maintenance activities should not have any negative impact on product quality and should normally be scheduled to take place at appropriate times, for example, outside production hours.

In case of system stoppages, appropriate quality management system procedures should be followed. Where necessary, the root cause and impact should be assessed and appropriate corrective and preventive action taken. Where necessary, qualification or requalification should be considered.
- 13.6 HEPA filters should be changed by a competent person and this should be followed by installed filter leakage testing.
- 13.7 Records should be kept for a sufficient period of time.

References and further reading

References

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Further reading

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Annex 9

Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions

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Background

In recent years both formal and informal collaboration among national regulatory authorities (NRAs) has significantly improved. This, in turn, has strengthened medicines regulatory systems, thereby improving the availability of good quality, safe and effective medical products for patients. A number of regional and supraregional groupings of NRAs are developing, which will facilitate collaboration.

During a World Health Organization (WHO) training symposium on the subject of collaborative registration procedures for national medicines regulatory authorities held in Kenya in September 2016, delegates recommended that the gap in common guidance on best practice for performing desk assessment should be filled. It was proposed that WHO, in collaboration with regulators from Member States, develop guidance that NRAs might leverage in their national regulatory practice and decision-making.

Up to now, there has been no general guidance on approaches and best practices for desk assessment. Desk assessments are conducted in order to verify and confirm compliance with good manufacturing practices (GMP), good laboratory practices (GLP) and good clinical practices (GCP) of foreign facilities for manufacture of finished pharmaceutical products (FPPs) and active pharmaceutical ingredients (APIs), quality control laboratories (QCLs), contract research organizations (CROs) and clinical trial sites.

1. Introduction

NRAs worldwide use systems for the authorization and post-marketing surveillance of medical products that depend upon the assessment of submitted dossiers, variations files and the inspection of FPP and API manufacturers, QCLs and CROs involved in the development, manufacture and distribution of a medical product. Inspections are performed to verify dossier data and to provide evidence that the FPP and API manufacturers, QCLs, CROs and clinical trial sites comply with the relevant good practice (GxP) guidelines and requirements. Thereafter, routine inspections may be conducted depending on the risk rating of the facility.

The performance of on-site inspection of manufacturing, testing and clinical trials as well as the supply and distribution chain outside the NRA's domestic territory is a resource-intensive activity and one that often lies on the critical path to regulatory decision-making. Furthermore, the hosting of multiple regulatory inspections and audits is also a significant overhead for the sites inspected, which adds to the cost of producing the products. Even the best-resourced NRAs face certain limitations and therefore it is regulatory best

practice to use quality risk management when prioritizing inspection activities. To make the best use of the limited inspection resources and minimize the need for repeated inspections, it is good practice for national authorities to leverage available and reliable evidence of compliance and noncompliance with good practice requirements as part of their risk-based inspection planning process, such that there is no on-site inspection without good cause.

Verification and confirmation of compliance with GMP by a manufacturer of an FPP or API in a foreign country may be based on the assessment of evidence that includes the report of a recent inspection of the manufacturer by a competent regulatory authority or another internationally recognized organization.

One element of this risk-based approach is the desk assessment of inspection information from reliable and trusted sources by national or regional authorities in order to decide whether to perform a further inspection before reaching a final decision on marketing authorization, renewal of marketing authorization or another regulatory action. Whereas a desk assessment for GMP and GCP verification and confirmation has been a method used by some organizations and agencies like the WHO Prequalification Team (1), European Member States Agencies (coordinated by the European Medicines Agency (EMA) for centralized marketing authorizations) (2) and the Australian Therapeutic Goods Administration (TGA) (3) for some years, for others it is emerging as an option to be considered.

Such agencies have relied on regulatory decisions made by other agencies, based on bilateral or multilateral agreements depending on the decisions made independently by each individual authority. While not a prerequisite, a range of international and regional formal agreements may be utilized to facilitate the effective management of regulatory decisions in order to increase access to good quality, safe and effective products on the market. These include mutual recognition agreements (MRAs), cooperation agreements (CAs) and memoranda of understanding (MoUs).

Mutual recognition works well if there are common technical standards (including documentation), good regulatory practices; clear procedural legislation in the form of agreement-tracking tools to support the process, trust and political will, with no interference in technical decisions. On the other hand, CAs or MoUs are an option where there is minimal legal obligation. It is also possible to perform desk assessments without a formal agreement.

A desk assessment may be used by an NRA to assess compliance with GMP, GLP and GCP by facilities that manufacture FPPs and APIs. It can also be used to assess CROs, clinical trial sites and outsourced QCLs, where there is an established MRA, CA or MoU, or recognition of a decision made by a competent regulatory authority; Pharmaceutical Inspection Co-operation Scheme (PIC/S) member; or through a WHO prequalification process.

The procedure for the desk assessment will depend on whether the facility was previously inspected by a competent regulatory authority, PIC/S member or under the WHO prequalification scheme, or if an MRA, CA or MoU exists.

The desk assessment process involves submission of documentary evidence by the applicant, usually a manufacturer or representative, to the NRA to demonstrate the conformity of all sites involved in FPP or API manufacturing, or of an outsourced QCL, CRO or clinical trial site to GMP (the reference is added in the relevant citation), GLP or GCP, respectively. The evidence provided is assessed to determine the level of compliance based on the accepted standards and the scope of the application. The outcome of the assessment process is used as the basis for a regulatory decision that serves as a prerequisite for granting the marketing authorization for a medical product.

Acceptance of data from clinical trial(s) to support a marketing authorization application will rely upon conformance with GCP, including review and approval by an institutional ethics committee where the study was conducted and on obtaining and documenting informed consent of the study subjects if applicable (4).

The option to undertake a desk assessment does not preclude an on-site inspection if the outcome of the assessment does not confirm compliance with the stipulated practices. The confirmation may be granted for a specified period and the process may be subject to recovery of costs. It is important to determine the number of times a desk assessment may be performed before it becomes necessary to conduct a physical inspection, taking into consideration the outcome of the desk assessment, i.e. the number, nature and impact of observations and the integrity of the data provided.

2. Aim and objectives of the guidance

This guidance aims at providing an approach for use by NRAs for assessing compliance with GMP, GLP or GCP using documentation issued by other NRAs in lieu of conducting an inspection of a specific site.

The use of the desk assessment as described in this guidance is intended to provide a way to reduce the necessity for duplication and the frequency of inspections while relying on authentic and reliable documentary evidence from other regulatory authorities. Desk assessment should also reduce the inspection resources needed by both the manufacturing site and the NRAs and result in broader availability of high-quality medicinal products to patients globally. It may also be used by NRAs for continuous evidence-based regulatory decisions and follow-up on quality assurance issues that go beyond marketing authorization.

The guidance also lists the key documents to be submitted by other regulatory authorities and/or manufacturers that provide reliable information about the status of compliance with good practices in manufacturing, quality control and clinical trials of a specified medical product. The essential information and documents that need to be available to conduct the desk assessment in relation to the most relevant GxPs, in this context GMP, GLP and GCP, are described.

The objective of this guidance is to:

- ensure that a standardized procedure is followed for desk assessment of inspection documentation and reports issued by trusted, competent regulatory authorities and of records of corrective actions from inspected sites;
- facilitate a convergent approach and model for exchange and use of inspection information in national and regional decision-making concerning the necessity to perform preapproval and surveillance inspections.

3. Scope of the guidance

This guidance applies to all FPP and API manufacturers (including biologicals and vaccines manufacturers, all sites where APIs are being imported, repackaged or relabelled, and investigational medical product manufacturers), outsourced QCLs, CROs and clinical trial sites that are subjected to GxP inspections in foreign countries. However, the NRA may use desk assessments to set up risk-based inspection plans without loss of regulatory oversight through physical inspections.

The guidance has general geographical applicability for regulatory authorities and United Nations agencies in order to support ongoing harmonization initiatives and optimum use of limited resources. It covers the information and evidence required to undertake a desk assessment process, but not the procedure for on-site inspection, except the process of tracking and review of completion of corrective and preventive action (CAPA). On-site inspection is covered in a separate WHO guidance document (5, 6).

Desk assessment procedures can be used for preapproval, renewal and surveillance inspections. Caution is needed when assessing sites that have failed to meet the specified standard after GxP inspections. However, desk assessments may be appropriate for a site that has failed an inspection, in order to confirm the failure and thus avoid the need for a physical inspection. The NRA takes the ultimate decision on whether it is appropriate to perform a desk review or whether an on-site inspection would be needed.

4. Glossary

The definitions given below apply to the terms used in this guidance. They may have different meanings in other contexts.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

agent or local technical representative. Every applicant who is not resident in the country of the national regulatory authority (NRA) should appoint a person in that country to be an agent (local technical representative). The appointment should be notified to the NRA by submitting a letter of appointment supported by powers of attorney duly notarized in the country of origin, and registered with the registrar of companies in the country of the NRA.

applicant. A person who applies for marketing authorization of a medical product to the national regulatory authority, who must be the owner of the product. The applicant may be a manufacturer or the party applying for a product certificate. After the product is registered, the applicant becomes the marketing authorization holder.

bioequivalence. Two medical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailability, in terms of rate (C_{\max} and t_{\max}) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

clinical trial (or clinical study). Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamics effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

competent regulatory authority. Any organization that has a legal authority or power to perform a designated regulatory function for authorization of a medical product: the national regulatory authority in the Member State.

cooperation agreement. A formal business document outlining the basic terms of an agreement with another individual, group or entity. It is one of the first steps towards a more detailed contract. Alternative names include, but are not limited to, memorandum of understanding, cooperation contract or collaboration agreement.

desk assessment. The evaluation of documentary evidence by a competent regulatory authority recognized by the national regulatory authority, for compliance with the required good practices (good manufacturing practices (GMP), good laboratory practices and good clinical practices) in support of marketing authorization and other regulatory decisions. Desk assessment may be performed in support of a new marketing authorization, or for routine GMP inspection (including in the frame of specified product(s) life-cycle management as required).

finished pharmaceutical product. A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

good clinical practices. In this context the term means a standard for design, conduct, performance, monitoring, auditing, recording, analysis and reporting of clinical trials in a way that provides assurance that the data and reported results are credible, accurate and that the rights, safety and well-being of trial subjects are protected.

good laboratory practices. A quality system concerned with the organizational process and the conditions under which nonclinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.

good manufacturing practices (GMP). That part of quality management which ensures that products are consistently produced and controlled according to the quality standards appropriate to their intended use and as required by the marketing authorization, clinical trial authorization or product specification. GMP are concerned with both production and quality control. GMP are aimed primarily at managing and minimizing the risks inherent in pharmaceutical manufacture to ensure the quality, safety and efficacy of products.

information sharing. An exchange of data between individuals or entities outside the traditional organizational boundaries, to achieve a common goal in terms of better policies and to deliver better services. This may mean that one party is disclosing information while the other is collecting the information or both parties are mutually disclosing and collecting information.

manufacture. All operations of purchase of materials and products, production, quality control, release, storage, distribution of medical products and the related controls.

manufacturer. A manufacturer is a natural or legal person who holds a manufacturing authorization and has responsibility for manufacturing of a medical product or active pharmaceutical ingredient.

marketing authorization (product licence, registration certificate). A legal document issued by the competent regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or

other recognized specifications of its ingredients and of the final product itself and includes details of packaging, labelling and shelf life.

medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

memorandum of understanding (MoU). A formal agreement between two or more parties. Companies and organizations can use MoUs to establish official partnerships. MoUs are not legally binding but they carry a degree of seriousness and mutual respect, stronger than a gentlemen's agreement.

mutual recognition agreement. This is defined as the reciprocal adoption or acceptance of regulatory decisions or outcomes in other partner states in form of a legal agreement. It is stronger than a gentlemen's agreement and is usually binding.

Pharmaceutical Inspection Co-operation Scheme (PIC/S). This is a non-binding, informal cooperative arrangement between regulatory authorities in the field of good manufacturing practices of medical products for human or veterinary use.

pharmaceutical product. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

quality control. All measures taken, including the setting of specifications, sampling, testing and analytical clearance, to ensure that raw materials, intermediates, packaging materials and finished pharmaceutical products conform with established specifications for identity, strength, purity and other characteristics

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes and resources, and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality system. The sum of all features that are necessary to implement an organization's quality policy and meet quality objectives. It includes organizational structure, responsibilities, procedures, systems, processes and resources. Typically these features will be addressed in different kinds of documents, such as the quality manual and documented procedures.

5. Essential elements of desk assessment

5.1 High-level support and cooperation

Interagency communication can facilitate greater regulatory convergence. This in turn can increase the efficiency and quality of medical product development

and the NRA review processes as well as improving patients' access to quality medical products. This not only entails accessing information from the public websites of other NRAs, such as guidelines, decisions and product recalls, but also actively sharing information between NRAs, in particular with respect to inspection findings during application review and for decision-making.

The legal framework and governance structure of the NRA should include provisions on support and collaboration with other agencies in making regulatory decisions. Legal provisions (laws and regulations) that allow reliance on foreign NRA inspections and enforcement actions based on well-defined criteria should be established and implemented. Such recognition can take the form of MRAs, CAs or MoUs between collaborating inspectorates and could entail agreements that would enable bilateral or multilateral commitment and exchange of information on specified sites.

MRAs are usually binding and may require inspectorates at the same level of development with the appropriate organization and funding to fulfil the responsibility of protecting and promoting public health. Where such recognition exists, fewer requirements are needed to determine compliance with GMP, GLP and GCP of foreign manufacturing sites, CROs and outsourced QCLs, given the level of cooperation and trust established.

5.2 Commonality of quality management systems in inspectorates

There should be a quality system in place based on recognized international standards, namely the WHO quality management system (QMS) or International Organization for Standardization (ISO) QMS standards. The QMS should be established, implemented and maintained throughout the period of recognition or reliance. The primary purpose of a QMS is to ensure that adequate quality standards are maintained.

Adopting common standards for quality system requirements (within GMP, GLP or GCP of the NRA) helps to achieve consistency in inspection standards between inspectorates and thus facilitates mutual recognition and reliance.

5.3 Convergent standards of good practices

WHO has published standard requirements for compliance with GMP (7) and other good practices including *Good practices for pharmaceutical quality control laboratories* (8) and GCP (4, 9). These serve as a measure of the standards established by the manufacturers in order to deliver and supply a good quality and safe product. The NRA should have similar standards of GxP in order to facilitate uniform desk assessment.

5.4 Reliability and accuracy of information

Applicants are responsible for ensuring that information provided for desk assessment is reliable and not false or misleading.

Mechanisms and controls should be established to ensure that the information provided by the applicant is authentic, legible, current and accurate. There should be strong confidence that the information provided relates to the same strength and specifications of the product and to the same site, workshop or production line (use of unique facility identifiers should be considered); and should accurately relate to the product under assessment, without any false information.

Controls should be established and documented by the NRA to ensure that the information provided by the applicant is secured and remains confidential.

5.5 Management tools to support consistent and objective assessment

Well-structured and up-to-date assessment tools and procedures should be adopted to enable uniform and consistently objective assessment of the documents provided. Personnel involved in the assessment process should have an acceptable level of training and experience with GMP, GLP or GCP. They should also be trained to use the assessment tools and procedures consistently without bias, and to be able to detect inconsistent and inaccurate information regarding the product under assessment. Validated electronic assessment tools (software applications) may be used to perform the desk assessments. Although paper-based systems may also be used, electronic tools are preferred.

5.6 Risk-based assessment of available information

Even the best-resourced NRAs are subject to limitations in terms of time, funding and personnel, and therefore it is regulatory best practice to apply quality risk management as defined and outlined in ICH Q9: Quality risk management, in prioritizing inspection activities (10, 11). The aim of the desk assessment process should be to provide to the NRA, in a timely manner, the required assurance that the site in question demonstrates an acceptable level of GxP for the FPP, API or trial under assessment.

The assessment should take into consideration and focus on the critical products and critical processes in the manufacture of a specified product in relation to patient risk, based on the knowledge that other competent and trusted inspectorates have inspected and approved the site of manufacture.

Key factors to consider include the origin of the information and its authenticity, the location of the site of manufacture, complexity and type of the product (whether sterile or biological) and the risk to the patient (12).

5.7 Mutual trust and confidence among inspectorates

Joint inspections may be conducted by countries within the same region or countries that are party to a relevant agreement. Through such interactions, regulators may be able to build confidence, share information and experiences in order to be able to rely on others' inspection outcomes and regulatory decisions. Joint inspections also serve as a basis for desk assessments through building mutual trust and identifying barriers to reliance on other regulators' inspection outcomes and devising solutions to overcome them. Building mutual trust and confidence involves exchange of information, identifying areas of collaboration, work sharing and eventually binding through a legal agreement between collaborating NRAs.

Some competent NRAs are already using these models successfully. Examples include the United States of America (USA) Food and Drug Administration's MRA with the European Union, Health Canada's MRA with the European Union, and the TGA's risk-based desktop assessment process. The TGA's process comprises MRA and compliance verification pathways, which are essentially desk reviews. Those two pathways can result in cost savings for both the manufacturer, who does not have to bear the cost of hosting another inspection, and the regulator, who saves on personnel time and other resources.

5.8 Quality assurance of the desk assessment process

Quality assurance of the desk assessment process involves inspiring confidence that the requirements of the assessment process will be fulfilled. This would require documented evidence of compliance of the inspectorate function with a QMS¹ over a period of three to five years.

NRAs should create a cycle for the process of reviewing desk assessments, including timelines for applicants' responses.

5.9 Communication of assessment outcomes

Communication of the outcome of the desk assessment process should be transparent and timely. Communication should focus on the quality of the product and the regulatory decisions between the authorities in the importing country and exporting country, the manufacturers and any other relevant third party, such as procurement agencies. The outcome of the desk assessment should be communicated to the applicant whether the result is an approval, a deferment or a rejection of an application for GxP assessment, and to the responsible NRA.

¹ For example, ISO/International Electrotechnical Commission (IEC) 17020 *Conformity assessment – requirements for the operation of various types of bodies performing inspection*, PIC/S *Quality management system for inspectorates* or ICH Q9 *Quality risk management*.

If a rejection leads to a regulatory decision to conduct an on-site inspection, a statement of the reasons should be provided, with details of the documents, information and regulatory requirements taken into account in reaching the decision. An appeal mechanism, including a time frame within which applicants may lodge an appeal, should also be in place. The NRA should reserve the right to conduct an inspection of any site.

6. Sources of good information and related challenges

Trusted sources of information are available either in the public domain or from the NRAs. The amount of detail provided in the information may vary depending on applicable restrictions and rights of the owners. Websites of NRAs may provide information on non-compliant facilities, market complaints and product recalls, among others.

Certificates, reports or other documents issued by competent regulatory authorities also provide information about a specified manufacturer, outsourced QCL, CRO or clinical trial site.

6.1 Official websites with databases

NRAs and organizations such as WHO and EMA have websites where information on facilities' compliance and noncompliance with GxP is available. Some websites provide GMP certificates and inspection reports together with other information about medicines, pharmaceutical manufacturing facilities, QCLs and clinical trials. Information may also be obtained on medicine sampling and results of the testing, including samples that failed analysis, product recalls and rapid alerts. The website consulted should be current and regularly updated. Certificates presented by applicants for marketing authorization should be verified using the information available on the websites of NRAs or by contacting the relevant NRA directly. The NRA is responsible for checking that information is current and complete.

6.2 Authenticity of documents

It is important that documentary evidence provided by the applicant as the basis for granting approval for GMP, GLP or GCP be current, accurate and authentic. It is the responsibility of the applicant to ensure this. The applicant should include a cover letter with the application stating that all the documents submitted are authentic and correct. NRAs may request that information such as inspection reports and certificates granted by NRAs be notarized or certified.

Submission of inaccurate or false information may result in declaration of the manufacturer, QCL or CRO as noncompliant.

6.3 Failure to submit documentary evidence

If the applicant is unable to provide adequate documentary evidence, including information on current compliance, or to submit the documents before a specified deadline, or fails to submit documents as required, the application for desk assessment may be rejected, leading to a decision to conduct an on-site inspection. In such circumstances, approval of GMP, GLP or GCP should only be granted after the on-site inspection has been conducted, and the manufacturer, CRO, clinical trial site or outsourced QCL has been found compliant.

7. Submission and assessment of documentary evidence and information

7.1 Submission of application for desk assessment and documentary evidence

Prior to assessment, an application for desk assessment for each site should be submitted by the applicant to the NRA. Applications may be required for preapproval, renewals and surveillance inspections, as specified by the NRAs in the respective inspection guidelines and procedures.

7.2 Assessment of documentary evidence and information

Desk assessment involves a detailed evaluation of the specified documentary evidence supplied by the applicant. It will include an assessment of reports of recent inspections of the relevant manufacturing site undertaken by a competent regulatory authority, together with other available regulatory information. Desk assessment for compliance of facilities manufacturing FPPs and APIs with GMP, GLP or GCP can be used where the NRA has an agreement or understanding on exchange of information, such as an MRA, CA or MoU.

In accordance with international agreements with certain countries, the NRA may accept compliance of a foreign site with GMP, GLP or GCP requirements based on a current certificate or approval letter issued by the regulatory agency of the other party to the MRA.

Marketing authorization may be granted by the NRA on the basis of a current certificate or approval letter issued within the scope of an MRA. The scope of the manufacturing activities indicated in the application should be within the scope of the activities covered by the certificate or approval letter.

Generally, where an MRA has been established:

- a. a copy of the manufacturing authorization granted by national authorities together with a certified translation, where this is not in English, may suffice.

Where a CA or other bilateral or multilateral arrangement has been established, the document specified in a. above should be provided in addition to the following essential documents:

- b. a site master file (13) whose approval date was not more than one year ago, and any forecast modifications, together with legible colour printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2 format;
- c. a list of all the products and dosage forms manufactured on-site. The list should include proprietary names and International Nonproprietary Names (INN);
- d. a copy of the last inspection report issued by the NRA with a certified translated copy where this is not in English, and GMP, GLP or GCP certificates or an approval letter with a certified translated copy where this is not in English (production-line specific);
- e. current full inspection report(s) for inspections performed by a competent regulatory authority in the past three to five years, with a certified translated copy where this is not in English;
- f. proof of CAPA implementation and final decision by the NRA related to observations or deficiencies noted in the latest inspection report or any warning letter or equivalent regulatory action (production-line specific);
- g. the most recent product quality review(s) (PQR)(s) of the concerned product(s); PQR(s) (4) or equivalent documentation covering all required subsections and trend results should be presented; proprietary information for vaccines is not required;
- h. the completed batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant product(s);
- i. a list of any recalls in the past three years related to products with quality defects.

The following documents may be evaluated while performing desk assessments:

- a confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product(s) has been performed and all matters dealt with;
- master batch manufacturing and packaging record(s) of the product(s) of interest;

- a copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product;
- out-of-stock situations.

The evidence lists required for desk assessment of compliance with GMP, GLP or GCP for each type of facility and collaborative arrangement are listed in Table A9.1 and the specific documentary evidence required is presented in Table A9.2.

Table A9.1

Type of facility and evidence documents required for desk assessment^a

Type of facility	Where an MRA exists	Where a CA or MoU exists; or member of PIC/S; or competent NRA regulator; or WHO prequalification scheme	Where no MRA, CA or MoU exists; or non-member of PIC/S; or WHO prequalification scheme
Nonsterile products facilities <ul style="list-style-type: none"> • FPP • API 	Evidence list A	Evidence list B	On-site GMP inspection
Sterile products facilities <ul style="list-style-type: none"> • FPP • API 	Evidence list A and certification to relevant ISO standards for sterilization facility ^b	Evidence lists B and C	On-site GMP inspection
Outsourced (contract) testing laboratory; and outsourced sterilization	Evidence list A	Evidence list D	On-site laboratory inspection On-site GMP inspection

Table A9.1 *continued*

Type of facility	Where an MRA exists	Where a CA or MoU exists; or member of PIC/S; or competent NRA regulator; or WHO prequalification scheme	Where no MRA, CA or MoU exists; or non-member of PIC/S; or WHO prequalification scheme
CRO or clinical trial site <ul style="list-style-type: none"> • clinical facility • clinical laboratory • bioanalytical laboratory • company performing pharmacokinetics statistical analysis 	Evidence list E	Evidence lists E and F	On-site GLP or GCP inspection

API: active pharmaceutical ingredient; CA: cooperation agreement; CRO: contract research organization; FPP: finished pharmaceutical product; GCP: good clinical practices; GLP: good laboratory practices; GMP: good manufacturing practices; ISO: International Organization for Standardization; MoU: memorandum of understanding; MRA: mutual recognition agreement; NRA: national regulatory authority; PIC/S: Pharmaceutical Inspection Co-operation Scheme.

^a Explanations of the evidence lists are provided in Table A9.2.

^b If applicable to the manufacturing facility or activity.

A list of the documents that should be provided for desk assessment is given in Table A9.2. The documents required for desk assessment of manufacturing sites are indicated in evidence lists A, B, C and D; for outsourced QCL, they are indicated in evidence lists A and D and for CROs and clinical trial sites, they are indicated in evidence lists E and F.

Table A9.2

Documentary evidence requirements for desk assessment

	Required evidence	Comments and exceptions
Evidence list A	Current GMP certificate or approval letter GLP or ISO/IEC 17025 certification for outsourced laboratory	Certificates must be sufficient to cover the scope of the GMP compliance application

Table A9.2 *continued*

	Required evidence	Comments and exceptions
Evidence list B	Current GMP certificate or approval letter	GMP agreements may be requested if the foreign manufacturer performs the release for supply function
	Current manufacturing licence	The manufacturing licence should show the scope of products and activities approved by the NRA
	Regulatory inspections conducted within the past three years and a copy of the most recent inspection report issued by the competent regulatory authorities as stated in Table A9.1	A list of all inspection reports applicable to the scope of the application is required. These may be sent to the NRA directly from the manufacturer CAPA evaluation for the recent inspection report should be provided
	Market complaints register	For the previous three years, including one investigation report for one of the complaints classified as high risk to public health The complaint register should be applicable to the products named in the application
	Details of any regulatory actions in the past three years	For example, product alerts, warning letters, import alerts, recalls due to defects
	Site master file, quality manual or equivalent	Site master file ^a Site master file is not required if the scope of the application is only for the step of release for supply
	List of products intended for supply in the recipient country	

Table A9.2 *continued*

	Required evidence	Comments and exceptions
	<ul style="list-style-type: none"> • PQR report; • process validation report; and • batch records (batch manufacturing, packaging and testing) for each product for which marketing authorization is being applied 	<p>The PQR reports should be provided for each product. If there are multiple products, one PQR report is required for each FPP dosage form for which an application is being made</p> <p>The batch records of a product for each FPP dosage form manufactured in the past 6 to 12 months; and the corresponding process validation reports and annual product quality review reports</p>
	List of reprocessed or reworked product batches in last year (or last two years)	
Evidence list C	Validation master plan	Not required if the scope of the application is only for the step of release for supply
	Aseptic processing and filling validation reports if applicable	Required if the application concerns products that are not terminally sterilized
Evidence list D	Current GMP certificate, or ISO/IEC accreditation certificate or WHO prequalification	<p>For outsourced testing laboratories, a GLP certificate issued by a recognized regulatory authority or a current ISO/IEC 17025 accreditation certificate or prequalification of the laboratory by WHO is required</p> <p>For outsourced sterilization facilities, certification to applicable ISO sterilization standards (e.g. ISO 11137, ISO 11135) is necessary</p>

Table A9.2 *continued*

	Required evidence	Comments and exceptions
	Quality manual, laboratory manual or equivalent	The quality manual or laboratory manual should be written in accordance with the principles of <i>WHO good practices for pharmaceutical quality control laboratories</i> (8), or as per the <i>ISO/IEC 17025 General requirements for the competence of testing and calibration laboratories</i> (14).
	Contract or agreement between the FPP or API manufacturer and the outsourced testing laboratory or sterilization institution	A copy of the contract or agreement clearly describing the roles and responsibilities of the manufacturer and the testing laboratory or sterilization institution should be submitted
	A list of tests a laboratory is authorized to perform as per the scope of its accreditation according to the ISO/IEC 17025 or WHO prequalification For botanical ingredients, evidence that authenticated standard reference materials are used	The scope of activities of the outsourced laboratory should include the type, range and volume of testing and/or calibration, validation and verification activities it undertakes
	Out-of-specifications (OOS) procedure	Records of three OOS including at least one assigned to a laboratory error
Evidence list E	Current GCP or GLP certificate or approval letter	GCP/GLP certificate or approval letter issued by the NRA; non-use of disbarred investigators or firms

Table A9.2 *continued*

	Required evidence	Comments and exceptions
Evidence list F	Clinical trial approval by the NRA	<p>Provide a list summarizing the approved trials and their outcome</p> <p>Provide complete study report if no application has been submitted for marketing authorization of a product</p> <p>Where applicable, reports from a data safety monitoring board or independent safety monitors should be provided</p>
	Copy of IRB/IEC clinical trial approval	<p>Provide approved protocol, amended protocol and consent form</p> <p>Provide a list of committee members of the IRB/IEC</p>
	Clinical trial master file	<p>Responsibilities of the sponsor and clinical investigator should be reported</p> <p>Records of management and assessment of subcontracted vendors should be provided</p> <p>Deviation management and procedures for handling the investigational product should be made available</p>
	Inspections conducted within the past three years and a copy of the most recent inspection report issued by the competent regulatory authority as stated in Table A9.1	<p>A list of all inspection reports applicable to the scope of the application is required. These may be sent to the NRA directly from the manufacturer or CRO</p> <p>Provide the following reports:</p> <ul style="list-style-type: none"> • reports by the NRA; • clinical monitoring reports by the sponsor or the CRO (if monitoring tasks were outsourced to a CRO)

Table A9.2 *continued*

Required evidence	Comments and exceptions
Concerns or alerts raised by the NRA and any other responsible authority	Provide details of investigation of any instances of noncompliance and how they were addressed

API: active pharmaceutical ingredient; CAPA: corrective and preventive action; CRO: contract research organization; FPP: finished pharmaceutical product; GLP: good laboratory practices; GMP: good manufacturing practices; IEC: independent ethics committee; IRB: institutional review board; ISO: International Organization for Standardization; NRA: national regulatory authority; PQR: product quality review.

^a Refer to WHO Technical Report Series, No. 961, Annex 14, for guidelines on compiling a site master file (13).

7.3 General requirements for documents

Documents to be submitted to NRAs as evidence of compliance should adhere to the following general requirements.

- All certificates and other supporting documents should be in English or in a nationally accepted language.
- Where the document is not in English or a nationally accepted language, it should be submitted with a certified translation.
- Translated documents must be accompanied by a signed and dated statement by the certified translator, stating that each is a true and accurate translation of the original document.
- Submitted documents should be the most recent and reflect current activities and practices, and dated (expired or superseded documentation cannot be used).
- Documents must provide sufficient information to cover the scope of activities for which confirmation of GxP compliance is sought.

All documents, whether the original format is paper or electronic, are to be submitted electronically (for example as DVDs CDs, etc.) and are not required to be certified as original copies unless requested by the NRA. Certification of a document may be requested if, for example, there is concern over the validity of the supplied documents. The NRA can request certified copies of original documents at any time. Certified copies must be legible and authenticated as true copies by either:

- an official of the regulatory agency of a country that is a party to an MRA, or a partner to an MoU or a CA, WHO prequalification, stringent regulatory authority, regulator; or

- a public notary (who must include details of the relevant practice certificate or licence number).

Figure A9.1

Model declaration form for the front page of a certified document

Declaration of authenticity

I, the undersigned, as a _____ for the state of _____, country _____

declare that the attached copy of the document issued by _____ and certified by me, is a true and accurate copy of an original document presented to me for certification.

_____ Date: ____/____/____
Full names [signature] day/month/year

8. Regulatory actions and reporting of serious instances of noncompliance

Regulatory actions should be taken by NRAs in response to the reporting of serious instances of noncompliance, such as a variation from the registered product that has a direct impact on the safety of a patient or subject, and follow applicable procedures for appropriate investigations.

The impact of the noncompliance should be assessed by the NRA to ascertain the potential risk to public health, supply and availability of affected medicines. This assessment should take into consideration the risk of exposure to national shortages having undesirable safety and financial implications.

The following are some of the actions that can be taken by the NRA in response to confirmed reports of serious noncompliance:

- issuance of a rapid public alert to collaborating partners;
- issuance of a noncompliance letter;
- suspension, revocation, withdrawal or cancellation of GMP, GLP or GCP certificate;
- suspension of certificate of suitability;
- institution of a recall;
- suspension of supply or importation;
- prosecution.

8.1 Communication and information exchange

There should be a mechanism for exchange of information among inspectorates, for example, a shared web-based portal for communication of serious instances of noncompliance in a timely and secure manner. The NRA should have a process for information exchange and use of identifiers for tracking enquiries and applicants' responses.

If facilities are found to have serious issues of noncompliance with GMP, GLP or GCP guidelines, this should be communicated to stakeholders and partners. The regulatory decision and action taken should be explained to the stakeholders, including the analysis of the risk and threats to the patient.

9. Responsibilities of the applicant

The main responsibilities of an applicant for GMP, GLP or GCP desk assessment are summarized below.

- Ensuring that all required evidence documents are submitted with applications for GMP, GLP or GCP desk assessment. Incomplete applications may be rejected.
- Remitting all application fees at the time of lodging an application for GMP, GLP or GCP desk assessment.
- Submitting applications for renewal of a GMP, GLP or GCP certificate prior to the expiry of the current certificate, according to a deadline specified by the NRA.
- Promptly submitting any additional information that may be requested by the NRA during an assessment. Failure to provide required documents in time may result in the application being rejected.

References and further reading

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Further reading

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Appendix 1

Model report format for desk assessment for finished pharmaceutical products and active pharmaceutical ingredient manufacturers

Part 1. General information		
a)	Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, fax, email address
b)	Particulars of the manufacturer	Name of manufacturer, physical address of manufacturer including the block and/or unit number, postal address of manufacturer (if different from physical address), 24-hour telephone number(s), fax, email address, contact person
c)	Activities performed on the site	For example, manufacture of APIs, manufacture of FPPs, intermediates or bulk packaging, laboratory testing, batch release, warehousing, primary and secondary packaging
d)	Date of last inspection by the NRA	Date when the last inspection was carried out, name of the national medicines regulatory authority that carried out the inspection
e)	Production and packaging lines applied for	For FPP: dosage form line, category: beta lactam, non-beta lactam, biologicals, vaccines, hormones, cytotoxic products For API: name of API
f)	Authorized representative of marketing authorization holder in the recipient country	For example, representative, agent

Table continued

Part 2. Documentary evidence (comment on adequacy of information provided)		
a)	Current site master file	Comment on date, completeness and adequacy in accordance with WHO or PIC/S guidelines for writing site master file
b)	List of all regulatory inspections carried out in the past three years	Name of all the regulatory authorities that carried out the inspection, dates when the inspection was carried out, inspection outcome
c)	Copy of valid manufacturing licence granted by the NRA together with a certified translation, if not in English	Number of manufacturing licence, name of regulatory authority that granted the licence, validity of the manufacturing licence and scope
d)	Copy of valid GMP certificate granted by the national medicines regulatory authority together with a certified translation, if not in English	Number of GMP certificate, name of NRA that granted the certificate, validity of the GMP certificate and scope
e)	List of products manufactured at the site and those to be exported to the country of import	List of products, dosage form (where applicable), list of registered products and those to be registered
f)	Notarized copy of inspection report(s) from the national medicines regulatory authority and/or that from WHO prequalification (whichever is applicable) carried out within the past three to five years	<ul style="list-style-type: none"> • Name of the regulatory authority that carried out the inspection, dates of the inspection, scope of inspection, findings and recommendations, list of findings of noncompliance, conclusion • CAPA reports submitted and found satisfactory for the most recent inspection (adequacy of CAPA, timelines)
g)	Performance of the company's products on the market over the past three years	<p>Any product alerts, warning letters, market complaints, product failure, product recall or any unacceptable findings for the product(s) in scope</p> <p>Any product alerts, warning letters, market complaints, product failure, product recall, or any unacceptable findings for the product(s) in scope</p>

Table *continued*

h)	Reports of product quality review	For products for which marketing authorization is being sought or renewed: assess the consistency of the processes, trends, specifications, process changes, recalls, returns, market complaints, deviations from critical parameters, in-process controls, quality control tests, stability study data (select product of interest)
i)	Validation master plan	Validation policy, utilities qualification, equipment qualification, procedures, protocols, reports, cleaning, personnel qualification, process validation, analytical method validation, computer validation, revalidation, requalification, validation matrix
j)	Process validation for one of the products marketed or to be registered in the country of import	Comment on adequacy
k)	One batch manufacturing record (BMR) for each product together with the master batch record including the packing and analytical part (with a certified translation of the original BMR where applicable); BMR should refer to a product marketed or to be registered in the country of import	Comment on adequacy
l)	Out-of-specification (OOS) procedure: records of three OOS including at least one assigned to a laboratory error	
m)	List of reprocessed or reworked product batches in the past two years	

Table *continued*

Part 3. Recommendation

1. Recommended for a GMP compliance approval?
(Provide recommendation based on the results of the assessment done in Parts 1 and 2)

2. If Yes, list production lines, product, pharmaceutical active ingredient recommended:

3. If No, state reasons and the relevant sections of the guideline(s) below:

Part 4. Evaluation team

First assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

Second assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

API: active pharmaceutical ingredient; CAPA: corrective and preventive action; FPP: finished pharmaceutical product; GMP: good manufacturing practices; NRA: national regulatory authority; PIC/S: Pharmaceutical Inspection Co-operation Scheme.

Appendix 2

Model report format for desk assessment of quality control laboratories

Part 1. General information	
a) Particulars of the applicant	Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, email address
b) Particulars of the quality control laboratory (QCL)	Name of QCL, physical address of QCL, postal address of the laboratory (if different from physical address), 24-hour telephone number(s), email address, contact person
c) Date of last inspection by SRA, WHO or accreditation body for ISO/IEC 17025	Name of NRA or accreditation body that carried out the inspection, dates when the inspection was carried out and the inspection outcome
Part 2. Documentary evidence (comment on adequacy of information provided)	
a) Copy of appropriate certificate or approval granted by a recognized regulatory authority or accreditation certificate granted by accreditation body for ISO/IEC 17025 together with a certified translation, if not in English	Number/reference of appropriate certificate or approval or ISO/IEC 17025 certificate, name of regulatory authority that granted the certificate and validity of the certificate
b) Scope of accreditation	Indicate the analytical methods and techniques
c) Current quality manual, laboratory manual or equivalent	Comment on adequacy ^a
d) Contract between the manufacturer and contract laboratory and its subcontractors if applicable (where testing is outsourced)	Comment on adequacy of the agreement stating responsibilities of the parties

Table continued

e)	List of all inspections carried out in the past three years by a regulatory authority or accreditation body	Provide the list of regulatory authority or accreditation body indicating the name, date of inspection and outcome in the inspection
f)	Copy of inspection report(s) from regulatory authority or accreditation body and/or from WHO prequalification (whichever is applicable) carried out within the past three to five years	Name of the regulatory authority or accreditation body that carried out the inspection, dates of the inspection, scope of inspection, findings and recommendations, list of instances of noncompliance, conclusion
g)	CAPA reports submitted and found satisfactory for the most recent inspection	Comment on adequacy
h)	Register of OOS, OOS procedure and investigation reports of at least three OOS assigned to laboratory error in past one year handled	Comment on adequacy

Part 3. Recommendation

1. Recommended for a GMP compliance approval?
(Provide recommendation based on the results of the assessment done in Parts 1 and 2)
2. If Yes, state laboratory testing activities/product analysed:
3. If No, state reasons and the relevant sections of the guideline(s) below:

Table *continued*

Part 4. Evaluation team

First assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

Second assessor

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

CAPA: corrective and preventive action; ISO/IEC: International Organization for Standardization/International Electrotechnical Commission; NRA: national regulatory authority; OOS: out of specification; SRA: stringent regulatory authority.

^a Refer to WHO good practice for pharmaceutical quality control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 1 (WHO Technical Report Series, No. 957).

Appendix 3

Model report format for desk assessment for contract research organizations and clinical trial sites

Part 1(i). General information – study

- | | | |
|----|---|--|
| a) | Particulars of the applicant | Name of applicant, physical address, postal address of applicant (if different from physical address), 24-hour telephone numbers, email address |
| b) | Particulars of the organization | Name of research organization, physical address, postal address (if different from physical address), 24-hour telephone number(s), fax, email address |
| c) | Title of the study | |
| d) | Particulars of the bioanalytical laboratory | Name of bioanalytical laboratory, physical address of bioanalytical laboratory, postal address of the laboratory (if different from physical address), 24-hour telephone number(s), fax, email address |
| e) | Particulars of the sponsor | Name of sponsor, 24-hour telephone number(s), fax, email address, contact person |

Part 1(ii). General information – site quality management system

- | | | |
|----|--|---|
| a) | Date of last inspection by NRA (if applicable) | Dates when the last inspection was carried out; name of the national medicines regulatory authority that carried out the inspection |
| b) | Particulars of the investigator's current curriculum vitae and/or qualifications | |

Table *continued*

Part 2(i). Documentary evidence – study		
a)	Copy of institutional review board (IRB)/independent ethics committee clinical trial/bioequivalence (BE) study approval	For multicentre trials, only the study approval issued by the IRB/IEC of the coordinating investigator of the trial is required
b)	Copy of clinical trial/BE approval granted by a competent national medicines regulatory authority with a certified translation, if not in English	Name of the approving authority, validity of approval (study)
c)	Copy of clinical trial/BE/bioavailability study protocol and any amendments ^b	Comment on the trial design, selection and withdrawal of subjects, treatment of subjects, assessment of efficacy, assessment of safety, statistics, data handling and record-keeping, ethics, financing and insurance, quality control and quality assurance, and publication policy
d)	Copy of investigator's brochure	Confidentiality statement, physical chemical and pharmaceutical properties and formulation, nonclinical studies, effects in humans, summary of data and guidance for the investigator
e)	Copy of current clinical trial/BE reports including safety reports	Comment on adequacy and compliance with the protocol (study)
f)	Copy of clinical trial monitoring report by the sponsor or contract research organization (CRO)	
Part 2 (ii). Documentary evidence – site quality management system		
a)	Copy of current GCP/GLP certificate or regulatory approval	
b)	Number of clinical trials/BE study approvals granted by a national medicines regulatory authority in the past five years, with a certified translation, if not in English	State number of approved clinical trials/BE studies and their outcomes, name of the approving authority, validity of approval

Table *continued*

c)	Copy of current clinical trial master file ^a (make reference to the quality assurance mechanism for CRO) Documentation on the responsibilities of the sponsor and clinical investigator, management and assessment of subcontracted vendors should be provided.	Comment on adequacy of deviation management and procedures for handling the investigational product
d)	List of all inspections carried out in the past three years	Clinical monitoring reports by the sponsor or the CRO (if monitoring tasks were outsourced to a CRO)
e)	Copy of inspection report(s) from national medicines regulatory authority and/or that from WHO prequalification (whichever is applicable) carried out within the past three to five years	Including bioanalytical method validation and compliance with GLP
f)	Provide evidence of NRA oversight including concerns raised and alerts, if any	
g)	Copy of study monitoring report by the sponsor or CRO (where applicable)	

Part 3: Recommendation

1. Recommended for a GCP compliance approval?
(Provide recommendation based on the results of the assessment done in Parts 1 and 2)
2. If Yes, study/clinical trial site recommended:
3. If No, state reasons and the relevant sections of the guideline(s) below:

Table *continued***Part 4. Evaluation team****First assessor**

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)**Second assessor**

Signed: _____ Date: _____

Name: _____ Position: _____
(BLOCK CAPITALS)

GCP: good clinical practices; GLP: good laboratory practices; NRA: national regulatory authority.

- ^a Guidelines for good clinical practice E6 (R1), Current Step 4 Version, 10 June 1996. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf).
- ^b Guidance for organizations performing in vivo bioequivalence studies (revision). In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996).

Annex 10

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products

Introduction and background

The guidance on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was published as Annex 2 in the World Health Organization (WHO) Technical Report Series, No. 953, 2009 (1).

The aim of these regulatory guidelines is to outline the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area. The guidelines cross-refer to the series of related documents published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2) and other WHO guidelines.

It was recommended that at the time of their publication these guidelines should also be applied to products that are already being marketed, making allowance for an appropriate transition period, for example, they could become applicable upon re-registration or upon re-evaluation.

The 2009 guidance not only followed the usual consultation process, but it was also the result of numerous discussions with the various regulatory forums, including ICH. As a result, the ICH parties withdrew one of their guidance texts (Q1F) and published the following text on their website:

“Explanatory Note on the Withdrawal of ICH Q1F for the ICH Website

ICH Q1 F Stability Data Package for Registration Applications in Climatic Zones III and IV defined storage conditions for stability testing in countries located in Climatic Zones III (hot and dry) and IV (hot and humid), i.e. countries not located in the ICH regions and not covered by ICH Q1 A (R2) Stability Testing for New Drug Substances and Drug Products. ICH Q1 F described harmonised global stability testing requirements in order to facilitate access to medicines by reducing the number of different storage conditions. In the course of the discussions which led to the development of the guideline, WHO conducted a survey amongst their member states to find consensus on 30 °C/65% [relative humidity] RH as the long-term storage conditions for hot and humid regions. As no significant objections were raised in this survey, 30 °C/65% RH was defined as the long-term storage condition for Climatic Zone III/IV countries in ICH Q1F. The document was adopted by the ICH Steering Committee in February 2003 and subsequently implemented in the ICH regions.

However, based on new calculations and discussions, some countries in Climatic Zone IV have expressed their wish to include a larger safety margin for medicinal products to be marketed in their region than foreseen in ICH Q1F. As a consequence, several countries and regions have revised their own stability testing guidelines, defining up to 30 °C/75% RH as the long-term storage conditions for hot and humid regions. Due to this divergence in global stability testing requirements, the ICH Steering Committee has decided to withdraw ICH Q1F and to leave definition of storage conditions in Climatic Zones III and IV to the respective regions and WHO (http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/).

In assessing the impact of the withdrawal of ICH Q1F on intermediate testing conditions defined in ICH Q1A (R2), the decision was reached to retain 30 °C/65%RH. However, regulatory authorities in the ICH regions have agreed that the use of more stringent humidity conditions such as 30 °C/75% RH will be acceptable should the applicant decide to use them.”¹

Based on recent developments, an analysis was commissioned to evaluate whether the existing guidelines would need to be updated.

During the joint meeting on regulatory guidance for multisource products with the Medicines Quality Assurance Group and the Prequalification of Medicines Team assessment group held in Copenhagen from 8 to 9 July 2016, this analysis was discussed in detail and feedback provided by the participants on the report as well as on the various sections of the existing guidelines. In conclusion the participants agreed that a revision of this text would be timely.

¹ http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q1F/Q1F_Explanatory_Note.pdf.

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1. Introduction

1.1 Objectives of these guidelines

The aim of these guidelines is to outline the core stability data package required for registration of active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs), replacing the previous WHO guidelines in this area (1). However, alternative approaches can be used when they are scientifically justified. Further guidance can be found in guidelines published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (2), in the WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part* (3), WHO *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part* (4) and WHO *guidelines on the active pharmaceutical ingredient master file procedure* (5).

It is recommended that these guidelines should also be applied to products that are already being marketed, for example, upon re-registration or upon re-evaluation.

1.2 Scope of these guidelines

These guidelines apply to new and existing APIs and address information to be submitted in original and subsequent applications for marketing authorization of their related FPP for human use. These guidelines may generally apply to stability testing for biologicals; however, there are additional requirements specific to such products and further guidance can be found in ICH guideline Q5C (2).

1.3 General principles

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability testing programme also includes the study of product-related factors that influence its quality, for example, interaction of the API with excipients, container-closure systems and packaging materials. In fixed-dose combination FPPs (fixed-dose combinations (FDCs)) the interaction between two or more APIs also has to be considered.

As a result of stability testing, a retest period for the API (in exceptional cases, for example, for unstable APIs, a shelf life is given) or a shelf life for the FPP can be established and storage conditions can be recommended. An API can be considered unstable (under the conditions studied, in a particular type of packaging, etc.) when a significant change is observed.

Various analyses have been done to identify suitable testing conditions for WHO Member States based on climatic data, to enable each Member State to decide on long-term (real-time) stability testing conditions. Those Member States that have notified WHO of the long-term stability testing conditions they require when requesting a marketing authorization are listed in “Long-term stability testing conditions as identified by WHO Member States”.²

2. Guidelines

2.1 Active pharmaceutical ingredient

2.1.1 General

Information on the stability of the API is an integral part of the systematic approach to stability evaluation. Potential attributes to be studied during stability testing of an API are listed in the examples of testing parameters (Appendix 1). **The selection of potential attributes and time points to be tested should be justified.**

The retest period or shelf life assigned to the API by the API manufacturer should be derived from stability testing data.

2.1.2 Stress testing

Stress testing of the API can help identify the likely degradation products, which in turn can help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability-indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

For an API the following approaches may be used:

- when available, it is acceptable to provide the relevant data published in the scientific literature to support the identified degradation products and pathways;
- when no published data are available, stress testing should be performed.

Stress testing may be carried out on a single batch of the API. It should include the effect of temperature (in 10 °C increments (for example, at 50 °C, 60 °C) above the temperature used for accelerated testing), humidity (for example,

² http://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UupdatedMarch2015.pdf?ua=1, accessed 1 March 2017.

75% relative humidity (RH) or greater) and, where appropriate, oxidation and photolysis of the API. The testing should also evaluate the susceptibility of the API to hydrolysis across a justified range of pH values when in solution or suspension (6).

Assessing the necessity for photostability testing should be an integral part of a stress testing strategy. More details can be found in other guidelines (2).

The objective of stress testing is to identify primary degradation products and not to completely degrade the API. The conditions studied should cause degradation to occur to a small extent, typically 10–30% loss of API as determined by assay when compared with non-degraded API. The target should be chosen so that some degradation occurs, but not enough to generate secondary products. For this reason, the conditions and duration may need to be varied when the API is especially susceptible to a particular stress factor. In the total absence of degradation products after 10 days the API is considered stable under the particular stress condition. However, in this case the stress conditions employed should be justified.

Although examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

2.1.3 Selection of batches

The requirements that follow are not intended to apply to variations; these are covered in section 2.2.12 Variations.

Data from stability studies on at least three primary batches of the API should normally be provided. The batches should be manufactured at a minimum of pilot scale by the same synthesis route as production batches, and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The overall quality of the batches of API placed on stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

2.1.4 Container-closure system

The stability studies should be conducted on the API packaged in a container-closure system that is the same as, or simulates, the packaging proposed for storage and distribution.

2.1.5 Specification

Stability studies should include testing of stability-indicating attributes of the API, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes. A guide to the potential attributes to be tested in the stability studies is provided in Appendix 1.

Validated stability-indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies (7, 8).

2.1.6 Testing frequency

For long-term studies, the frequency of testing should be sufficient to establish the stability profile of the API.

For APIs with a proposed retest period or shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year, and annually thereafter throughout the proposed retest period or shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where it is expected (based on development experience) that results from accelerated studies are likely to approach significant change criteria, additional testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design. When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

2.1.7 Storage conditions

In general, an API should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage and shipment.

Storage condition tolerances are defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect

stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The following requirements for data at the time of submission are not generally intended to apply to variations; instead see section 2.2.12 Variations. For new APIs, the long-term testing should normally have taken place over a minimum of 12 months for the number of batches specified in section 2.1.3 at the time of submission, and should be continued for a period of time sufficient to cover the proposed retest period or shelf life. For existing APIs, data covering a minimum of six months may be submitted. Additional data accumulated during the period while the registration application is being assessed should be submitted to the authorities when submitting data in response to outstanding questions. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for APIs are detailed in sections 2.1.7.1–2.1.7.3. The general case applies if the API is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

If long-term studies are conducted at $25\text{ °C} \pm 2\text{ °C}/60\% \text{ RH} \pm 5\% \text{ RH}$ and “significant change” occurs at any time during six months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case, testing at the intermediate storage condition should include all long-term tests, unless otherwise justified, and the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

“Significant change” for an API is defined as failure to meet its specification.

2.1.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	$25\text{ °C} \pm 2\text{ °C}/60\% \text{ RH} \pm 5\% \text{ RH}$ or $30\text{ °C} \pm 2\text{ °C}/65\% \text{ RH} \pm 5\% \text{ RH}$ or $30\text{ °C} \pm 2\text{ °C}/75\% \text{ RH} \pm 5\% \text{ RH}$	12 months or 6 months as described in point 2.1.7
Intermediate ^b	$30\text{ °C} \pm 2\text{ °C}/65\% \text{ RH} \pm 5\% \text{ RH}$	6 months

Table *continued*

Study	Storage condition	Minimum time period covered by data at submission
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored (see “Long-term stability testing conditions as identified by WHO Member States”). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. 25 °C/60% RH or 30 °C/65% RH for zone II.

^b If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

2.1.7.2 Active pharmaceutical ingredients intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months or 6 months as referred to in section 2.1.7
Accelerated ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to storage testing at 25 °C/60% RH or 30 °C/65% RH.

Data on refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months’ testing at the accelerated storage condition, the proposed retest period should be based on the data available at the long-term storage condition.

If significant change occurs within the first three months’ testing at the accelerated storage condition a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the API for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test an API for the whole six months when a significant change has occurred within the first three months.

2.1.7.3 Active pharmaceutical ingredients intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	$-20\text{ }^{\circ}\text{C} \pm 5\text{ }^{\circ}\text{C}$	12 months or 6 months as referred to in section 2.1.7

In the rare case of any API of nonbiological origin being intended for storage in a freezer, the retest period or shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for APIs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. $5\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$ or $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ or $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g. during shipping or handling.

2.1.7.4 Active pharmaceutical ingredients intended for storage below $-20\text{ }^{\circ}\text{C}$

APIs intended for storage below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

2.1.8 Stability commitments

When the available long-term stability data on primary batches do not cover the proposed retest period or shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval in order to firmly establish the retest period or shelf life.

Where the submission includes long-term stability data on three production batches covering the proposed retest period or shelf life, a post-approval commitment is considered unnecessary. Otherwise one of the following commitments should be made:

- if the submission includes data from stability studies on three production batches, a commitment should be made to continue these studies through the proposed retest period or shelf life;
- if the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, up to a total of at least three, in long-term stability studies through the proposed retest period or shelf life;
- if the submission does not include stability data on production batches, a commitment should be made to place the first three

production batches (see section 2.1.3) on long-term stability studies through the proposed retest period or shelf life.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

See also 2.1.11 Ongoing stability studies.

2.1.9 Evaluation

The primary stability programme should be described in a written protocol and the results presented in a formal report as outlined in 2.1.11.

The purpose of the stability study is to establish – based on testing a minimum of three batches of the API, unless otherwise justified, and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological and microbiological tests) – a retest period or shelf life applicable to all future batches of the API manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period or shelf life.

The data may show so little degradation and so little variability that it is apparent from looking at them that the requested retest period or shelf life will be granted. Under these circumstances it is normally unnecessary to go through the statistical analysis.

One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. *P* values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period or shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction). Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the retest period or shelf life can be undertaken if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (please refer to ICH Q1E).

Any evaluation should cover not only the assay but also the levels of degradation products and other stability-indicating attributes.

2.1.10 Statements and labelling

A storage statement should be established for display on the label based on the stability evaluation of the API. Where applicable, specific instructions should be provided, particularly for APIs that cannot tolerate freezing or excursions in temperature. Terms such as “ambient conditions” or “room temperature” should be avoided.

The recommended labelling statements for use when supported by the stability studies are provided in Appendix 2.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

After this retest period a batch of API destined for use in the manufacture of an FPP could be retested and then, if in compliance with the specification, could be used immediately (e.g. within 30 days). If retested and found compliant, the batch does not receive an additional period corresponding to the time established for the retest period. However, an API batch can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For APIs known to be labile (e.g. certain antibiotics) it is more appropriate to establish a shelf life than a retest period.

2.1.11 Ongoing stability studies

The stability of the API should be monitored according to a continuous and appropriate programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products). The purpose of the ongoing stability programme is to monitor the API and to determine that the API remains, and can be expected to remain, within specifications under the storage conditions indicated on the label, within the retest period or shelf life in all future batches.

The ongoing stability programme should be described in a written protocol and the results presented in a formal report that should be available on site.

The protocol for an ongoing stability programme should extend to the end of the retest period or shelf life and should include, but not be limited to, the following parameters:

- number of batch(es) and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency;
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the API labelling, should be used);
- other applicable parameters specific to the API.

At least one production batch per year of API (unless none is produced during that year) should be added to the stability monitoring programme and generally should be tested at least every 6 months in the first year and then annually to confirm the stability (7).

In certain situations additional batches should be included in the stability programme and may require more frequent testing. For example, a stability study should be initiated after any significant change or significant deviation of the synthetic route, process or container-closure system that may have an impact upon the stability of the API (refer to section 2.2.12 Variations).

Out-of-specification (OOS) results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant finished product manufacturer. The possible impact on batches on the market should be considered in consultation with the relevant finished product manufacturers and the competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained and should be available on site. This summary should be subjected to periodic review.

2.2 Finished pharmaceutical product

2.2.1 General

The design of the stability studies for the FPP should be based on knowledge of the behaviour and properties of the API, information from stability studies on the API and on experience gained from preformulation studies, similar marketed formulations and investigational FPPs. The likely changes during

storage and the rationale for the selection of attributes to be tested in the stability studies should be stated.

2.2.2 Stress testing

Photostability testing, which is an integral part of stress testing, should be conducted on at least one primary batch of the FPP if appropriate. More details can be found in other guidelines (2).

Additional stress testing of specific types of dosage forms may be appropriate, e.g. cyclic studies for semi-solid products or freeze-thaw studies for liquid products.

2.2.3 Selection of batches

The requirements that follow are not generally intended to apply to variations, which are covered in section 2.2.12 Variations.

For FPPs containing new APIs, data from stability studies should be provided on at least three primary batches of each proposed strength of the FPP. Two of the three batches should be at least pilot-scale batches and the third batch can be smaller, if justified (see example below).

For FPPs containing existing APIs (e.g. generics), data should be provided on not less than two batches of at least pilot scale, or in the case of an uncomplicated³ FPP (e.g. immediate-release solid FPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale and a second batch which may be smaller (e.g. for solid oral dosage forms, 25 000 or 50 000 tablets or capsules) of each proposed strength of the FPP.

The primary batches should be of the same formulation and packaged in the same container-closure system as that proposed for marketing. The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing.

When a batch size smaller than pilot scale is used as a primary batch, data or a discussion is required to confirm that the smaller batch is representative of the intended production size, including its formulation and method of manufacture.

Where possible, batches of the FPP should be manufactured using different batches of the API(s).

³ The term "complicated FPP" includes sterile products, metered dose inhaler products, dry powder inhaler products and transdermal delivery systems. Solid oral products considered "complicated" include modified-release FPPs, products containing problematical APIs such as ritonavir and FDCs containing APIs such as rifampicin or an artemisinin.

Stability studies should be performed on each individual strength, dosage form and container type and size of the FPP unless bracketing or matrixing is applied (refer to ICH Q1D).

2.2.4 Container-closure system

Stability testing should be conducted on the dosage form packaged in the primary container-closure systems proposed for marketing. If the secondary container-closure system has protective properties, and labelling clearly indicates that the product is to be stored in the primary and secondary packaging (e.g. “store tablets in blisters in the provided cartons”), or if the product is packaged in a semi-permeable container where components from the secondary packaging can migrate into the product, the secondary packaging may also form part of the packaging system for stability samples. Any available studies carried out on the FPP outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

2.2.5 Specification

Stability studies should include testing of stability-indicating attributes of the FPP, i.e. those that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological and microbiological attributes, preservative content (e.g. antioxidant or antimicrobial preservatives) and functionality tests (e.g. for a dose delivery system). Examples of testing parameters in the stability studies are listed in Appendix 1. Analytical procedures should be fully validated and stability-indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf-life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during development of the pharmaceutical product with the product in its final formulation (except for preservative concentration) intended for marketing. A single primary stability batch of the FPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

2.2.6 Testing frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the FPP.

For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every three months over the first year, every six months over the second year and annually thereafter throughout the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g. 0, 3 and 6 months), from a six-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, testing should be increased either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g. 0, 6, 9 and 12 months), from a 12-month study is recommended.

The initial date of storage should be considered t_0 and stability time points should be defined as a date with respect to t_0 . For example, if t_0 is 1 January 2020 then the one-month time point corresponds to either 1 February or 31 January 2020. For each time point, samples should be withdrawn and tested as per the protocol. Testing should be completed as soon as possible. Deviations from the protocol should be recorded and justified.

Reduced designs, i.e. matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified (refer to ICH Q1D).

2.2.7 Storage conditions

Stability data must demonstrate stability of the medicinal product throughout its intended shelf life under the climatic conditions prevalent in the target countries. Merely applying the same requirements appropriate to other markets could potentially lead to substandard products if stability studies are conducted at the storage conditions for countries in Climatic Zone I/II when the products are supplied in countries in Climatic Zones III and IV.

In general an FPP should be evaluated under storage conditions with specified tolerances that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment and subsequent use with due regard to the climatic conditions in which the product is intended to be marketed.

The orientation of the product during storage, i.e. upright, on the side or inverted, as well as the rationale for the orientation, may need to be included in a

protocol where contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids and semisolids), or where there has been a change in the container-closure system.

Storage condition tolerances are usually defined as the acceptable variations in temperature and RH of storage facilities for stability studies. The equipment used should be capable of controlling the storage conditions within the ranges defined in these guidelines. The storage conditions should be monitored and recorded. Short-term environmental changes due to opening of the doors of the storage facility are accepted as unavoidable. The effect of excursions due to equipment failure should be assessed, addressed and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effects assessed.

The following requirements for data at the time of submission are not generally intended to apply to variations; instead refer to section 2.2.12 Variations. At the time of submission, the long-term testing should cover a minimum of six months for FPPs containing existing APIs or 12 months for FPPs containing new APIs and should be continued for a period of time sufficient to cover the proposed shelf life. The period of data collection required at the time of submission may be shortened in some circumstances, for example, to address shortages of medicines.

Additional data accumulated during the assessment period of the registration application should be submitted to the authorities when submitting data in response to outstanding questions. Data from the accelerated storage condition and from the intermediate conditions, where appropriate, can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated and, where appropriate, intermediate storage conditions for FPPs are detailed in the sections below. The general case applies if the FPP is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

2.2.7.1 General case

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	12 months or 6 months as referred to in section 2.2.7

Table continued

Study	Storage condition	Minimum time period covered by data at submission
Intermediate ^b	30 °C ± 2 °C/65% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic zone in which the FPP is intended to be marketed. Testing at a more severe long-term condition can be an alternative to storage at 25 °C/60% RH or 30 °C/65% RH.

^b If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25 °C ± 2 °C/60% RH ± 5% RH and “significant change” occurs at any time during 6 months’ testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. In this case the initial application should include a minimum of six months’ data from a 12-month study at the intermediate storage condition.

In general, “significant change” for an FPP is defined as:

- a change from the initial content of API(s) of 5% or more detected by assay, or failure to meet the acceptance criteria for potency when using biological or immunological procedures;
- any degradation product exceeding its acceptance criterion;
- failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams, partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

- failure to meet the acceptance criterion for pH; or
- failure to meet the acceptance criteria for dissolution for 12 dosage units.

2.2.7.2 FPPs packaged in impermeable containers

Parameters required to classify the packaging materials as permeable or impermeable depend on the characteristics of the packaging material, such

as sealing, thickness and permeability coefficient. The suitability of the packaging material used for a particular product is determined by its product characteristics. Containers generally considered to be moisture-impermeable include glass ampoules.

Sensitivity to moisture or potential for solvent loss is not a concern for FPPs packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus stability studies for products stored in impermeable containers can be conducted under any controlled or ambient RH condition.

2.2.7.3 FPPs packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological and microbiological stability. This evaluation can be carried out under conditions of low RH, as discussed below. Ultimately it should be demonstrated that aqueous-based FPPs stored in semi-permeable containers could withstand environments with low RH.

Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long-term ^a	25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH	12 months or 6 months as referred to in section 2.2.7
Intermediate ^b	30 °C ± 2 °C/35% RH ± 5% RH	6 months
Accelerated	40 °C ± 2 °C/not more than (NMT) 25% RH	6 months

^a Whether long-term stability studies are performed at 25 °C ± 2 °C/40% RH ± 5% RH or 30 °C ± 2 °C/35% RH ± 5% RH is determined by the climatic condition under which the FPP is intended to be marketed. Testing at 30 °C/35% RH can be an alternative to the storage condition at 25 °C/40% RH.

^b If 30 °C ± 2 °C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

Products meeting the specifications when stored under the accelerated conditions and the long-term storage conditions appropriate to the intended market, as specified in the table above, have demonstrated the integrity of the packaging in semi-permeable containers. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate

that the pharmaceutical product would not have significant water loss throughout the proposed shelf life if stored at 25 °C/40% RH or 30 °C/35% RH.

For long-term studies conducted at 25 °C ± 2 °C/40% RH ± 5% RH, that fail the accelerated testing with regard to water loss and show significant change with respect to any other parameters, additional testing at the “intermediate” storage condition should be performed as described under the general case to evaluate the temperature effect at 30 °C.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semi-permeable container after an equivalent of three months’ storage at 40 °C and not more than (NMT) 25% RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of three months’ storage at 40 °C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studies at the low RH as recommended in the table above (for either long-term or accelerated testing) is to perform the stability studies under higher RH and to derive the water loss at the low RH through calculation. This can be achieved by experimentally determining the permeation coefficient for the container-closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container-closure system can be experimentally determined by using the worst-case scenario (e.g. the most diluted of a series of concentrations) for the proposed FPP.

Example of an approach for determining water loss

For a product in a given container-closure system, container size and fill, an appropriate approach for deriving the rate of water loss at the low RH is to multiply the rate of water loss measured at an alternative RH at the same temperature, by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative RH over the storage period should be demonstrated.

For example, at a given temperature, e.g. 40 °C, the calculated rate of water loss during storage at NMT 25% RH is the rate of water loss measured at 75% RH multiplied by 3.0, the corresponding water loss rate ratio.

Low-humidity testing conditions	Alternative testing condition	Ratio of water loss rates	Calculation
25 °C/40% RH	25 °C/60% RH	1.5	(100–40)/(100–60)
30 °C/35% RH	30 °C/65% RH	1.9	(100–35)/(100–65)
30 °C/35% RH	30 °C/75% RH	2.6	(100–35)/(100–75)
40 °C/NMT 25% RH	40 °C/75% RH	3.0	(100–25)/(100–75)

Valid water loss rate ratios at RH conditions other than those shown in the table above can also be used.

2.2.7.4 FPPs intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long-term	5 °C ± 3 °C	12 months or 6 months as referred to in section 2.2.7
Accelerated ^a	25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH	6 months

^a Whether accelerated stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is based on a risk-based evaluation. Testing at a more severe accelerated condition can be an alternative to the storage condition at 25 °C/60% RH or 30 °C/65% RH.

If the FPP is packaged in a semi-permeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of these guidelines, except where explicitly noted below.

If significant change occurs between three and six months' testing at the accelerated storage condition, the proposed shelf life should be based on the data available from the long-term storage condition.

If significant change occurs within the first three months' testing at the accelerated storage condition, a discussion should be provided addressing the effect of short-term excursions outside the label storage condition, e.g. during shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the FPP for a period shorter than three months but with more frequent testing than usual. It is considered unnecessary to continue to test a product throughout six months when a significant change has occurred within the first three months of accelerated studies at the specific condition chosen in accordance with the risk analysis.

2.2.7.5 FPPs intended for storage in a freezer

Study	Storage condition	Minimum time period covered by data at submission
Long-term	-20 °C ± 5 °C	12 months or 6 months as referred to in section 2.2.7

For FPPs intended for storage in a freezer, the shelf life should be based on the long-term data obtained at the long-term storage condition. In the absence of an accelerated storage condition for FPPs intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g. $5\text{ }^{\circ}\text{C} \pm 3\text{ }^{\circ}\text{C}$ or $25\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$ or $30\text{ }^{\circ}\text{C} \pm 2\text{ }^{\circ}\text{C}$) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

2.2.7.6 FPPs intended for storage below $-20\text{ }^{\circ}\text{C}$

FPPs intended for storage at temperatures below $-20\text{ }^{\circ}\text{C}$ should be treated on a case-by-case basis.

2.2.8 Stability commitments

One or more of the following commitments should be made.

- When the available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies post-approval throughout the proposed shelf life. This is the primary batch stability commitment.
- If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to place the next production batches, up to a total of at least three, on long-term stability studies throughout the proposed shelf life and on accelerated studies for six months. This is the production batch stability commitment.
- For each product, an ongoing stability programme is required to monitor the product over its shelf life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. See 2.2.13. This is the ongoing stability commitment.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

2.2.9 Evaluation

The primary stability programme should be described in a written protocol and the results presented in a formal report as outlined in 2.2.13.

A systematic approach should be adopted to the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests,

including particular attributes of the dosage form (e.g. dissolution rate for solid oral dosage forms). *Where appropriate, a summary of additional knowledge and an understanding of stability gained from supporting studies, modelling, predictive tools, etc., may be incorporated to support knowledge gained from the primary stability programme.*

The purpose of the stability study is to establish, based on testing a minimum number of batches of the FPP as specified in section 2.2.3, a shelf life and label storage instructions applicable to all future batches of the FPP manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the statistical analysis.

One approach for analysing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g. *P* values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic or cubic function on an arithmetic or logarithmic scale. As far as possible, the choice of model should be justified by a physical and/or chemical rationale and should also take into account the amount of available data (parsimony principle to ensure a robust prediction).

Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the long-term data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken, if justified. This justification should be based on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size and the existence of supporting stability data. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data (refer to ICH Q1E).

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes.

2.2.10 **Statements and labelling**

A storage statement should be established for the label based on the stability evaluation of the FPP. Where applicable, specific instructions should be provided, particularly for FPPs that cannot tolerate freezing. Terms such as “ambient conditions” or “room temperature” should be avoided.

There should be a direct link between the storage statement on the label and the demonstrated stability of the FPP. An expiry date should be displayed on the container label.

The labelling statements recommended for use, if supported by the stability studies, are provided in Appendix 2. Information on the interpretation and conversion of storage statements for products approved in zone II when the products are to be distributed in zone IV is provided in Appendix 3.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements could be used in cases where the results of the stability testing demonstrate limiting factors (see Appendix 2).

2.2.11 **In-use and hold time stability**

The purpose of in-use stability testing is to provide information for the labelling on the preparation, storage conditions and utilization period of multidose products after opening, reconstitution or dilution of a solution. Examples include an antibiotic injection supplied as a powder for reconstitution, or a moisture-sensitive or hygroscopic solid oral FPP in a large format multidose container (e.g. high density polyethylene (HDPE) bottle of 500 tablets). In general, a 30-day in-use period is normally considered acceptable without further supporting data.

As far as possible the test should be designed to simulate the use of the FPP in practice, taking into consideration the filling volume of the container and any dilution or reconstitution before use. At intervals comparable to those that occur in practice, appropriate quantities should be removed by the withdrawal methods normally used and described in the product literature.

The physical, chemical and microbial properties of the FPP that are susceptible to change during storage should be determined over the period of the proposed in-use shelf life. If possible, testing should be performed at intermediate time points and at the end of the proposed in-use shelf life on the final amount of the FPP remaining in the container. Specific parameters, e.g. for liquids and semisolids: the content and effectiveness of preservatives need to be studied.

A minimum of two batches, at least pilot-scale (with the exceptions outlined in 2.2.3), should be subjected to the test. At least one of these batches should be chosen towards the end of its shelf life. If such results are not available, one batch should be tested at the final point of the submitted stability studies.

This testing should be performed on primary batches of the reconstituted or diluted FPP or the solid oral FPP (as above), throughout the proposed in-use period as part of the stability studies at the initial and final time points and, if long-term data covering the shelf life are not available at the time of submission, at 12 months or the last time point at which data will be available.

In general this testing need not be repeated on commitment batches (see 2.2.8).

Consideration should also be given to hold-time studies of bulk products, e.g. coated tablets prior to final packaging. For example, when the bulk product may be stored for a period exceeding 30 days before being packaged and/or shipped from a manufacturing site to a packaging site, the stability of the bulk product in the intended bulk container should be evaluated and studied. Similar considerations should apply to intermediates that are stored and used for periods exceeding 30 days. Further guidance can be found in the WHO *General guidance on hold-time studies* (9).

2.2.12 Variations

Once the FPP has been registered, additional stability studies are required whenever variations are made that may affect the stability of the API or FPP. The applicant should investigate whether or not the intended change will have an impact on the quality characteristics of APIs and/or FPPs and consequently on their stability. The scope and design of the stability studies for variations are based on the knowledge and experience acquired on APIs and FPPs.

The available variation guidelines should be consulted for guidance on the expectations regarding stability requirements to support changes to the API and FPP. Note that the requirements of the guidelines of the specific regulatory authority or region prevail for a given region; however, in the absence of such guidelines, the WHO Prequalification Team: Medicines guidelines can be applied (10). Depending on the variation, either the results of a stability study or a commitment to conduct such as study is required. Variation guidelines are specific detailed guidelines, therefore the following are general categories and the guidelines should be referred to for the exact circumstances and requirements. In the aforementioned guidance document (10), changes requiring supporting data include certain changes to the API retest period or storage conditions, and to the FPP formulation, manufacturing process, container-closure system, shelf life, in-use period and storage conditions. Other changes, such as certain changes to the API certificate of suitability, certificate of prequalification, manufacturing

site or manufacturing process, or certain changes to the FPP manufacturing site, batch size or container-closure system, require a commitment for stability studies to support the variations.

The results of these stability studies should be communicated to the regulatory authorities concerned, following the applicable requirements stipulated in the variation guidelines for the region.

2.2.13 Ongoing stability studies

After a marketing authorization has been granted, the stability of the FPP should be appropriately monitored according to a continuous programme that will permit the detection of any stability issue (e.g. changes in levels of degradation products or dissolution profile) associated with the formulation in the container-closure system in which it is marketed. The purpose of the ongoing stability programme is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the storage conditions on the label. The ongoing stability programme should be described in a written protocol and results formalized as a report.

The protocol for an ongoing stability programme should extend to the end of the shelf-life period and should include, but not be limited to, the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable. The batch size should be recorded, if batch sizes differ;
- relevant physical, chemical, microbiological and biological test parameters with acceptance criteria or reference to the attached specifications;
- reference to test methods;
- description of the container-closure system(s);
- testing frequency (generally at 6 months and annual time points is sufficient for ongoing studies);
- description of the conditions of storage (standardized conditions for long-term testing as described in these guidelines, and consistent with the product labelling, should be used); and
- other applicable parameters specific to the FPP.

The protocol for the ongoing stability programme can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (for example, the frequency of testing as above, or when updating to meet revised recommendations).

The number of batches and frequency of testing should provide sufficient data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability programme (unless none is produced during that year). The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol (refer to ICH Q1D).

In certain situations additional batches should be included in the ongoing stability programme. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or container-closure system. Any reworking, reprocessing or recovery operation should also be considered for inclusion. Refer to section 2.2.12 for further details.

OOS results or significant atypical trends should be investigated. Any confirmed significant change or OOS result should be reported immediately to the relevant competent authorities. The possible impact on batches on the market should be considered in consultation with the relevant competent authorities.

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

3. Glossary

The definitions provided below apply to the words and phrases used in these guidelines. Although an effort has been made to use standard definitions as far as possible, they may have different meanings in other contexts and documents. The following definitions are provided to facilitate interpretation of the guidelines. The definitions are consistent with those published in other WHO quality assurance guidelines. The Quality Assurance of Medicines Terminology Database was established in August 2005 and includes the definitions of terms related to quality assurance of medicines. This database is intended to help harmonize terminology and to avoid misunderstandings that may result from the different terms and their interpretations used in various WHO publications. The main publications used as a source of information to create the Quality Assurance of Medicines Terminology Database are the quality assurance guidelines included in the thirty-sixth and subsequent reports of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

accelerated testing. Studies designed to increase the rate of chemical degradation and physical change of an active pharmaceutical ingredient or finished pharmaceutical product by using exaggerated storage conditions as part of the stability testing programme. The data thus obtained, in addition to those derived from long-term stability studies, may be used to assess longer-term chemical effects under non-accelerated conditions and to evaluate the

impact of short-term excursions outside the label storage conditions, as might occur during shipping. The results of accelerated testing studies are not always predictive of physical changes.

active pharmaceutical ingredient. Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body.

batch. A defined quantity of starting material, packaging material or finished pharmaceutical product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

bracketing. The design of a stability schedule such that only samples at the extremes of certain design factors, e.g. strength and package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or very closely related in composition (e.g. for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container-closure system (refer to ICH Q1D).

climatic zone. The zones into which the world is divided based on the prevailing annual climatic conditions (see reference to the living document “Long-term stability testing conditions as identified by WHO Member States”⁴).

commitment batches. Production batches of an active pharmaceutical ingredient or finished pharmaceutical product for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

container-closure system. The sum of packaging components that together contains and protects the dosage form. This includes primary packaging

⁴ http://www.who.int/medicines/areas/quality_safety/quality_assurance/StabilityConditionsTable2UupdatedMarch2015.pdf?ua=1, accessed 1 March 2017.

components and secondary packaging components, if the latter are intended to provide additional protection to the finished pharmaceutical product. A packaging system is equivalent to a container-closure system.

dosage form. The form of the finished pharmaceutical product, e.g. tablet, capsule, elixir or suppository.

excipient. A substance or compound, other than the active pharmaceutical ingredient and packaging materials, that is intended or designated to be used in the manufacture of a finished pharmaceutical product.

existing active pharmaceutical ingredient. An active pharmaceutical ingredient that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by the World Health Organization, but requires the filing of a dossier. This would include, for example, new product dossiers and variations to multisource products.

expiry date. The date given on the individual container (usually on the label) of a product up to and including which the active pharmaceutical ingredient and finished pharmaceutical product are expected to remain within specifications if stored under the long-term conditions at which stability was established. It is set for each batch by adding the shelf life to the date of manufacture.

finished pharmaceutical product. A product that has undergone all stages of production, including packaging in its final container and labelling. A finished pharmaceutical product may contain one or more active pharmaceutical ingredients.

impermeable containers. Containers that provide a permanent barrier to the passage of gases or solvents, e.g. sealed aluminium tubes for semisolids, sealed glass ampoules for solutions and aluminium/aluminium blisters for solid dosage forms (refer to 2.2.7.2).

in-use period. A period of time during which a reconstituted preparation of the finished dosage form in a multidose container, or a moisture-sensitive product in a large-format final container (e.g. high-density polyethylene (HDPE) bottles of 500) can be used after opening.

long-term stability studies. Experiments on the physical, chemical, biological, biopharmaceutical and microbiological characteristics of an active pharmaceutical ingredient or finished pharmaceutical product, during and beyond the expected shelf life and storage periods of samples under the storage conditions expected in the intended market. The results are used to establish the retest period or the shelf life, to confirm the projected retest period and shelf life, and to recommend storage conditions.

matrixing. The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples

for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same finished pharmaceutical product should be identified as, for example, covering different batches, different strengths, different sizes of the same container-closure system, and, possibly in some cases, different container-closure systems (refer to ICH Q1D).

new active pharmaceutical ingredient. Active pharmaceutical ingredient that has not been previously authorized as a medicine for use in humans in the country in question.

ongoing stability study. The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf life) of the active pharmaceutical ingredient, or confirm or extend the shelf life of the finished pharmaceutical product.

pilot-scale batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger, unless otherwise adequately justified.

primary batch. A batch of an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP) used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf life, as the case may be. Primary batch requirements are outlined in 2.1.3 and 2.2.3 for the API and FPP, respectively.

production batch. A batch of an active pharmaceutical ingredient or finished pharmaceutical product manufactured at production scale by using production equipment in a production facility as specified in the application.

provisional shelf life. A provisional expiry date that is based on acceptable accelerated and available long-term data for the finished pharmaceutical product to be marketed in the proposed container-closure system.

release specification. The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of an active pharmaceutical ingredient or finished pharmaceutical product at the time of its release.

retest date. The date after which an active pharmaceutical ingredient should be re-examined to ensure that the material is still in compliance with the specification and thus is still suitable for use in the manufacture of a finished pharmaceutical product.

retest period. The period of time during which the active pharmaceutical ingredient (API) is expected to remain within its specification and, therefore, can

be used in the manufacture of a given finished pharmaceutical product (FPP), provided that the API has been stored under the defined conditions. After this period, a batch of API destined for use in the manufacture of an FPP should be retested for compliance with the specification and then used immediately. A batch of API can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

semi-permeable containers. Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by adsorption onto one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semi-permeable containers include plastic bags and semi-rigid, low-density polyethylene (LDPE) pouches for large-volume parenterals and LDPE and high-density polyethylene (HDPE) ampoules, bottles and vials.

shelf life. The period of time during which an active pharmaceutical ingredient (API) or finished pharmaceutical product (FPP), if stored under the conditions in which stability was established, is expected to comply with the specification as determined by stability studies on a number of batches of the API or FPP. The shelf life is used to establish the expiry date of each batch.

shelf-life specification. The combination of physical, chemical, biological and microbiological tests and acceptance criteria that an active pharmaceutical ingredient or finished pharmaceutical product should meet throughout its retest period or shelf life.

significant change. (See sections 2.1.7 and 2.2.7.)

“Significant change” for an active pharmaceutical ingredient (API) is defined as failure to meet its specification. In general “significant change” for a finished pharmaceutical product is defined as: a 5% or more change in assay from its initial content of API(s), or failure to meet the acceptance criteria for potency when using biological or immunological procedures.

Any degradation product exceeding its acceptance criterion.

1. Failure to meet the acceptance criteria for appearance, physical attributes and functionality test (e.g. colour, phase separation, resuspendability, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g. softening of suppositories, melting of creams or partial loss of adhesion for transdermal products) may be expected under accelerated conditions.

Also, as appropriate for the dosage form:

2. failure to meet the acceptance criterion for pH; or
3. failure to meet the acceptance criteria for dissolution for 12 dosage units.

specification. A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges or other criteria for the tests described. It establishes the set of criteria to which an active pharmaceutical ingredient or finished pharmaceutical product should conform to be considered acceptable for its intended use. See *Release specification* and *Shelf-life specification*.

stability-indicating methods. Validated analytical procedures that can detect the changes with time in the chemical, physical or microbiological properties of the active pharmaceutical ingredient (API) or finished pharmaceutical product, and that are specific so that the content of the API, degradation products and other components of interest can be accurately measured without interference.

stability studies (stability testing). Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period (or shelf life) of an active pharmaceutical ingredient or the shelf life of a finished pharmaceutical product.

stress testing (of the active pharmaceutical ingredient (API)). Studies undertaken to elucidate the intrinsic stability of an API. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

stress testing (of the finished pharmaceutical product (FPP)). Studies undertaken to assess the effect of severe conditions on the FPP. Such studies include photostability testing and specific testing on certain products (e.g. metered-dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

supporting stability data. Supplementary data, such as stability data on small-scale batches, related formulations, and products presented in containers not necessarily the same as those proposed for marketing, and scientific rationales that support the analytical procedures, the proposed retest period or the shelf life and storage conditions.

utilization period. See in-use period.

variations. A change to any aspect of a pharmaceutical product, including but not limited to, the change of use of a starting material, a change to formulation, method or site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

References

1. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-third report. Geneva: World Health Organization; 2009: Annex 2 (WHO Technical Report Series, No. 953).
2. The following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines (<http://www.ich.org>) may be consulted in the context of stability testing:
 - ICH Q1A (R2): Stability testing of new drug substances and products.
 - ICH Q1B: Photostability testing of new drug substances and products.
 - ICH Q1C: Stability testing of new dosage forms.
 - ICH Q1D: Bracketing and matrixing designs for stability testing of new drug substances and products.
 - ICH Q1E: Evaluation for stability data.
 - ICH Q2R1): Validation of analytical procedures: text and methodology.
 - ICH Q3A: Impurities in new drug substances.
 - ICH Q3B: Impurities in new drug products.
 - ICH Q5C: Quality of biotechnological products: stability testing of biotechnological/biological products.
 - ICH Q6A: Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.
 - ICH Q7: Good manufacturing practice guide for active pharmaceutical ingredients.
 - ICH Q8: Pharmaceutical development.
 - ICH Q9: Quality risk management.
 - ICH Q11: Development and manufacture of drug substances (chemical entities and biotechnological/biological entities).
3. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 6 (WHO Technical Report Series, No. 986).
4. Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 4 (WHO Technical Report Series, No. 970).
5. Guidelines on active pharmaceutical ingredient master file procedure. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-second report. Geneva: World Health Organization; 2008: Annex 4 (WHO Technical Report Series, No. 948).
6. Guidelines for registration of fixed-dose combination medicinal products. Appendix 3: Pharmaceutical development (or preformulation) studies. Table A1: Typical stress conditions in preformulation stability studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-ninth report. Geneva: World Health Organization; 2005: Annex 5 (WHO Technical Report Series, No. 929).

7. Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937) and forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992).
8. WHO good manufacturing practices: main principles for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
9. General guidance on hold time studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 4 (WHO Technical Report Series, No. 992).
10. Prequalification Programme – Priority Essential Medicines. A United Nations Programme managed by WHO. Information for applicants (<http://mednet3.who.int/prequal/>).

Appendix 1

Examples of testing parameters

Section I for active pharmaceutical ingredients

In general, appearance, assay and degradation products should be evaluated for all active pharmaceutical ingredients (APIs). Since some related substances might only be identified as degradation products in the outcome of the stability studies, all specified related substances should be monitored as part of API stability studies. Other API parameters that may be susceptible to change should also be studied where applicable (e.g. particle size and/or polymorphism when relevant for low-solubility APIs).

Section II for finished pharmaceutical products

The following list of parameters for each dosage form is presented as a guide to the types of tests to be included in a stability study. In general, appearance, assay and degradation products should be evaluated for all dosage forms, as well as the preservative and antioxidant content if applicable.

The microbial quality of multiple-dose sterile and non-sterile dosage forms should be controlled. Challenge tests should be carried out at least at the beginning and at the end of the shelf life. Such tests would normally be performed as part of the development programme, for example, within primary stability studies. They need not be repeated for subsequent stability studies unless a change has been made which has a potential impact on microbiological status.

It is not expected that every test listed be performed at each time point. This can also apply to sterility testing, which may be conducted for most sterile products at least at the beginning and at the end of the stability test period. A validated container-closure integrity test may be used in lieu of sterility testing. Tests for pyrogens and bacterial endotoxins may be limited to the time of release. Sterile dosage forms containing dry materials (powder-filled or lyophilized products) and solutions packaged in sealed glass ampoules may need no additional microbiological testing beyond the initial time point. The level of microbiological contamination in liquids packed in glass containers with flexible seals or in plastic containers should be tested at least at the beginning and at the end of the stability test period; if the long-term data provided to the regulatory authorities for marketing authorization registration do not cover the full shelf-life period, the level of microbial contamination at the last time point should also be provided. Weight loss from plastic containers should be reported over the shelf life.

The list of tests presented for each dosage form is not intended to be exhaustive, nor is it expected that every test listed be included in the design of a stability protocol for a particular finished pharmaceutical product (FPP) (for example, a test for odour should be performed only when necessary and with due consideration for the analyst's safety).

The storage orientation of the product, i.e. upright versus inverted, may need to be included in a protocol when contact of the product with the closure system may be expected to affect the stability of the products contained (e.g. liquids or semisolids), or where there has been a change in the container-closure system.

Tablets

Dissolution, disintegration, water content and hardness/friability. Dispersible tablets should additionally be tested for disintegration (with a limit of not more than 3 minutes) and fineness of dispersion.

Capsules

- hard gelatin capsules: brittleness, dissolution, disintegration, water content and level of microbial contamination;
- soft gelatin capsules: dissolution, disintegration, level of microbial contamination, pH, leakage and pellicle formation.

Oral solutions, suspensions and emulsions

Formation of precipitate, clarity (for solutions), pH, viscosity, extractables, level of microbial contamination.

- Additionally for suspensions, dispersibility, rheological properties, mean size and distribution of particles should be considered. Also polymorphic conversion may be examined, if applicable.
- Additionally for emulsions, phase separation, mean size and distribution of dispersed globules should be evaluated.

Powders and granules for oral solution or suspension

Water content and reconstitution time.

Reconstituted products (solutions and suspensions) should be evaluated as described above under "Oral solutions suspensions and emulsions" after preparation according to the recommended labelling, through the maximum intended use period.

Metered-dose inhalers and nasal aerosols

Some parameters listed may be assessed during development and not be required subsequently in stability studies. Dose content uniformity, labelled number of medication actuations per container meeting dose content uniformity, aerodynamic particle size distribution, microscopic evaluation, water content, leak rate, level of microbial contamination, valve delivery (shot weight), extractables/leachables from plastic and elastomeric components, weight loss, pump delivery, foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump. Samples should be stored in upright and inverted/on-the-side orientations.

For suspension-type aerosols, microscopic examination of appearance of the valve components and the container's contents for large particles, changes in morphology of the API particles, extent of agglomerates, crystal growth, foreign particulate matter, corrosion of the inside of the container or deterioration of the gaskets.

Nasal sprays: solutions and suspensions

Clarity (for solution), level of microbial contamination, pH, particulate matter, unit spray medication content uniformity, number of actuations meeting unit spray content uniformity per container, droplet and/or particle size distribution, weight loss, pump delivery, microscopic evaluation (for suspensions), foreign particulate matter and extractables/leachables from plastic and elastomeric components of the container, closure and pump.

Topical, ophthalmic and otic preparations

Included in this broad category are ointments, creams, lotions, pastes, gels, solutions, eye drops and cutaneous sprays.

- Topical preparations should be evaluated for clarity, homogeneity, pH, suspendability (for lotions), consistency, viscosity, particle size distribution (for suspensions, when feasible), level of microbial contamination/sterility and weight loss (when appropriate).
- Evaluation of ophthalmic or otic products (e.g. creams, ointments, solutions and suspensions) should include the following additional attributes: sterility, particulate matter and extractable volume.
- Evaluation of cutaneous sprays should include: pressure, weight loss, net weight dispensed, delivery rate, level of microbial contamination, spray pattern, water content and particle size distribution (for suspensions).

Suppositories

Disintegration and dissolution (at 37 °C) and as appropriate for the type, net filled content, rupture time, melting and solidification, liquefaction/softening time, leakage, pellicles and pH.

Small volume parenterals (SVPs)

Colour, clarity (for solutions), particulate matter, pH, sterility, endotoxins.

Stability studies for powders for injection solution should include monitoring for colour, reconstitution time and water content. Specific parameters to be examined at appropriate intervals throughout the maximum intended use period of the reconstituted drug product, stored under condition(s) recommended on the label, should include clarity, colour, pH, sterility, pyrogen/endotoxin and particulate matter. It may be appropriate to consider monitoring of sterility after reconstitution into a product, e.g. dual-chamber syringe, where it is claimed that reconstitution can be performed without compromising sterility.

- The stability studies for suspension for injection should include, in addition, particle size distribution, dispersibility, specific gravity, resuspendability, rheological properties and dissolution (when applicable). Content uniformity may be considered a stability-indicating parameter for the primary stability studies of a depot injection such as depomedroxyprogesterone acetate (DMPA) (refer to the WHO Prequalification Team-medicines (PQTm) DMPA guidance document published on the PQTm website: who.int/prequal/).¹
- The stability studies for emulsion for injection should include, in addition, phase separation, viscosity, mean size and distribution of dispersed phase globules.

Large volume parenterals (LVPs)

Colour, clarity, particulate matter, pH, sterility, pyrogen/endotoxin and volume.

Transdermal patches

In vitro release rates, leakage, level of microbial contamination/sterility, peel and adhesive forces.

¹ https://extranet.who.int/prequal/sites/default/files/documents/46%20DMPA_Aug2015_0.pdf.

Appendix 2

Recommended labelling statements

1. Active pharmaceutical ingredients

The statements that should be used if supported by the stability studies for active pharmaceutical ingredients (APIs) are listed in Table A10.1.

Table A10.1

Recommended labelling statements for active pharmaceutical ingredients

Testing condition under which the stability of the API has been demonstrated	Recommended labelling statement ^a
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure during accelerated stability studies)	"Do not store above 25 °C" ^b
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C" ^b
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

^a During storage, shipment and distribution of the API, the current *Good trade and distribution practices (GTDP) for pharmaceutical starting materials* are to be observed (1). Details on storage and labelling requirements can be found in *WHO guide to good storage practices for pharmaceuticals* (2).

^b "Protect from moisture" should be added as applicable.

2. Finished pharmaceutical products

The statements that should be used if supported by the stability studies for finished pharmaceutical products (FPPs) are listed in Table A10.2.

Table A10.2
Recommended labelling statements for finished pharmaceutical products

Testing condition under which the stability of the FPP has been demonstrated	Recommended labelling statement ^a
25 °C/60% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 25 °C"
25 °C/60% RH (long-term) 30 °C/65% RH (intermediate, failure during accelerated stability studies)	"Do not store above 25 °C" ^b
30 °C/65% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C" ^b
30 °C/75% RH (long-term) 40 °C/75% RH (accelerated)	"Do not store above 30 °C"
5 °C ± 3 °C	"Store in a refrigerator (2 °C to 8 °C)"
-20 °C ± 5 °C	"Store in freezer"

^a During storage, shipment and distribution of the FPP, the current *good distribution practices (GDP)* for pharmaceutical products are to be observed (3). Details on storage and labelling requirements can be found in *WHO guide to good storage practices for pharmaceuticals* (2).

^b "Protect from moisture" should be added as applicable.

In principle, FPPs should be packed in containers that ensure stability and protect the FPP from deterioration. A storage statement should not be used to compensate for inadequate or inferior packaging. Additional labelling statements that could be used in cases where the result of the stability testing demonstrates limiting factors are listed in Table A10.3.

Table A10.3
Additional labelling statements for use where the result of the stability testing demonstrates limiting factors

Limiting factors	Additional labelling statement, where relevant
Finished pharmaceutical products (FPPs) that cannot tolerate refrigeration	"Do not refrigerate or freeze" ^a
FPPs that cannot tolerate freezing	"Do not freeze" ^a
Light-sensitive FPPs	"Protect from light"

Table A10.3 *continued*

Limiting factors	Additional labelling statement, where relevant
FPPs that cannot tolerate excessive heat, e.g. suppositories	"Store and transport not above 30 °C"
Hygroscopic FPPs	"Store in dry condition"
Packaging (with the packaging format specified in the statement, e.g. bottle, blister)	"Store in the original package" "Keep the container in the outer carton" "Keep the container tightly closed in order to protect from light and moisture"

^a Depending on the pharmaceutical form and the properties of the FPP, there may be a risk of deterioration due to physical changes if subjected to low temperatures, e.g. liquids and semisolids. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

References

1. Good trade and distribution practices for pharmaceutical starting materials. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 6 (WHO Technical Report Series, No. 996).
2. Guide to good storage practices for pharmaceuticals. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-seventh report. Geneva: World Health Organization; 2003: Annex 9 (WHO Technical Report Series, No. 908).
3. Good distribution practices for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth-fourth report. Geneva: World Health Organization; 2010: Annex 5 (WHO Technical Report Series, No. 957).

Appendix 3

Interpretation of storage statements for products approved in climatic zone II when the products are to be distributed in zone IV

In order to ensure the safe use of medicines in recipient countries, the wording on labelling storage statements must be considered in the context of both the region in and for which the stability studies were conducted and the region(s) in which the products are intended to be distributed.

For example, for products approved in a zone II region the stability testing has usually been conducted at accelerated conditions and at zone II long-term conditions. Demonstrated stability at zone II conditions may result in a label storage statement of “Store between 15 and 30 °C” in line with the convention of some zone II regions. A product with such a statement, received in a zone IV country, would be expected to have demonstrated stability at zone IVa or IVb long-term stability conditions. However, when the stability was demonstrated at zone II long-term conditions, the appropriate statement for distribution in a zone IV region would be “Do not store above 25 °C”.

Typical examples of the storage statements for products approved in zone II, with examples of the stability data on which the statements are based and the corresponding WHO-recommended storage statement for distribution in zone IV are provided in Table A10.4.

Table A10.4

Examples of stability data and storage statements for products approved in climatic zone II and WHO-recommended storage statements (for zone IV) based on the same data

Storage statement for products approved in zone II	Examples of stability data on which the statements are based	WHO-recommended storage statement for products to be distributed in zone IVa
This medicinal product does not require any special storage conditions (or similar, i.e. no temperature mentioned) (EU)	Zone II + accelerated (finished pharmaceutical product (FPP) is stable at long-term conditions, with no significant change at accelerated conditions)	“Do not store above 25 °C. Protect from moisture”

Table A10.4 *continued*

Storage statement for products approved in zone II	Examples of stability data on which the statements are based	WHO-recommended storage statement for products to be distributed in zone IVa
This medicinal product does not require any special storage conditions (EU)	Zone II + Zone IVb + accelerated (FPP is stable at long-term conditions (zones II and IVb), with no significant change at accelerated conditions)	"Do not store above 30 °C"
Do not store above 30 °C (EU)	Zone IVa + accelerated (FPP is stable at long-term conditions, with significant change at accelerated conditions)	"Do not store above 30 °C, avoid excursions. Protect from moisture"
Store at 15 °C to 30 °C (USA, Canada) OR Store at 25 °C; excursions permitted to 15 °C to 30 °C (USA) OR Store at controlled room temperature (15–30 °C). (Canada)	Zone II + accelerated (FPP is stable at long-term conditions, with no significant change at accelerated conditions)	"Do not store above 25 °C. Protect from moisture"

Note: Zone II is 25 °C/60% RH, zone IVa is 30 °C/65% RH and zone IVb is 30 °C/75% RH.

Note: IVa may be acceptable in lieu of IVb when humidity is not an issue, for example, for storage in glass containers (see 2.2.7.2 of the main text of the Annex).

Annex 11

Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

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1. Background information

Management of diseases known to be of major relevance to public health in countries with limited regulatory resources is often jeopardized by delayed access to new or needed therapies. Although many medicines successfully pass a regulatory review process conducted by internationally respected regulatory bodies, also known as stringent regulatory authorities (reference SRAs), or may in addition have been prequalified by the World Health Organization (WHO), local regulatory approvals tend to consume additional time and resources of national regulatory authorities (NRAs) before these therapies can be made available to patients.

To address this issue, WHO proposes a scheme for NRAs and pharmaceutical manufacturers to facilitate registrations of the vaccines and pharmaceutical products, including biotherapeutic products approved by reference SRAs.¹ WHO recognizes the scientific evaluation of medicines by reference SRAs as they apply similarly stringent standards for quality, safety and efficacy to those recommended by WHO.

Based on WHO experience with the Collaborative procedure of WHO-prequalified pharmaceutical products and vaccines,² it is possible to facilitate and accelerate national registration processes by provision of detailed assessment and inspection outcomes generated by respected regulatory bodies.³ Assessment and inspection reports of reference SRAs made available in addition to the registration dossiers can facilitate the adoption of national regulatory decisions by assuring NRAs about the positive risk–benefit profile of a product and that its quality is identical with the product already approved elsewhere. Normally, publicly available versions of assessment and inspection outcomes do not provide all the necessary information in sufficient detail to enable regulatory decisions to be adopted. Therefore, detailed assessment and inspection outcomes that include commercially sensitive data must be shared. Whether to make such information sharing possible is up to interested pharmaceutical manufacturers, which

¹ In addition to medicines approved by the conventional marketing authorization process, the Procedure is applicable to special “approval” mechanisms like the scientific opinion process according to Article 58 of Regulation (EC) No. 726/2004, in the European Union (EU).

² Collaborative procedure between the World Health Organization (WHO) Prequalification Team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 8 (WHO Technical Report Series, No. 996), 263-304.

³ Under the Collaborative procedure for WHO-prequalified pharmaceutical products and vaccines, the assessments and inspections are organized by WHO, although WHO cannot be considered as a regulatory body.

should provide consent to information exchange among reference SRAs and NRAs, to which a product is submitted for regulatory approval. Pharmaceutical manufacturers benefit from accelerated and facilitated regulatory processes. For their part, it is up to interested NRAs to provide sufficient assurance that shared data will be treated with necessary care and respect for confidentiality. Nonetheless, in some jurisdictions, publicly available information such as public assessment or inspection reports, and databases of compliance with good manufacturing practices (GMP) contain substantial summarized regulatory information that can facilitate the decision-making process in less well-resourced NRAs as well.

It should be stressed that the decision to apply the process for specific medicines is up to the NRAs concerned, which retain the prerogative to conclude their assessment through sovereign decisions on medicine registration within their national jurisdiction.

In addition to the facilitation of regulatory decisions on needed medicines and faster access to patients, the process also represents an avenue for harmonization of regulatory requirements and capacity-building.

The Procedure is applicable in principle to all types of medicines irrespective of whether the products are of an innovative or generic nature. The procedure is also applicable to biotherapeutic products and vaccines.

2. Glossary

For the purposes of this document, the following definitions and descriptions apply. They may have different meanings in other contexts.

biotherapeutic. A biological product with the indication of treating human diseases.

collaborative procedure of reference SRA-approved pharmaceutical products and vaccines (Procedure). Registration procedure in which assessment and national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (reference SRAs) is facilitated and accelerated by sharing of detailed assessment and inspection outcomes generated by a reference SRA.

manufacturer. Any person or legal entity engaged in the manufacture of a product subject to marketing authorization or licensure; or any person or legal entity that is an applicant or holder of a marketing authorization or product licence where the applicant assumes responsibility for compliance with the applicable product and establishment standards.

medicine. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings,

or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

participating authority or participating national medicines regulatory authority. National regulatory authority (NRA) that voluntarily agrees to implement this collaborative procedure and accepts the task of processing applications for registration of medicines approved by reference SRAs in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO Prequalification Team (WHO PQT) website (<http://www.who.int/prequal/>).

participating manufacturer. A manufacturer, which is a holder of a marketing authorization granted by a reference SRA for a medicine that is intended to be submitted, has been submitted or has been granted national registration by participating NRAs in line with principles of the Procedure.

participating stringent regulatory authority. A reference stringent regulatory authority that agrees to provide outcomes of its regulatory expertise (especially assessment and inspection reports) to applicants/authorization holders or inspected manufacturers, does not object to sharing of these documents with national medicines regulatory authorities and provides, under specified conditions in line with the principles of the Procedure, support to other parties involved in the Procedure.

pharmaceutical product. Any substance or combination of substances marketed or manufactured to be marketed for treating or preventing disease in human beings, or with a view to making a medical diagnosis in human beings, or to restoring, correcting or modifying physiological functions in human beings.

stringent regulatory authority.⁴ A regulatory authority which is:

- a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission,⁵ the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015)); or
- b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or

⁴ Clarification with respect to the definition of stringent regulatory authority. See WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: (WHO Technical Report Series, No. 1003), pp 34–35; and WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018 (WHO Technical Report Series, No. 1010), Section 10.1).

⁵ For the European Commission, products approved via the centralized procedure by the European Medicines Agency, decentralized procedure or mutual recognition in the European Union (EU) are eligible provided the respective NRA in the EU agrees to participate as a reference SRA in the Procedure.

- c) a regulatory authority associated with an ICH member through a legally binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015).

vaccine. A biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, one of its surface proteins or genetically-engineered material. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

variation. A change to any aspect of a medicine, including but not limited to, the change of use of a starting material, a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

3. Principles of collaborative procedure

Principles of the procedure (same product or defined deviations, available assessment and inspection outcomes, bridging information facilitating assessment of risk–benefit profile in new target environment, post-authorization variations and commitments in line with the SRA) are applicable to any regulated product. Nonetheless, there is a difference in the nature and scope of documents to be shared for different product categories. At present, the process is applicable to reference SRA-approved (innovative and generic medicines) and vaccines. Products approved through special mechanisms such as conditional marketing authorization or under exceptional circumstances are eligible for the procedure if there is a high unmet medical need of public health importance because access to the reference SRA assessment reports would help participating NRAs to understand the acceptability of the risk–benefit profile of such products.

Participation of all parties is voluntary and should be performed in compliance with relevant applicable legislation. All reference SRAs, NRAs and holders of marketing authorization for products considered to be therapeutically important by participating NRAs are welcome to participate. WHO plays a facilitating role in this process and in monitoring of its use and refinement of the details of the conditions.

The general approach is similar to the principles of Collaborative procedure of WHO-prequalified products in terms of information sharing, utilization of shared information, management of confidentiality and time frame. Instead of the WHO PQT, reference SRAs are the generators of the basic regulatory expertise in this procedure.

The dossiers submitted for national registration are organized in line with the globally harmonized common technical document (CTD) format to maximize use of data already submitted to reference SRAs. In the case of generic medicines, the technical part of the dossier is equivalent to the WHO PQT prequalification dossier requirements. The open part of the active pharmaceutical ingredient (API) master file is considered sufficient, unless the manufacturer is informed otherwise by the respective NRA. For innovative products (i.e. new drug applications (NDAs), biologicals licence applications for vaccines or self-standing applications) the submitted dossier consists of a rather simplified version of the reference SRA dossier (unless otherwise requested by the respective NRA) to reduce the volume of submissions to a manageable level, while including all data essential for national assessments. Such pragmatic simplification also reduces the risk of unnecessary dissemination of highly sensitive commercial information and can make the process more acceptable for pharmaceutical manufacturers.

The key role in the process is assigned to the pharmaceutical manufacturers, which conduct the procedure and organize the provision of relevant regulatory information generated by reference SRAs to participating NRAs. The conditions under which individual reference SRAs agree to make available the assessment and inspection reports for this purpose have to be confirmed with each reference SRA. It is planned that WHO will summarize the positions of willing reference SRAs as regards the availability of assessment and inspection reports and post this information on its website, similarly to the list of NRAs that have agreed in principle to apply the piloted procedure. It is expected that the reference SRAs that issued the marketing authorization will provide a certain amount of support and cooperation, if necessary (e.g. authentication of submitted documents in case of doubt). In general, to save the resources of reference authorities, the role of reference SRAs in the proposed process is minimized.

It is up to the participating NRAs to recognize which individual medicines would be eligible for registration under this procedure, considering the relevance of the medicine concerned for public health and existing NRA capacity.

Confidentiality of shared data is assured by mechanisms applied by participating parties (NRAs, reference SRAs, manufacturers and WHO). Participating NRAs make a special commitment in the respect that any information and documentation provided to them by applicants and reference SRAs (possibly mediated by WHO) pursuant to this procedure will be treated as confidential and access to this information will be allowed only to persons involved in the individual registrations who are bound by confidentiality undertakings (Appendix 1). Authorities that make such a commitment and agree to apply the principles of the Procedure will be publicly listed by WHO.

After initiation of the Procedure, switching to the normal registration process is possible, provided that the parties involved inform each other of this decision.

3.1 Principal roles of the participating parties

Participating NRAs express their interest in participating in the Procedure, their commitment to respect the principles of the Procedure and their confirmation of confidential treatment of commercially sensitive information by forwarding to WHO a completed copy of Appendix 1 to this Procedure. A focal person for communication on issues relevant for the Procedure will be designated in each participating NRA. A list of participating authorities is posted on the WHO PQT website (<http://www.who.int/prequal/>). For GMP requirements for the procedure, the NRAs should refer to *Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for marketing authorization of medical products* (WHO Technical Report Series, No. 1010, Annex 7, 2018). The guidelines provide the general approaches and best practices for desk assessment to verify and confirm compliance with GMP, good laboratory practices (GLP) and good clinical practices (GCP) of foreign facilities for manufacture of finished pharmaceutical products (FPPs) and APIs, quality control laboratories (QCLs) and contract research organizations (CROs)/clinical trial sites. The desk assessment of inspection reports is mostly sufficient to eliminate the need for site inspections.

Participating reference SRAs do not object to sharing their assessment and inspection reports with applicants or authorization holders to support access to needed medicines in line with the principles of the Procedure. Conditions and mechanisms by which the information will be shared, and the extent to which additional support can be offered to the participating NRAs are notified to WHO. A list of reference SRAs that agree to share the outcomes of their regulatory expertise in line with the principles of the Procedure and detailed conditions of information sharing are posted on the WHO PQT website (<http://www.who.int/prequal/>). An example of such a listing is provided in Appendix 2.

Participating manufacturers submit applications to NRAs and provide the assistance necessary to finalize the application in line with the Procedure. The participating manufacturers applying for registration have a major role in the national registration process and in the post-registration phase by carrying out the Procedure and providing any additional information requested. A primary obligation of the manufacturers is to inform the NRAs when a regulatory decision is taken by the reference SRA post-authorization, e.g. relating to non-compliance with GMP, withdrawal of the product, suspension of marketing authorization, or when the product is no longer authorized or marketed in the jurisdiction of the reference SRA.

WHO assists in the execution and maintenance of the Procedure, posts lists of participating NRAs and reference SRAs (including reference SRA conditions

for information sharing) on its website and collects information about the performance of the Procedure. Should the medicine be highly therapeutically relevant for WHO-supported treatment programmes, WHO actively facilitates information exchange among the reference SRAs involved and the participating NRAs. WHO provides information on products approved by participating NRAs through the facilitated registrations using the reference SRA procedure and makes it publicly available.

4. Medicines

Both innovative and generic medicines approved by reference SRAs are eligible for the Procedure. The medicines submitted for registration to the participating NRAs should be identical with medicines approved by reference SRAs. Within the context of this Procedure, identical products are characterized by the descriptions listed below. Note that should there be any deviations from this definition of “sameness”, these must be notified (e.g. different supply chain, specifications, stability or medical claims) and such deviations can be the reason for non-applicability of the Procedure.

For this Procedure, the same medicine is characterized by:

- the same qualitative and quantitative formulation;
- the same manufacturing site(s)⁶ for API and FPP including specific block(s)/unit(s), chain, processes, control of materials and final product, and in the case of vaccines also by the same batch release scheme;
- the same specifications for excipient, API and FPP;
- the same essential elements of product information.⁷

⁶ “Sameness” of the manufacturing sites for APIs and FPPs means that the specific site must be approved by the reference SRA for the specific product under consideration and included as part of the marketing authorization in the reference SRA country. Any additional sites, regardless of their GMP status, are not acceptable under this procedure. Any changes or variations to include additional sites should be approved by the reference SRA before inclusion in the submission to the participating NRAs.

⁷ The essential elements of product information include the indications, contraindications, posology (dosing), special warnings and precautions for use, adverse reactions, storage conditions, primary packaging and shelf life. For pharmaceutical products, differences in brand name, the name of the applicant, language, format and degree of detail of the product information, labelling of primary, secondary and tertiary packaging, among others, are not considered essential for the purposes of this Procedure. The language of the product information may be different as long as the information content is the same as that approved by the reference SRA.

4.1 Submissions format and content

- The dossiers submitted for national registrations are organized in International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) CTD format and contain data specified in Appendix 5. The scope of submitted technical data for innovators (i.e. NDAs or self-standing applications) represents a subset of the data submitted to reference SRAs that provides sufficient assurance about product identity, quality, safety and efficacy and meeting requirements for the NRAs. To the extent possible, API quality is confirmed by existing certification schemes (e.g. certificate of suitability (CEP)). The critical quality attributes of the excipients are taken into consideration and checked. In principle, only nonclinical and clinical summaries (ICH Module 2) are submitted instead of extensive full ICH Modules 4 and 5. However, the applicants are committed to submit these modules or specific nonclinical and clinical data if asked to do so by a participating NRA. The applicant should confirm with the respective NRAs whether full Modules 4 and 5 are required at the time of submission. It may be advantageous to submit, in addition to existing overviews, a “bridging report” that provides the summarized evidence on risks and benefits and justification of the relevance of the product for the countries for which marketing authorization is sought (Appendix 6).
- In the case of generic medicines the technical part of a dossier corresponds in Module 3 to the full scope of quality data on a finished dosage form (part 3.P) and data on the API correspond to the open part of the API master file (APIMF). Demonstrations of bioequivalence and biowaiver criteria are equivalent to the WHO PQT prequalification dossier requirements (www.who.int/prequal).
- In addition to technical data the applicants provide NRAs with:
 - valid assessment and inspection reports issued by reference SRAs;
 - quality information summary (QIS)-SRA(crp) (Appendix 4);
 - a declaration assuring the identity of the product with the medicine approved by the reference SRA, consent to communicate freely with the reference SRA on product-related matters, and additional commitments as specified in Appendix 7;
 - a declaration confirming same site and source including specific block(s) or unit(s) for API and FPP production;
 - commitment to conduct risk assessment or transport validation for supply of products to the NRA market, if such assessment or validation was not already covered as part of the dossier.

Should the local applicant be a different legal entity to the holder of reference SRA marketing authorization (or scientific opinion), the relationship should be clarified and agreements assuring information flow should be adjusted to reflect this situation.

Translation of documents required in the national language is the responsibility of the manufacturer. The method and extent of verification of translation accuracy are a matter of decision of individual NRAs.

Samples, if required, should be used for checks on appearance or packaging. Laboratory testing of registration samples is not recommended and random sampling and testing should be planned in the post-registration period. Mock-ups showing the graphic design of package labelling are an acceptable way to present the texts and symbols on the packaging.

Note, however, that participating authorities may require applicants to comply with specific additional national requirements. Each participating authority is encouraged to reduce the scope of specific national requirements to align them with the Procedure and harmonize its requirements with the international format and content of a regulatory dossier. Specific national requirements should be made public.

4.2 Registration process according to the Procedure

The process flow of the Procedure is shown in Figure A11.1 and described briefly below.

1. *Pre-submission phase*
 - a. Manufacturers considering registrations according to the Procedure should familiarize themselves with the principles of the Procedure, which NRAs are prepared to participate in the Procedure, and the conditions under which reference SRAs that have authorized their medicine will agree to share information and provide additional prospective support.
 - b. It is recommended that a participating manufacturer should confirm with the participating NRA(s) its interest in applying the Procedure for the given medicine before the submission.
 - c. The manufacturer also needs to provide the reference SRA with its consent to share the relevant regulatory information with participating NRA(s). A model of the content of such consent has been proposed (Appendix 3A), but it is up to individual applicants and reference SRAs to agree on the details of the wording.
 - d. In the case that the manufacturer does not have valid assessment and inspection reports available, these should

be requested from the respective reference SRA. Should the manufacturer need to obtain the agreement of the reference SRA before sharing the assessment and inspection reports, such agreement should be requested. The model for the proposed content of the request is shown in Appendix 3B.

- e. In the case of medicines that are relevant for WHO-supported disease treatment programmes, the manufacturer should agree with WHO the extent of WHO's coordination and support.
 - f. The manufacturer prepares the quality information summary (QIS) reference SRA (QIS-SRA (crp)) (Appendix 4) and the QIS should be verified and endorsed by the reference SRA that issued the marketing authorization.
 - g. The reference SRA should provide the required documentation, e.g. assessment and inspection reports (where applicable) and endorsement of the QIS-SRA(crp) within 30 days from receipt of the request from the manufacturer or applicant. The individual reference SRAs are invited to notify WHO about their timelines and deadlines for these activities to be posted publicly on the WHO websites referenced in the Procedure.
2. *Submission for registration*
 - a. The manufacturer submits the registration application to the participating NRAs within 90 days from the date of receipt of documentation from the reference SRA. Specific national requirements must be respected, but it is up to the NRAs to minimize national deviations from the internationally acceptable dossiers to the greatest extent possible. Application fees may be charged in accordance with national requirements.
 - b. The registration dossier is organized in CTD format and consists of data sets as specified in Appendix 5, including valid assessment and inspection reports issued by the reference SRA and a manufacturer or applicant's declaration.
 - c. In the case of submissions coordinated with WHO, the manufacturer informs WHO about applications submitted to individual NRAs and comes to an agreement with WHO as regards access to the shared data (Appendix 8).
 3. *NRAs' acceptance of products for registration in line with the Procedure and registration phase*
 - a. The participating NRA validates the applications and documents submitted, decides whether or not to apply the

Procedure in each specific case, and informs the applicant of its decision within 30 days.

- b. Should the NRA have any doubts about the authenticity or validity of any of the assessment or inspection reports submitted, it can ask the respective reference SRA for confirmation. The way in which confirmation is organized can vary between reference SRAs. The practical way is to share recent assessment and inspection reports as archived by the reference SRA.
- c. The NRA processes an application, benefiting from shared reference SRA regulatory outcomes and assurance about the identity of the medicine with the one approved by the reference SRA. It is up to individual NRAs to decide to what extent they accept, verify or reassesses the information provided before coming to a decision. A pragmatic approach is to verify product identity and assess only those areas that relate to use of the product in the country concerned and where failure to comply with regulatory standards could pose specific health risks. For example, these might include: review of stability data for the climatic conditions appropriate to the participating NRAs, if these are different from those approved by the reference SRA; risk management plans (RMPs); bridging report; and labelling and product information for products approved for use in reference SRA countries. Note that product approval through mechanisms such as Article 58 of the Regulation of the European Commission, Health Canada Access Programme, United States Food and Drug Administration tentative approval, or the Swissmedic Marketing Authorization for Global Health Products Procedure is already designed to address such contextual issues in the receiving countries. Participating NRAs should avoid retesting samples prior to authorization. In the other areas, the outcomes of assessments by trusted authorities are proposed to be adopted.
- d. Participating reference SRAs can be approached to provide additional explanation or justification, depending on the extent of an individual reference SRA's commitment to support the process. In the case of medicines prioritized by WHO, the Organization can arrange for responses to questions, discussion via tele- or videoconferences or joint meetings with reference SRA experts to facilitate the process.

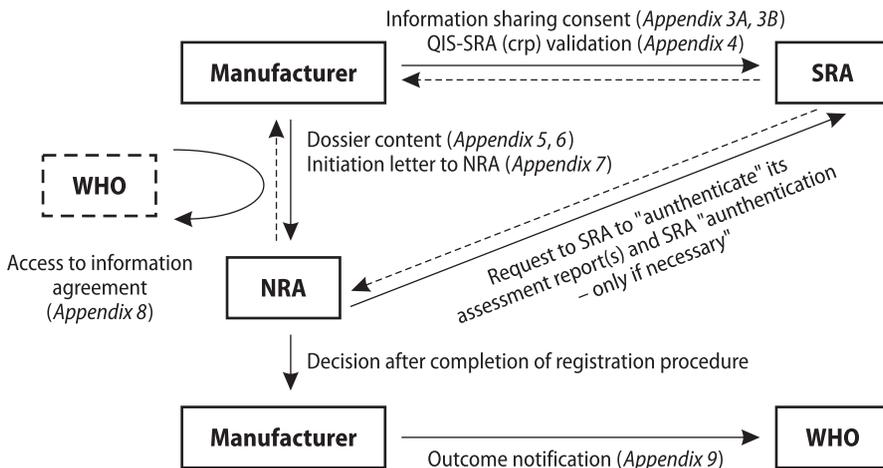
- e. Participating NRAs issue a decision within 90 calendar⁸ days of regulatory time⁹ from acceptance of the submission for processing according to the Procedure.
- f. Granting of registrations processed according to this Procedure is notified by the manufacturer to WHO to allow it to monitor the Procedure performance. Information about registered medicines, deviations from a reference SRA decision, dates of submission and experience is notified according to Appendix 9.

Figure A11.1

A summary of the steps in the Procedure and corresponding documentation

Preconditions to initiate the national registration in line with the Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (SRAs)

- national regulatory authorities (NRAs) agree to participate and follow the principles of the procedure (*Appendix 1*)
- SRAs define conditions of their participation (*Appendix 2*)



QIS: quality information summary; NRA: national regulatory authority; SRA: stringent regulatory authority.

⁸ Participating authorities should issue their national regulatory decisions at the earliest opportunity after being given access to the confidential information and documentation on a given product. If a participating authority does not issue its decision within 90 days of regulatory time, the reasons should be communicated to the applicant, and/or to the reference SRA, or to WHO, where applicable.

⁹ Regulatory time starts after a valid application for registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

5. Collaboration mechanisms for management of post-registration variations

5.1 General principles

The following principles are proposed to be respected during submissions of variations to medicines and vaccines registered or submitted for registration in line with the reference SRA Procedure. These principles take into account the existing reality of non-harmonized variation processes among NRAs that participated in the pilot reference SRA Procedure. The recommended approach to handling these variations is driven by the principle of non-interference with national legislation and decision-making while facilitating national decisions on variations by provision of essential information assuring that the medicine registered by the reference SRA procedure is of equivalent quality, and in line with the latest reference SRA decisions.

These guidelines focus on all variations relevant to countries that registered the product in line with the reference SRA Procedure. Variations that were submitted or notified to the reference SRA authority should be submitted to NRAs in participating countries to assure consistency of the regulatory status of the approved products between the reference SRA and NRAs over the product life-cycle. All variations that are approved by reference SRAs before an application for registration is submitted to the participating NRAs should be submitted and clearly identified in the initial submission to participating NRAs under this Procedure. It is not necessary to submit all changes, e.g. administrative changes that are relevant for the territory of the reference SRA only, or changes affecting the quality of the product that are specific to the reference SRA region. Variations that have local relevance in participating countries, which are not submitted or notified to the reference SRA should be submitted in line with national requirements.

The cover letter submitted with each variation should clearly indicate if a variation was submitted or notified to and approved or accepted by the reference SRA, or if a variation is only a national one.

Line extensions of already registered medicines (e.g. new formulations, additional strengths, new routes of administration, changes in active substance(s)), which were submitted to the reference SRA as a new application, are not considered as variations in this document.

At present, only variations are discussed. Management of other regulatory documents such as renewal submissions and outcomes, periodic benefit-risk evaluation report (PBRER) submissions and outcomes, submissions and outcomes concerning post-authorization measures and RMP updates will be the subject of future discussions. However, national guidance should be followed, should any of these documents and regulatory information already be required under existing national regulation.

5.2 Variations that are under assessment by reference SRAs at the time of submission of an application for registration to participating NRAs

All variations under the reference SRA assessment for which a decision is expected before finalization of the collaborative Procedure (registration process is expected to be complete within 90 days), should be identified in Appendix 4. Data supporting such variations should be included in the dossier submitted with the registration application.

The applicant should confirm and attest that the information submitted to the NRA is the same as that submitted to the reference SRA for the variation, where applicable.

The applicant should notify participating NRAs of the reference SRA's decision outcome(s) (and any conditions in the case of approval) within 30 days (preferably during exchange of questions and responses between the NRA and the applicant). If an assessment report is issued by the reference SRA, once the procedure is completed, a copy should be provided. In the case of variations not approved by the reference SRA, the applicant notifies NRAs about withdrawal (invalidation) of data related to the respective variation.

NRAs may consider reference SRA decisions on these variations during the registration process, thus avoiding the need to submit national variations immediately after the decision on registration is issued. In the case of variations not concluded by the reference SRA before the national registration is granted, the NRAs have the following options:

- consider these variations and grant registration, including conditional approval of not-yet reference SRA-approved variations; or
- defer the decision on registration until the reference SRA approval is obtained; or
- register the product based on the current reference SRA-approved conditions and await submission of variations according to section 4.3.

5.3 Variations approved by reference SRAs after national registrations are granted

Holders of registrations granted on the basis of the reference SRA Procedure are committed to keep NRAs informed about all variations or regulatory actions (e.g. urgent safety restrictions, suspensions of authorization) (Appendix 4, section 4b). The information should be provided in the form of the variation dossier submitted to the reference SRA. Holders of national registrations are

required to submit variations that have been approved (or accepted in the case of notification) by the reference SRA to relevant¹⁰ participating authorities without delay at the latest 30 calendar days after the reference SRA's decision has been made. Should national legislation in a participating country require additional data or samples which are not practical to submit within 30 calendar days, the variation should be submitted as soon as possible, with a plausible explanation. There is no need to submit variations that have not been approved or accepted by the reference SRA.

The same data as submitted and approved by the reference SRA should be submitted to NRAs. The applicant should therefore confirm and attest that the information (variation dossier) submitted to the NRA is the same as that submitted to the reference SRA for the variation where applicable. In the case that an assessment report has been issued, this should be submitted with the copy of the reference SRA decision or other document confirming the final position of the reference SRA. In the case that the variation modifies information submitted to the NRA in the reference QIS-SRA (crp), a new updated reference QIS-SRA (crp) should be submitted. The reference SRA should provide the required documentation, e.g. assessment and inspection reports (where applicable), and endorsement of the QIS-SRA (crp) within 30 days from receipt of the request from the manufacturer or applicant.

The NRAs should rely on the decision of the reference SRA to the extent possible, using expedited review pathways similar to the initial marketing authorization process under the reference SRA collaborative procedure. National decisions on such variations submitted in line with the reference SRA Procedure should not be taken by participating NRAs later than 30 calendar days following submission.

If the NRA disagrees with a notification, it should communicate this to the manufacturer within 30 days following the submission. Otherwise the notification shall be deemed accepted.

Should a participating NRA receive an application from a manufacturer for a variation that has not been previously approved by the relevant reference SRA (and it is not a case of deviation as described below in section 4.4), the product could deviate from the reference SRA-approved version and such variation merits special attention from the NRA.

The NRAs should make every effort to align their decisions. WHO can assist in such situations and mediate in communication between the parties involved.

¹⁰ Relevant variations are those variations that could impact quality, safety and efficacy in the receiving country. Examples of non-relevant variations include addition of a manufacturing site only for the market in the SRA's region.

5.4 **Variations in conditions of registration, which deviate from those approved by the reference SRA approval**

Deviations from the reference SRA's approved product characteristics, approved data and product information are possible provided the product is still considered – in principle – the same as the one approved by the reference SRA. All deviations from the conditions approved by the reference SRA should be identified in Appendix 4. All variations that differ from those approved by the reference SRA are subject to specific national variation guidelines in the participating countries. QIS: quality information summary; NRA: national regulatory authority; SRA: stringent regulatory authority.

Appendix 1

Agreement of the national regulatory authority to participate in the collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

Coordinated by the World Health Organization (WHO)

Details of national medicines regulatory authority (NRA)

Name of NRA: [Click here to enter text.](#) _____ (“the NRA”)

Postal address: [Click here to enter text.](#) _____

Country: [Click here to enter text.](#) _____

Telephone number (please include codes): [Click here to enter text.](#) _____

Email: [Click here to enter text.](#) _____

Scope of agreement

Applicants for national registration of a pharmaceutical product or vaccine approved by a stringent regulatory authority (reference SRA) (hereafter referred to as “Applicants”) may express their interest to the NRA for the assessment and accelerated registration of this product (“the Product”) in the country under the “*Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities*” (hereafter referred to as “the Collaborative procedure of reference SRA approved products” or “the Procedure”).¹

Subject to the NRA agreeing to participate in the Procedure and conduct such assessment and consider such accelerated registration of the product under the Procedure, the NRA hereby confirms for each such product that it will adhere to, and collaborate with, the Applicant for marketing authorization of the product and if relevant with the respective reference SRA and WHO in accordance with the terms of the Procedure.

¹ If the applicant for national registration is not the same as the reference SRA registration/marketing authorization holder, the reference SRA registration holder must confirm to the NRA with an authorization letter that the applicant is acting for, or pursuant to rights derived from, the reference SRA registration holder, and that the reference SRA registration holder agrees with the application of the Procedure in the country concerned.

Confidentiality of information

Any information and documentation relating to the product and provided by the Applicant or reference SRA to the NRA under the Procedure may include but shall not necessarily be limited to:

- the registration dossier as defined by the Procedure
- the full reference SRA assessment and inspection outcomes (reports);
- information and documentation on variations, as well as information and documentation on any actions taken by the reference SRA after national registration of the Product;
- all such data, reports, information and documentation being hereinafter referred to as “the Information”.

As regards sharing the outcomes of assessments and inspections, full reference SRA assessment and inspection reports are shared by Applicants with participating NRAs with the agreement of the respective reference SRA. Should any data in the assessment and inspection report be hidden for whatever reason, the nature and scope of missing data will be clearly indicated. Sharing of any data by the reference SRAs is subject to consent of the data owner.

The Applicant and reference SRA agree to make the Information available to the NRA exclusively for the purpose of the assessment and accelerated registration of the Product in the Country and any post-registration processes that may be required, in accordance with and subject to the terms of the Procedure (“the Purpose”). The NRA agrees to treat any Information provided by the Applicant and reference SRA as aforesaid as strictly confidential and proprietary to the Applicant, parties collaborating with the Applicant and/or reference SRA as relevant. In this regard, the NRA agrees to use such Information only for the Purpose and to make no other use thereof. Thus, the NRA undertakes to maintain the Information received from the Applicant and reference SRA in strict confidence, and to take all reasonable measures to ensure that:

- the Information received from the Applicant or reference SRA shall not be used for any purpose other than the Purpose;
- the Information shall only be disclosed to persons who have a need to know for the aforesaid Purpose and are bound by confidentiality undertakings in respect of such information and documentation, which are no less stringent than those contained herein.

The NRA warrants and represents that it has adequate procedures in place to ensure compliance with its aforesaid obligations.

The obligations of confidentiality and restrictions on use contained herein shall not cease on completion of the Purpose.

The obligations of confidentiality and restrictions on use contained herein shall not apply to any part of the Information which the NRA is clearly able to demonstrate:

- was in the public domain or the subject of public knowledge at the time of disclosure by the Applicant or reference SRA to the NRA under the Procedure; or
- becomes part of the public domain or the subject of public knowledge through no fault of the NRA; or
- is required to be disclosed by law, provided that the NRA shall in such event immediately notify the reference SRA and the Applicant in writing of such obligation and shall provide adequate opportunity to the reference SRA and/or the Applicant to object to such disclosure or request confidential treatment thereof.

Upon completion of the Purpose, the NRA shall cease all use and make no further use of the Information disclosed to it under the Procedure, and shall promptly destroy the Information received from the Applicant and the reference SRA, which is in tangible or other form and is not archived in accordance with archival procedures established by the NRA. The Purpose for each product shall be deemed completed as soon as:

- the reference SRA authorization holder/Applicant discontinues participation in the Procedure for the particular product;
- the Product is deregistered by the NRA and/or ceases to be authorized by reference SRA.

The NRA agrees that it has no right in or to the Information and that nothing contained herein shall be construed, by implication or otherwise, as the grant of a licence to the NRA to use the Information other than for the Purpose.

Should WHO staff or external experts independent on the Applicant or NRA be provided with an access to the Information in order to coordinate the Collaborative reference SRA procedure or provide an expert opinion, an access to the Information shall be subject to a confidentiality undertaking.

Timelines

In respect of each Product which the NRA accepts to assess and consider under the Procedure, the NRA undertakes to abide by the terms of the Procedure, including but not limited to the following timelines for processing each application:

- within 90 calendar days of regulatory time² after obtaining the assessment and inspection outcomes (reports) and validated QIS-SRA as well as receipt of validated submission, the participating NRA undertakes to take a final decision on the national registration of the Product;
- within 30 calendar days of regulatory time after obtaining the assessment outcomes (reports) and evidence of approval for variations and validated QIS-SRA (where applicable) as well as receipt of data submitted to the reference SRA for the variations, the participating NRA undertakes to take a final decision on the variation of the Product.

Miscellaneous

The NRA agrees that WHO may list its name on the WHO-PQT website as a participant in the reference SRA Procedure. Except as provided hereinbefore, neither party shall, without the prior written consent of the other party, refer to the relationship of the parties under this Agreement and/or to the relationship of the other party to the Product, the Information and/or the Purpose, in any statement or material of an advertising or promotional nature.

This Agreement shall not be modified except by mutual agreement of WHO and the NRA in writing. The NRA furthermore undertakes to promptly inform WHO/PQT of any circumstances or change in circumstances that may affect the implementation of this Agreement and its participation in the Procedure. This Agreement can be invalidated by a written note from the NRA to WHO. Validity of this Agreement expires at termination of the Procedure, which will be publicly announced.

Focal point(s) for communication

The NRA has designated the person(s) listed below to act as a focal point(s) for communication concerning the Procedure.

Title: _____

Name: _____

Position: _____

² Regulatory time starts after a valid application for the registration according to the Procedure has been received and access to the confidential information has been granted (whichever is the later) and continues until the date of decision on registration. The regulatory time does not include the time granted to the applicant to complete missing parts of the documentation, provide additional data or respond to queries raised by NRAs.

Email: _____

Telephone: _____

Title: _____

Name: _____

Position: _____

Email: _____

Telephone: _____

Agreed and accepted

For the NRA

Signature: Click here to enter text. _____

Name: Click here to enter text. _____

Title: Click here to enter text. _____

Place and date: Click here to enter text. _____



Appendix 2

Example of information included in the list of participating reference stringent regulatory authority(ies)

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
<p>Name and address of reference SRA Focal point for communication in matters related to the Procedure</p>	<p>Example 1 (EMA – current situation) EMA does not object to MAHs of centrally authorized medicines and holders of scientific opinions according to European Union Article 58 using final assessment and inspection reports in support of national registrations.</p>	<p>Example 1 (EMA – current position) It is expected that requests for authentication of documents will be exceptional. Subject to previous agreement with MAH (see Appendix 3 of the Procedure) the EMA can provide to the requesting NRA the full assessment reports or other relevant assessment documents.</p>	<p>Possible, on the understanding that these situations are exceptional and that such a request is channelled by WHO or the respective NRA, not by the manufacturer.</p>	<p>For example, the EMA supports the obligation of MAHs to keep national regulators informed of due major variations or line extensions; however, for the Procedure the EMA would suggest to focus on initial applications.</p>

Table continued

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
<p></p>	<p>However, when documents are provided to authorities in third countries by the MAH or holder of scientific opinion, personal information needs to be redacted. The “no objection statement” is provided by the EMA on request of individual MAHs. The request has to specify each NRA with which the assessment and inspection reports will be shared. The “no objection statement” is normally issued within 10 days.</p>	<p>As regards inspection reports, it is expected that the applicant will forward the latest inspection report(s) for the manufacturing site(s) to the participating NRA. Communication with the relevant Member State authority might be necessary to confirm authenticity of the inspection reports.</p>	<p></p>	<p></p>

Table continued

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
	<p>Example 2 (hypothetical reference SRA) Reference SRA does not object to MAHs of centrally authorized medicines and holders of scientific opinions according to Article 58 using final assessment and inspection reports in support of national registrations. However, when documents are provided to authorities in third countries by the MAH or holder of scientific opinion, personal information needs to be redacted.</p>			

Table continued

<p>Details of reference stringent regulatory authority (SRA) agreeing to proceed, in principle, in line with conditions of the Procedure</p>	<p>Provision of consent or “no objection statement” to share the assessment and inspection reports issued by the reference SRA</p>	<p>Agreement to authenticate the reference SRA-issued assessment and inspection reports on request of participating NRAs, which have received an application for registration according to the Procedure</p>	<p>Provision of additional explanation with scientific justification of granting authorization to NRAs, which have received an application for registration according to the Procedure</p>	<p>Reference SRA position on post-registration management of medicines registered by participating NRA using the Procedure</p>
	<p>The general statement confirming reference SRA position and conditions for sharing of the final assessment and inspection reports are made publicly available at www</p>			

EMA: European Medicines Agency; MAH: marketing authorization holder; NRA: national regulatory authority; SRA: stringent regulatory authority as stipulated by WHO.

Appendix 3A

Manufacturer's consent for information sharing with participating national regulatory authority(ies) and the World Health Organization

Date: _____ dd/mm/yyyy _____

To: _____

RE: <SRA> sharing of non-public information concerning <Product> with the <NRA(s)> and the World Health Organization (WHO)¹

Dear [<SRA>],

On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-referenced regulated product, I authorize the <SRA> to share the information described below (“Information”) only with <NRA focal point – contact person/function> and WHO <contact person/function> solely for the purpose of the *Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* <date; version>. Confidentiality agreements are in place between <manufacturer> and WHO.

I understand that the Information may contain confidential commercial or financial information or trade secrets that are exempt from public disclosure. I agree to hold <SRA> harmless for any injury caused by <SRA>'s sharing of the Information with the <NRA> and WHO under the terms set out herein.

Information authorized to be shared with the <NRA> and/or WHO:

- all available quality data on <Product>;
- all available nonclinical data on <Product>;
- all available clinical data on <Product>;
- any other document reasonably requested by the <NRA or WHO> during the evaluation procedure;

¹ During the *Collaborative procedure in national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* (WHO Technical Report Series No. 1010, 2018) WHO plays a facilitating role.

- all other information regarding GxP inspections and <Product> assessment.

Authorization is given to <SRA> to provide the Information without deleting confidential, commercial or financial, or trade secret information.

As indicated by my signature, I am authorized to provide this consent on behalf of <manufacturer> and my full name, title, address, telephone number and email address are set out below for verification.

Yours sincerely,

Name: _____

Title: _____

Address: _____

Manufacturer: _____

Email: _____

Telephone number: _____

Fax number: _____

cc:

Appendix 3B

Manufacturer's request for stringent regulatory authority's (SRA's) permission for sharing SRA-owned non-public information with participating national regulatory authority(ies) and the World Health Organization

Date: _____ dd/mm/yyyy _____

<manufacturer>

RE: Request to <SRA> for a permission to <manufacturer> to share <SRA>'s non-public information concerning <Product> with the <NRA(s)> and the World Health Organization (WHO)¹

Dear <reference SRA>,

<Manufacturer> as a <MAH> of the <SRA> authorized <Product>, hereby requests the <reference SRA's> permission to share <SRA>-owned non-public information concerning <Product> for the purpose of the *Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* assisted by WHO.

The information to be shared consists of

<SRA> final GxP inspection reports for Product <date; version>;

<SRA> Product assessment reports; and

<SRA> <other, please specify> documents/reports that may be needed in the context of this Procedure.

The information will be shared with the <NRA(s)> and WHO.

Yours sincerely,

Name: _____

Title: _____

SRA: _____

¹ During the *Collaborative procedure in national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (WHO Technical Report Series No. 1010, 2018)*, WHO plays a facilitating role.

Address: _____

Email: _____

Telephone number: _____

cc:



Appendix 4

Quality information summary of the finished pharmaceutical product or vaccine approved by the reference SRA (QIS- SRA (crp))

Foreword

Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities

The WHO *Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities* define a template for a simplified quality information summary (QIS) to outline the key quality parameters of a product approved by a stringent regulatory authority (reference SRA) for WHO prequalification. It was realized that this simplified QIS can be a useful instrument for sharing (under appropriate conditions of confidentiality) the essential quality parameters characterizing each medicine approved by SRAs in order to accelerate national decisions on registration. However, experience with the pilot-testing of the reference SRA *Collaborative procedure* revealed that the simplified WHO QIS does not contain certain data which would facilitate verification of “sameness” of the product for the purpose of the collaborative registration of reference SRA-approved medicines. Therefore the information content of the template was extended to the form of the “QIS-SRA (crp)”.

The QIS-SRA (crp) template should be completed by the applicant and verified by the reference SRA, ideally in the initial stage of the collaborative process, when the applicant (market authorization holder (MAH)) requests the reference SRA’s cooperation and grants consent to information sharing. Should data in the application for national registration deviate from data approved by the reference SRA, these should be clearly indicated and summarized in section B10. The QIS-SRA (crp) should be submitted as a part of the application for national registration together with other documents stipulated in the collaborative procedure for products approved by reference SRA. A copy should also be provided in Word format.

Whenever any variation to the approved product that affects the QIS-SRA (crp) has been approved by the reference SRA, the QIS-SRA (crp) should be revised (using track-changes mode) and resubmitted to the relevant regulatory authorities in Word format together with the regulatory letter or other relevant document confirming approval of the variation under consideration.

The QIS-SRA (crp) is specifically designed for the purpose of the SRA collaborative procedure and should not be confused with other formats of QIS that are used for the purpose of WHO prequalification.

When completing the QIS-SRA (crp) template, this covering *Foreword* should be deleted.

QUALITY INFORMATION SUMMARY OF THE FINISHED PHARMACEUTICAL PRODUCT OR VACCINE APPROVED BY THE REFERENCE SRA (QIS-SRA(crp))

A. Pharmaceutical product or vaccine subject to reference SRA collaborative procedure

A1 Reference SRA

A2. Product registration/authorization number assigned by the reference SRA

Information as currently approved by the reference SRA

A3. Proprietary name of finished pharmaceutical product (FPP) in the reference SRA country/region

A4. Innovator or multisource (generic) FPP

A5. Name of the holder of the reference SRA marketing authorization and official address

A6. International Nonproprietary Name (INN) of active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, solvate, etc.)

A7. Dosage form and strength

A8. Product description (as in Product information, e.g. white, film-coated, capsule-shaped tablets debossed with "X" and score line on one side and plain on other side)

A9. Primary and secondary packaging material(s) and pack size(s) (all pack types)

A10. Storage conditions (as in Product information)

A11. Shelf life of FPP (including in-use periods, where applicable)

A12. Names of all approved manufacturers of FPP, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, primary packaging site and release testing (indicate function of each site)

A13. FPP storage conditions and duration over which stability, as reported to the reference SRA, was established (e.g. $30 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ for 24 months, $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{RH}$ for 6 months):

Long-term (real time in months)	
Intermediate (duration in months)	
Accelerated (duration in months)	

B. Information that is considered confidentialia**Information as currently approved by the reference SRA**

B1. Names of all approved API manufacturers, physical address(es) of manufacturing site(s) (and unit if applicable), including intermediates, contractors and release testing (indicate function of each site)

B2. Active pharmaceutical ingredient master file/drug master file (APIMF/DMF version number(s) and date(s), if relevant)

Name of API	API manufacturer	APIMF/DMF version number(s) and date(s)

B3. API specifications of the FPP manufacturer

Standard (e.g. BP, Ph.Eur., Ph.Int., USP, in-house) ^a		
Specification reference number and version		
Test	Acceptance criteria	Analytical procedure (type/source/version)
Description		
Identification		
Impurities		
Assay		
Others, please specify		

Composition of all components purchased as mixtures (e.g. colourants, coatings, capsule shells, imprinting inks):

B6. FPP manufacture			
Master production document reference number and version			
B7. FPP specifications			
Standard (e.g. BP, Ph.Int., USP, in-house) ^a			
Specification reference number and version/ effective date			
Test	Acceptance criteria (release)	Acceptance criteria (shelf life)	Analytical procedure (type/source/version)
Description			
Identification			
Impurities			
Assay			
Others, please specify			
B8. Pharmacokinetic/safety/efficacy-related information used for reference SRA approval of multisource products. Indicate:			
Type of study	"X" in appropriate box	Comparator product	
Bioequivalence			
BCS-based biowaiver			
Other (specify)			
No study			
Notes/ clarifications			

^a BP: British Pharmacopoeia; Ph.Eur: European Pharmacopoeia; Ph.Int.: The International Pharmacopoeia; USP: United States Pharmacopoeia.

B9. List of variations pending in the reference SRA up to the date of verification		
Variation number	Variation	Type of variation according to reference SRA regulations

B10. Discussion of differences between national application and data approved by the reference SRA		
Deviation reference no.	Data submitted for national registration which deviates from data approved by the reference SRA presented above. Mention also deviations in content of Product information, especially those related to indications, contraindications and posology.	Explanatory note

C1. Confirmation of content and verification by the reference SRA		
Date of completion by the applicant	Name of person representing the applicant who completed the QIS-SRA	Position in the organization
Date of verification by the reference SRA <i>Part B10 is exempted from verification</i>	Person representing the reference SRA who verified the QIS-SRA information	Position in the organization

Change history to QIS-SRA (crp) and Product information

Date of revision (reported variation ^a)	Description of revision/variation

^a Variations approved by the reference SRA **after** national registration of the FPP and affecting **only** the QIS-SRA and/or Product information should be reported in the change history.

Appendix 5

Proposed documentation for collaborative procedure for reference SRA-approved pharmaceutical products and vaccines

Notes:

The format of the documentation corresponds to common technical document (CTD) in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) format/content. For practical reasons nonclinical (Module IV) and clinical data (Module V) are replaced by summaries included in Module II. Should there be a need for more extensive data from Module IV and Module V, these are available on request.

Confidentiality of submitted data and non-disclosure to a third party is – in addition to relevant national legislation and organizational measures applied by national regulatory authorities (NRAs) participating in the Procedure – assured by a commitment on confidentiality that represents an integral part of the Procedure¹ (Appendix 1), is signed by representatives of participating NRAs and archived by WHO.

Adapted Module 1

	Documentation to be provided	Comments
1.0 Letter of application		Cover letter in English, French, or as applicable to the region
Attachments to the letter:		
Appendix 3A of the reference stringent regulatory authority (SRA) Procedure		

¹ Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, facilitated by WHO.

Table *continued*

	Documentation to be provided	Comments
Appendix 3B of the reference SRA Procedure		
Appendix 4	Includes information as specified in Commitment letter 1 (additional administrative data) and Commitment letter 2 (additional stability data for climatic zones). Any differences in the dossier submitted to the reference SRA should be explained, including differences in product information.	Submitted in English or French as applicable to the region
1.1 Comprehensive table of contents (TOC)	Comprehensive TOC including Module 1 information	
1.2 Quality information summary (QIS-SRA)	This will be included instead of a country-specific application form	Refer to Appendix 9 for the QIS-SRA template To be included in the adapted Module 1
1.3 Product information		
1.3.1 Package insert or summary of product characteristics	Product information as applicable for the region where the application will be submitted	Submitted in English or French as applicable to the region
1.3.2 Patient information leaflet or package leaflet	Mock-ups	Submitted in English or French as applicable to the region
1.3.3 Labelling	Mock-ups	Language and information to reflect national requirements

Table continued

	Documentation to be provided	Comments
1.4 Marketing authorization from reference SRA		
1.4.1 Marketing authorization from reference SRA	Yes	
1.4.2 Assessment report from reference SRA (Access to the full assessment report from the reference SRA, if available)	Agreement from the manufacturer to allow reference SRA to share the report with WHO and national regulatory authorities (NRAs). Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Note that this type of document is available only for products registered in Europe, via the Centralized Procedure. Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between reference SRA and NRAs.
1.5 Good manufacturing practices (GMP) certification		
1.5.1 Copy of the GMP certificate of the active pharmaceutical ingredient (API) supplier, if available	Yes If not available, statement signed by qualified person (QP) from the finished pharmaceutical product manufacturing site to be provided	Currently, this is not always available. No legalization is required.
1.5.2 Copy of the GMP certificate of the finished pharmaceutical product (FPP) manufacturer(s)	Yes	No legalization is required.

Table *continued*

	Documentation to be provided	Comments
1.5.3 GMP inspection report of the manufacturing site(s) (FPP) from any reference SRA	Agreement from the manufacturer to allow the reference SRA to share the report with WHO and NRAs. Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between the reference SRA and NRAs.
1.6 Other documentation		
If generic dossier: <ul style="list-style-type: none"> – full GCP inspection report of the bioequivalence study from any reference SRA, if any; – bridging report (where applicable) especially for innovative medicines (Appendix 6); – information on local representatives or distributor. 	Agreement from the manufacturer to allow reference SRA to share the report with WHO and NRAs. Prior to sharing, the reference SRA and manufacturer should agree on the content of the document that is shared. If fully justified, sentences referring to highly confidential information and/or highly sensitive data and/or not related to the product assessment data could be masked.	Public reports are preferred as they already contain all useful information, except those considered to give a competitive advantage. The sharing process is facilitated by WHO, between the reference SRA and NRAs.

Module 2 summaries

Module 2 should be complete as submitted to the reference SRA.

Note: In the case of generic medicines for which a Clinical summary is not available, the Clinical overview (Module 2.5) should be included.

Module 3 Quality documentation

Complete Module 3 as submitted to the reference SRA, except corresponding open part of the active pharmaceutical ingredient master file (APIMF) is submitted, unless indicated otherwise according to the requirements of the participating NRA. If climatic zone III–IV stability data are not available, the commitment and protocol should be provided for stability studies under the appropriate climatic conditions for the receiving country. Any preliminary data under the required climatic conditions for the participating NRA should be provided. The stability data should be assessed by the reference SRA, where applicable or possible.

Additional region-specific information for Module 3 should be provided, where applicable.

Module 4 non-clinical documentation

Data to be provided only if required by the participating NRAs according to their national requirements, otherwise, these data are on request.

Module 5 clinical documentation

For innovative medicines, data to be provided only if required by the participating NRAs according to their national requirements, otherwise, these data are available on request. For generic products, complete documentation on bioequivalence studies should be provided in the submission in-line with WHO Guidelines on registration requirements to establish interchangeability² and applicable national regulatory requirements for participating NRAs.

² WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: (WHO Technical Report Series, No. 1003, Annex 6), 181-236.

Appendix 6

Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries

It is expected and is general practice that medicines authorized for use by reference SRAs are approved for the conditions of use relevant for the respective reference SRA territory. When a reference SRA-approved product is submitted for the regulatory approval in a country where conditions of use or the benefit–risk profile of the medicine may differ, it is assumed that the applicant for registration (marketing authorization) is able to support the application by providing evidence of a positive benefit–risk profile for the proposed conditions of use for the country concerned. Since reference SRA assessments may not always account for specific circumstances that can significantly affected the benefit-risk of a medicine in countries/regions outside the SRA's region, , the reference SRA assessment reports can be considered incomplete to enable appropriate benefit-risk evaluation in those settings. Currently only the European Medicines Agency (EMA)'s scientific opinion according to Article 58 of Regulation (EC) No. 726/2004, in the EU, may be considered to extensively address these questions.

Differences in target population, epidemiology and other features of the disease, concomitantly used medicines and hence the interaction potential, local treatment and diagnostic modalities and other factors can substantially affect the benefit–risk profile of a medicine. There can also be issues related to certain quality parameters, especially in relation to the stability under different climatic conditions. Therefore, to provide regulators in target countries with information relevant to the use of the product in their countries it is proposed to develop a bridging report supplementing the reference SRA assessment report (quality, safety) and the quality and clinical overviews provided in Module 2 of the common technical document (CTD).

Such a bridging report should, in particular, provide the applicants with the justification of the:

- comparability of the studied population to the target population (e.g. ethnicity, gender representation, age groups) as regards demonstration of safety and efficacy;
- relevance of reference SRA-approved conditions of use as regards epidemiology and disease pattern in the target countries as well

as other implications for efficacy and safety, e.g. feasibility of monitoring and precautionary measures (e.g. resistance testing or therapeutic drug monitoring);

- interactions with food and with other medications relevant in the target countries that are not discussed in the reference SRA's assessment report;
- therapeutic role of a product and its recommended use according to relevant national and international treatment guidelines;
- other related quality issues, including but not limited to, storage conditions and conditions of administration and use.

Such a report is justified where the reference SRA assessment report does not sufficiently cover these elements of assessment. Provision of a bridging report should not be mandatory, but can substantially facilitate conduct of the regulatory assessment, reduce the number of potential regulatory questions and shorten the duration of the regulatory approval process. Such a report can be valid for more than one country, where conditions of use of the medicine are considered, in principle, to be similar. Similarly to the the case of overviews submitted in Module 2, the bridging report may be prepared by the applicant, or by expert(s) contracted by an applicant, who will attach their professional CV(s).

Appendix 7

Expression of interest to national regulatory authority

Date: _____ dd/mm/yyyy _____

To: _____

RE: declaration to the <national regulatory authority (NRA)> to initiate and proceed with registration of <Product> in line with the Procedure

Dear <NRA>,

On behalf of <manufacturer>, the <marketing authorization holder (MAH)> in <stringent regulatory authority (reference SRA) country/region> of the <Product> that is registered with the <reference SRA> under the <reference number>, and solely for the purpose of the “*Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities*” (The Procedure – <date; version>) organized by WHO.

I, <manufacturer representative name> certify that:

1. The product submitted for registration is identical in all aspects of manufacturing and quality to that currently approved by the <reference SRA> under the <reference number>, including formulation, method and site(s) of manufacture, sources of active and excipient starting materials, quality specifications and control methods of the product and starting material, packaging, shelf life and product information.

If applicable:

The only exception(s) to the conditions approved by the <reference SRA> are:

<Deviations from current reference SRA approval, explanations and related commitments>.

2. Submitted assessment and inspection reports are complete reports as issued by the <reference SRA>. The <reference SRA> has been authorized by the <manufacturer> to share with <NRA focal point> all <Product> related regulatory information, including information

of a confidential nature. A copy of the authorization letter to the <reference SRA> is attached as <Appendix No. 1>.

If applicable:

The only data hidden in the assessment and/or inspection report of the <reference SRA> concern <nature and scope of missing data> and are hidden because of <reason>.

3. Information included in the registration dossier is identical with data currently approved by the <reference SRA>. As for the purpose of the Procedure, Module IV of the registration dossier in CTD format containing nonclinical data and Module V containing clinical data are replaced by respective summaries included in Module II, the <manufacturer> commits to submit without delay the non-submitted data on request of the <NRA>.
4. On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-mentioned SRA regulated product, I hereby commit to
 - a. Supplying any additional information in accordance with local regulations or upon request from the <NRA> as soon as possible during the process.
 - b. Should the registration be granted, submitting in accordance with local regulations without delay all relevant variations as approved by the <SRA country/region>.
 - c. Supplying in accordance with local regulations any information about <SRA> regulatory actions relevant to the <Product>, including suspension or termination of registration, should it happen for whichever reason.

Signature

<Appendix No. 1>: Copy of the authorization letter to the <SRA (reference SRA)>

If appropriate:

- Current storage conditions approved by the <SRA country/region> are <storage conditions approved by reference SRA>. On behalf of <manufacturer>, the <MAH> in <SRA country/region> of the above-referenced regulated product, I hereby commit to supplying within <time period> results of stability data applicable to Zones III-IVa or IVb should any of these stability zones be applicable to your country.

In addition, <NRA> will be informed of any out-of-specification (OOS) results during the study and protocol for the relevant applicable zones.

- The WHO focal person (s) <name/s> has/have been provided with the <Product> dossier to facilitate the Procedure and is/are authorized by the <manufacturer> to communicate on the Product-related issues with <NRA representatives >. By this letter the <NRA> is authorized to share with WHO all <Product> related regulatory information and communicate for the purpose of the Procedure on the <Product> related regulatory issues, including exchange of confidential information.
- Should the local applicant be a different legal entity from a holder of reference SRA marketing authorization or from a holder of scientific opinion in the case of European Union Article 58 procedures, the relationship should be clarified and agreements assuring information flow should be adjusted to this situation.

Appendix 8

Confidential disclosure agreement

This Agreement, effective as from the last date of signature, is between: _____
_____, of the one part,

and

WORLD HEALTH ORGANIZATION (“WHO”), 20 Avenue Appia, 1211 Geneva 27, Switzerland, of the other part.

WHEREAS, _____ has developed certain information and data relating to _____ which it considers to be confidential and its proprietary property (such confidential information and data being hereinafter collectively referred to as the “Information”).

WHEREAS, _____ is willing to release the Information to WHO, to enable WHO to assess such Information and conduct activities relating to the Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities, including but not limited to collaboration with _____ (the “Purpose”), provided that WHO undertakes to regard the Information as confidential and the property of _____, and release it only to persons who are bound by like obligations of confidentiality and non-use, as are contained in this Agreement.

NOW IT IS HEREBY AGREED as follows:

1. The Parties hereto agree that any disclosure of Information by _____ to WHO will be subject to the following terms and conditions.
2. Any Information which is supplied directly by _____ in written or other tangible form shall be marked by _____ as “confidential”. Any Information which is supplied indirectly by _____, such as from a Stringent Regulatory Authority with _____’s consent, need not be marked “confidential”. Any Information which is disclosed by _____ in oral form shall be confirmed by it in written summary form within 30 days from the date of oral disclosure.

3. In accepting the Information, WHO agrees with _____ as follows:
- a) WHO shall regard the Information disclosed by _____ as confidential and the property of _____. In this regard, WHO agrees to use such Information only for the Purpose (as defined above) and to make no other use thereof, unless and until a further agreement is executed with _____ governing the use thereof;
 - b) nothing in this Agreement shall prevent _____ from disclosing the Information to any third party; and
 - c) WHO has no right in or to the Information of _____.
4. WHO undertakes to maintain the Information received from _____ in confidence. In connection with the foregoing, WHO shall take all reasonable measures to ensure that the Information received from _____ shall not be used for any purpose other than the Purpose (as defined above) and shall not be disclosed to any person who does not have a need to know for the aforesaid Purpose and is not bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.

For the avoidance of doubt, WHO shall be entitled to disclose the Information to third parties collaborating with WHO in connection with the Purpose (including, without limitation, with the relevant regulatory and other authorities of WHO Member States), provided that such third parties are bound by similar obligations of confidentiality and restrictions on use as contained herein.

The obligations of confidentiality and restrictions on use contained in this Agreement shall continue for a period of five (5) years from the date of disclosure by _____ to WHO.

5. The obligations of confidentiality and restrictions on use contained in this Agreement shall not apply to any part of the Information which WHO is clearly able to demonstrate:
- a) was lawfully in its possession and known to it prior to disclosure by _____ hereunder, as evidenced by documents antedating the date of disclosure; or
 - b) was in the public domain or the subject of public knowledge at the time of disclosure by _____ hereunder; or
 - c) becomes part of the public domain or the subject of public knowledge through no fault of WHO; or
 - d) becomes available to WHO from a third party not in breach of a legal obligation of confidentiality to _____ in respect thereof; or

- e) was subsequently and independently developed by or on behalf of WHO, as shown by written records, by persons who had no knowledge of such Information; or
 - f) is required to be disclosed by law, provided that WHO shall in such case immediately notify _____ in writing of such obligation and shall provide adequate opportunity to _____ to object to such disclosure or request confidential treatment thereof (provided always, however, that nothing contained herein shall be construed as a waiver of the privileges and immunities enjoyed by WHO and/or to submit WHO to any national court jurisdiction).
6. WHO undertakes that it will disclose the Information only to those persons who need to receive the Information of _____ for the Purpose (as defined above).
 7. WHO undertakes to ensure that all persons who receive the Information disclosed to WHO hereunder shall be bound by similar obligations of confidentiality and restrictions on use as contained in this Agreement.
 8. Nothing contained in this Agreement shall be construed, by implication or otherwise, as an obligation to enter into any further agreement relating to any of the Information or as the grant of a licence to WHO to use the Information other than for the Purpose (as defined above).
 9. Upon completion of the aforesaid Purpose and in the absence of any further written agreement between the Parties, WHO shall cease all use, shall make no further use of the Information disclosed to it hereunder, and shall, upon written request from _____, promptly return to _____ all of the Information received which is in tangible form, except that WHO may retain one copy of the Information in its files to determine any continuing obligations hereunder.
 10. This Agreement constitutes the entire understanding of the Parties hereto with respect to the subject matter hereof and shall not be modified except by mutual agreement in writing.
 11. Without the prior written consent of the other Party, neither Party shall, in any statement or material of an advertising or promotional nature, refer to the relationship of the Parties under this Agreement, or to the relationship of the other Party to the Information and/or the Purpose.
 12. Any matter relating to the interpretation or the execution of this Agreement which is not covered by its terms shall be resolved by reference to the laws of Switzerland. Any dispute relating to the interpretation or application of this

Agreement shall, unless amicably settled, be subject to conciliation. In the event of failure of the latter, the dispute shall be settled by arbitration. The arbitration shall be conducted in accordance with the modalities to be agreed upon by the Parties or, in absence of agreement, with the rules of arbitration of the International Chamber of Commerce. The Parties shall accept the arbitral award as final. It is agreed furthermore that nothing contained in this Agreement shall be construed as a waiver of any of the privileges and immunities enjoyed by WHO under national and international law, and/or as submitting WHO to any national court jurisdiction.

Made in two (2) original copies,

World Health Organization

By: _____

By: _____

Title: _____

Title: _____

Date: _____

Date: _____



Appendix 9

Notification of an outcome of the national registration provided by the participating manufacturer to the World Health Organization

Details of pharmaceutical manufacturer using the Procedure¹

Manufacturer: Click here to enter text. _____

Country: Click here to enter text. _____

Address: Click here to enter text. _____

Focal point: Click here to enter text. _____

Telephone number (please include codes): Click here to enter text. _____

Email: Click here to enter text. _____

Details of pharmaceutical product or vaccine (the Product) subject to the Procedure

Name of the Product: Click here to enter text. _____

Active pharmaceutical ingredient (s): Click here to enter text. _____

Strength: Click here to enter text. _____

Dosage form: Click here to enter text. _____

Course of the Procedure

Country: Click here to enter text. _____

Regulatory authority: Click here to enter text. _____

Date of submission of the application: Click here to enter text. _____

Date of acceptance of the application (if different from submission date): Click here to enter text. _____

Date of issuance of a decision: Click here to enter text. _____

Length of process interruption/clock-stop (if applicable):² Click here to enter text. _____

¹ Collaborative procedure in assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities – facilitated by WHO.

² Time provided by NRA to the applicant to complete data or respond to regulatory questions.

Decision on registration

Granted, rejected, withdrawn: [Click here to enter text.](#) _____

Registration number (if applicable): [Click here to enter text.](#) _____

Registration granted in line with the reference SRA decision or with deviations, please comment: [Click here to enter text.](#) _____

Compliance with the Procedure, other observations and recommendations

In the course of the Procedure the following deviations were observed and recorded: [Click here to enter text.](#) _____

Any other observations and recommendations: [Click here to enter text.](#) _____

For the manufacturer

Signature:

Name: [Click here to enter text.](#) _____

Title: [Click here to enter text.](#) _____

Place and date: [Click here to enter text.](#) _____



SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, seventh edition.

2017 (CD-ROM and online)

Quality Assurance of Pharmaceuticals. WHO guidelines, good practices, related regulatory guidance and GXP-training materials

Updated, comprehensive edition, 2017 (CD-ROM and online)

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-first report.

WHO Technical Report Series, No. 1003, 2017 (236 pages)

International Nonproprietary Names (INN) for pharmaceutical substances

Cumulative List No. 17

2017 (available on CD-ROM only)

The selection and use of essential medicines

Report of the WHO Expert Committee (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List for Children)

WHO Technical Report Series, No. 1006, 2017 (602 pages)

Biological Standardization

Report of the WHO Expert Committee on Biological Standardization

WHO Technical Report Series, No. 1004, 2016 (591 pages)

The Expert Committee on Specifications for Pharmaceutical Preparations works towards clear, independent and practical standards and guidelines for the quality assurance of medicines. Standards are developed by the Committee through worldwide consultation and an international consensus-building process. The following new guidelines were adopted and recommended for use: WHO guidelines on good herbal processing practices for herbal medicines; Guidelines on good manufacturing practices for the manufacture of herbal medicines; Considerations for requesting analysis of medicines samples; WHO model certificate of analysis; WHO guidance on testing of “suspect” falsified medicines; Good pharmacopoeial practices – Chapter on monographs for compounded preparations; Good pharmacopoeial practices – Chapter on monographs on herbal medicines; Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products; Guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions; Stability testing of active pharmaceutical ingredients and finished pharmaceutical products; and Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities.

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