WHO Technical Report Series

1019

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-third report

World Health Organization

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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

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Contents

Abbreviations

AMR	antimicrobial resistance
API	active pharmaceutical ingredient
APIMF	API master file
ASEAN	Association of Southeast Asian Nations
ATMP	Advanced Therapy Medicinal Product
BCS	Biopharmaceutics Classification System
CRS	chemical reference substance
EAP	WHO Expert Advisory Panel on *The International Pharmacopoeia* and Pharmaceutical Preparations
ECBS	Expert Committee on Biological Standardization
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EDQM	European Directorate for the Quality of Medicines and Healthcare
EOI	expression of interest
EQAAS	WHO External Quality Assurance Assessment Scheme
EML	WHO *Model List of Essential Medicines*
EU	European Union
FPP	finished pharmaceutical product
GCP	good clinical practices
GMP	good manufacturing practices
GPW13	WHO's 13th General Programme of Work
GXP	good practices
HPLC	high-performance liquid chromatography
HVAC	heating, ventilation and air-conditioning
IAEA	International Atomic Energy Agency
IAU	Innovation, Access and Use (WHO team)
ICDRA	International Conference of Drug Regulatory Authorities

ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substances
INN	International Nonproprietary Name
IMWP	International Meeting of World Pharmacopoeias
ICDRA	International Conferences of Drug Regulatory Authorities
MQA	Medicines Quality Assurance (WHO)
NRA	national regulatory authority
PDG	Pharmacopoeial Discussion Group
PIC/S	Pharmaceutical Inspection Cooperation Scheme
PQ	WHO Prequalification (level)
PQT	WHO Prequalification Team
R&D	research and development
RHT	Regulation of Medicines and Other Health Technologies (unit)
RSS	Regulatory System Strengthening (WHO team)
QA	quality assurance
3S	smart safety surveillance
SOP	standard operating procedure
TB	tuberculosis
TLC	thin-layer chromatography
TRS	WHO's Technical Report Series
UN	United Nations
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USFDA	United States Food and Drug Administration
WFI	water for injection
WHO	World Health Organization

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 22–26 October 2018

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Dr Petra Dörr, Bern, Switzerland

Ms Gugu Nolwandle Mahlangu, Harare, Zimbabwe (*Chair*)

Mrs Lynda M Paleshnuik, Ottawa, Canada

Dr Jitka Sabartova, Prague, Czechia (*Rapporteur*)

Dr Daisaku Sato, Tokyo, Japan (*Co-Chair*)

Dr Luisa Stoppa, Rome, Italy

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Dr Zuma Munkombwe, Lusaka, Zambia

Professor Alain Nicolas, Paris, France

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[2] Unable to attend: Dr Marius Brits, Potchefstroom, South Africa; Professor Shaohong Jin, Beijing, China; Mrs Agnes Sitta Kijo, Dar es Salaam, United Republic of Tanzania; Dr Haruhiro Okuda, Tokyo, Japan; and nominee from the United States Food and Drug Administration (USFDA), Silver Spring, United States of America (USA).

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Dr Andrea Lodi, Head of Laboratory, European Directorate for the Quality of Medicines and Healthcare, Council of Europe, Strasbourg, France

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[3] Unable to attend: European Commission (EC), Brussels, Belgium; European Medicines Agency (EMA), London, United Kingdom of Great Britain and Northern Ireland; United Nations Industrial Development Organization (UNIDO), Vienna, Austria; World Bank Group, Washington, USA; World Customs Organization (WCO), Brussels, Belgium; and World Intellectual Property Organization (WIPO), Geneva, Switzerland.

[4] See European Directorate for the Quality of Medicines and Healthcare (EDQM).

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World Health Organization (WHO)[8]

Deputy Director-General for Programmes

Dr Soumya Swaminathan, Deputy Director-General for Programmes

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Dr Yves Mathieu, Volunteer

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Dr Sabine Kopp, Group Lead (Secretary of the Expert Committee)

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[6] Unable to attend: British Pharmacopoeia, London, United Kingdom of Great Britain and Northern Ireland; Farmacopea Argentina, Buenos Aires, Argentina; Indian Pharmacopoeia Commission, Ghaziabad, India; Indonesian Pharmacopoeia Commission, Jakarta, Indonesia; Japanese Pharmacopoeia, Tokyo, Japan; Pharmacopoeia of the People's Republic of China, Beijing, China; Pharmacopoeia of the Republic of Korea, Chungcheongbuk-do, Republic of Korea; Pharmacopoeia of Ukraine, Kharkov, Ukraine; and Pharmaceutical Inspection Co-operation Scheme (PIC/S), Geneva, Switzerland.

[7] Unable to attend: The Global Fund to Flight AIDS, Tuberculosis and Malaria, Geneva, Switzerland; and The Stop TB Partnership, Geneva, Switzerland.

[8] Unable to attend: Ms Emer Cooke, Head, Regulation of Medicines and other Health Technologies (EMP/RHT); Mrs Adriana Velazquez Berumen, Senior Adviser, Innovation, Access and Use (EMP/IAU); Mr Rutendo Kuwana, Technical Officer, Prequalification Team (EMP/RHT/PQT); Dr Mario Festin, Medical Officer, Reproductive Health and Research (FWC/RHR/HRX).

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Innovation, Access and Use (EMP/IAU)
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International Nonproprietary Names (INN/RHT/TSN)
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Mr Michael Ward, Coordinator

Mr David Woo, Technical Officer

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Representation from WHO regional offices[9]

Permanent Missions, Geneva, Switzerland[10]

Mr Ahmed MH Abobakr Al-Daghari, Second Secretary, Permanent Mission of the Republic of Yemen to the United Nations Office and Other International Organizations in Geneva

[9] Unable to attend: Regional Office for Africa; Regional Office for the Americas; Regional Office for the Eastern Mediterranean; Regional Office for Europe; Regional Office for South-East Asia; and Regional Office for the Western Pacific.

[10] Unable to attend: Mr Lundeg Purevsuren, Ambassador, Permanent Representative of Mongolia to the United Nations Office and Other International Organizations in Geneva.

Declarations of interest

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

Dr N.J. Al Lawati, Professor M. Bermejo Sanz, Dr V. Dias Sousa, Dr P. Dörr, Dr M.H. Eimunjeze, Dr J. Gordon, Ms S. Gunasekaran, Ms G.N. Mahlangu, Dr J. Miller, Dr Z. Munkombwe, Mrs L. Paleshnuik, Dr J. Sabartova, Dr D. Sato, Professor G. Scriba, Dr M. Smid and Dr L. Stoppa reported no conflicts 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 (GMP) 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 Fifty-third meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) took place in Geneva, Switzerland, from 22 to 26 October 2018.

Participants of the meeting were welcomed by Dr Mariângela Simão, Assistant Director-General, Access to Medicines, Pharmaceuticals and Vaccines, on behalf of the WHO Director-General, Dr Tedros Ghebreyesus. Dr Simão described the Director-General's vision as:

> a world in which everyone can live healthy, productive lives, regardless of who they are or where they live.

Dr Tedros had additionally emphasized that:

> under his leadership, an enhanced and independent WHO will take a science-led and innovation-based approach that is results oriented and responsive, maximizes inclusive partnerships, and ensures a collective priority-setting with all stakeholders. In particular, he will champion country ownership so that countries are at the table as full and equal partners, to guide and make the decisions that will affect the health of their populations.

WHO's 13th General Programme of Work (GPW13) was adopted by the World Health Assembly in May 2018, with three strategic priorities:

1. To advance universal health coverage;
2. To address health emergencies;
3. To promote healthier populations.

GPW13 has set three targets to ensure that, by 2023, 1 billion more people benefit from universal health coverage, 1 billion more people are better protected from health emergencies, and 1 billion more people enjoy better health and well-being.

WHO estimates that achieving this "triple billion" target could save 29 million lives. To deliver the strategic priorities, WHO is pursuing a transformation agenda with four workstreams: (i) norms and standards; (ii) global goods; (iii) communication; and (iv) core values.

All key WHO technical and corporate processes will underpin the strategic shifts of GPW13. One of the WHO reform processes, which include the transformation agenda and implementation of United Nations Development System reform, relates to how WHO initiates, develops, implements and evaluates its normative and standard-setting products. Discussion is taking place with a view to redesigning the processes in such a way that all normative and standard-

setting products undergo prespecified (quality assurance [QA]) pathways. Each part of the process is being reviewed, including how different types of normative and standard-setting products should be classified in WHO.

Dr Simão stated that the Expert Committee's structure is the "backbone" of WHO's standard-setting process. Attention on how WHO develops guidelines and standards has increased. New measures for declarations of interest, the selection of experts and collaboration with non-state actors have therefore been implemented. Dr Simão welcomed the ECSPP's strong links with other WHO activities, such as the support of national regulatory authorities (NRAs), the WHO Prequalification Team (PQT), the Expert Committee on Biological Standardization (ECBS), the Expert Committee on the Selection and Use of Essential Medicines, as well as programmes addressing antimicrobial resistance (AMR) and specific diseases. This is also reflected in a new strategy of the Regulation of Medicines and Other Health Technologies (RHT) unit and the impact assessment of the PQT. Dr Simão informed meeting participants that the WHO Secretariat has prepared a range of documents to help future discussions and reminded the experts that they are invited to participate on a personal basis and not as representatives of their employers. Dr Simão's words were echoed by Dr Francois-Xavier Lery, Coordinator for the Technologies, Standards and Norms group, who stressed the importance of the changes in the way that WHO works. Dr Lery emphasized that WHO does not work in isolation and that it values the support and assistance it receives from others.

Election of chairpersons and rapporteurs

Participants then proceeded to introduce themselves. Ms Gugu Nolwandle Mahlangu was appointed Chair of the meeting, and Dr Daisaku Sato was appointed as Co-Chair. Dr Jitka Sabartova and Dr Adriaan van Zyl were selected as Rapporteurs.

Dr Sabine Kopp, Secretary to the Expert Committee, briefly gave an introduction on WHO and its 194 Member States, 6 regional offices, over 150 country offices and some 700 organizations supporting WHO. Dr Kopp outlined the work of the World Health Assembly and WHO Executive Board and explained the structure of the RHT unit. It was noted that the Expert Committee is an advisory committee to the Director-General and, through him, to the Member States. Giving an overview of the ECSPP, Dr Kopp pointed out that it was originally established to deal with quality control only but that its responsibility has expanded over time, responding to World Health Assembly decisions, to include good manufacturing practices (GMP), the distribution process, and all areas where quality is important. There are currently some 90 official WHO guidance texts for medicines QA and related regulatory standards, in addition to those found in *The International Pharmacopoeia* (*1*).

Biographical details of all ECSPP participants had been posted on the WHO Medicines Quality Assurance (MQA) website for the sake of transparency. All members of the Expert Committee and temporary advisers had submitted declarations of interests prior to attending the meeting. Two members of the Expert Committee declared interests but these had been evaluated and were not judged as conflicts that would preclude the persons concerned from participating in the meeting.

1. General policy

1.1 Process for the development of WHO norms and standards

Members of the Expert Committee were presented with a proposal to formalize a process for the development of guidelines on QA, which reflects the actual process used for many years. In February 2018, the WHO Secretariat circulated a document on the proposed process for comments by members of the WHO Expert Advisory Panel on *The International Pharmacopoeia* and Pharmaceutical Preparations (EAP). Following consolidation of comments received and further discussions thereafter, the document was recirculated and posted on the MQA website for months prior to presentation to the ECSPP.

The QA guidelines include quality guidelines and regulations, good practices (known as GXP) and technical regulatory guidance. The QA guidelines are developed and maintained up to date under the aegis of the ECSPP, in line with WHO rules and procedures governing expert committees, adopted by Member States. QA guidelines are the recognized WHO technical standards to support the whole life-cycle of medicines, from development through to production, marketing authorization and distribution, up to the post-marketing phase.

To reflect the constant technical progress, it is crucial that QA guidelines and guidance texts are kept up to date and that WHO procedures to elaborate or review them are flexible enough to allow for rapid interventions by regulators, while maintaining a rigorous public consultation process with all stakeholders. QA guidelines provide an important element of the quality dimension for the medicines in the *WHO Model List of Essential Medicines* (EML) (*2*) and in WHO treatment guidelines. Major WHO programmes and partners, such as the Prequalification Team-Medicines, the United Nations Children's Fund (UNICEF) and The Global Fund to Fight AIDS, Tuberculosis and Malaria, rely heavily upon the quality specifications set out in *The International Pharmacopoeia* (*1*) and in the QA guidelines.

The primary objective of the procedure is to establish a standardized process when developing new QA guidelines. By increasing transparency and communication, the aim is to involve a wide range of stakeholders who are able to bring different perspectives to common issues. In addition, the transparency and promotion of internationally standardized practices could improve the cooperation between national medicines regulatory authorities and stakeholders when developing quality standards, leading to an optimization of resources on a global scale and reducing the duplication of work.

QA guidelines are developed following recommendations by WHO governing bodies, the International Conference of Drug Regulatory Authorities (ICDRA), the ECSPP, international organizations and United Nations agencies

and other WHO programmes and activities, or in response to major public health needs, and are thereafter adopted by the ECSPP. The steps that are followed when developing new QA guidelines and guidance texts have been outlined as a 10-phase procedure (see Annex 1). The different steps leading to the development of a new WHO QA guideline for medicines are reported in the note "Schedule for the adoption process", outlining the development history of a text from its draft to its adoption, which is included in each working document that is circulated and posted on the MQA website for comments.

In accordance with the WHO rules and procedures, the QA guidelines adopted by the ECSPP are published in WHO's Technical Report Series (TRS) after every meeting of the ECSPP. The ECSPP report includes all the newly adopted guidelines, including GXP and regulatory guidance texts. It provides recommendations to the WHO Director-General and to WHO Member States. The report is presented to WHO's governing bodies for final comments, endorsement and implementation by Member States. The report of the ECSPP therefore constitutes WHO technical guidance in MQA and regulatory matters.

The Expert Committee procedure was adopted in the closed session (Annex 1).

1.2 Participation in meetings of the Expert Committee on Specifications for Pharmaceutical Preparations

The WHO Secretariat informed the Expert Committee that the ECSPP meeting is by invitation only. Expert Committee members and technical advisers are invited in their personal capacities. The meeting is organized in accordance with the various WHO procedures governing the running of expert committee meetings and the implementation of the new WHO *Framework of engagement with non-State actors* (*3*) adopted by WHO Member States.

The meeting is split into three different types of sessions as follows:

1. an open session with Expert Committee members, technical advisers, international organizations, state actors, Member States' mission representatives and non-state actors;
2. a private session with Expert Committee members, technical advisers, international organizations and state actors;
3. a closed session with Expert Committee members only.

All decisions of the Expert Committee are taken, by the Expert Committee members, in the closed session.

The Expert Committee noted these three different types of sessions and also recommended that the WHO Secretariat explore possibilities for securing the contributions from all relevant parties (such as the pharmacopoeias for

the sessions on quality control specifications and others in the field of GXP or QA matters), whether they are state actors or non-state actors, to the private sessions of the Expert Committee.

1.3 Open session

This session was open to invited participants, international organizations, state actors and non-state actors, as well as permanent missions to the United Nations Office in Geneva if they expressed an interest in participating.

1.3.1 Introduction and welcome

Dr Simão, Assistant Director-General, welcomed a representative of the Permanent Mission of the Republic of Yemen to the United Nations Office and Other International Organizations in Geneva, and the non-state actors to the open session of the meeting. This open session had been arranged in order to respond to the interest raised by Member States during the World Health Assemblies and WHO Executive Board meetings over a number of years, in learning more about how the Expert Committee works and which topics it covers.

Dr Simão noted that WHO is the only organization with a mandate to protect global health and that the development, establishment and promotion of international standards for pharmaceuticals are among the functions laid down in its constitution. WHO's technical guidance on medicines quality is designed to serve regulatory authorities of all Member States, as well as United Nations (UN) agencies and other major international bodies. It provides a technical platform for convergence as recommended by the ICDRA. At a time when access to essential medicines is a pressing issue on the sustainable development agenda, the ECSPP's standard-setting work was said to make a unique and critical contribution towards more equitable access to needed medicines of assured quality.

The ECSPP provides a wide spectrum of written and physical standards to enable testing of medicines for their quality during their full life-cycle, from development to distribution to patients. The Expert Committee also recommends regulatory guidelines of importance to the regulation of multisource medicines designed to be used globally, be it in hot and humid climates, large or small countries, or well-developed or less-developed settings. The outcome is intended to protect patients and to facilitate access to quality medicines. Much of the Expert Committee's work is aimed at increasing convergence in the area of QA and regulatory guidance, in order to facilitate efficient synergies among and within the respective authorities and pharmacopoeias, and to reduce the duplication of efforts and, thus, costs. The outputs of the Expert Committee are designed to serve all Member States, especially their national and regional regulatory authorities, UN agencies, and regional and interregional harmonization efforts,

and to underpin important public health initiatives, including the prequalification and procurement of quality medicines through major international bodies, such as The Global Fund to Fight AIDS, Tuberculosis and Malaria, and international organizations such as UNICEF.

2. General updates and matters for information

Following a further summary of WHO and its activities (including GPW13) by Dr Sabine Kopp, a series of presentations introduced meeting participants to a range of WHO activities related to the work of the Expert Committee.

2.1 Cross-cutting pharmaceutical quality assurance issues

2.1.1 Local manufacturing

Dr Jicui Dong presented recent work in promoting the local production of quality-assured medical products under the Local Production Programme within the Regulatory System Strengthening (RSS) team. A strategy has been drafted to promote quality local production in transitioning countries, aiming to enable domestically funded procurement to access locally produced, quality-assured medical products. The Second Interagency Consultation on Local Production was convened with UN agencies and international partners, to continue the dialogue and collaboration on promoting quality local production, and culminating with establishment of the Interagency Pharmaceutical Coordination Group Subcommittee on Local Production, with WHO serving as the Secretariat. At the 18th ICDRA that took place in Dublin, Ireland, the pre-ICDRA Workshop on Local Production was organized to explore the role of regulators in local production. A workshop is being organized in collaboration with The New Partnership for Africa's Development and the United States Pharmacopeia/ Promoting the Quality of Medicines programme for African manufacturers on key enablers for successful local production and the supply of quality-assured essential medicines. Meetings have also been held related to local production globally, such as two that took place in Beijing, China: the High Level Meeting for China–Africa Health Cooperation and a WHO Director-General High Level Roundtable that looked at access to essential medicines and other health commodities, as well as promotion of local production in Africa.

Two documents are under development within the Local Production Programme. The first is for risk-based selection of essential medicines for local manufacturing in low- and middle-income countries. The second is to assist assessment of the feasibility of sustainable quality local production and to identify gaps in areas that enable local production to be feasible and sustainable, such as policy coherence, the business environment, infrastructure, regulatory systems and the current status of the industry. Results of the assessment can then inform the development of a holistic national strategy and roadmap towards promoting quality local production.

The Expert Committee noted the update.

2.1.2 Member State mechanism

Ms Pernette Bourdillon Esteve spoke about the Member State mechanism, which is the political response to substandard and falsified pharmaceutical products. It is complemented by WHO's operational response: the *WHO Global Surveillance and Monitoring System for substandard and falsified medical products* (*4*). Substandard and falsified medicines have concerned WHO and its governing bodies for many years. In this regard, the Member State mechanism tries to turn political will into something more practical. Every stakeholder along the entire supply chain must demand quality and must have due diligence procedures in place. However, efforts to ensure quality along the supply chain must be accompanied by efforts to detect substandard or falsified products. Once a substandard product is detected, it can be dealt with, so there needs to be a means of detection and a means to assess what went wrong. A regulatory approach is needed to detect and prevent substandard products, but a judicial approach may be chosen to deal with falsified ones.

Since no laboratory can assess every single product, it is important to have a variety of tools that can be used according to the context. A lot of substandard and falsified products do contain some amount of active pharmaceutical ingredients (APIs), so very specific tools are needed. Over half of the substandard products in the WHO database are antimicrobials or antibiotics, so there is a possibility of knowing what type of product is likely to be problematic. The Member State mechanism is governed by a steering committee that meets three times a year; in addition, one meeting is held each year where all Member States are invited to attend. Every 2 years, the Member State mechanism reports to the World Health Assembly on progress and recommendations, through the WHO Executive Board. The next comprehensive report will be submitted to the 72nd World Health Assembly in May 2019.

The Expert Committee noted the update.

2.1.3 Expert Committee on Biological Standardization

Dr Ivana Knezevic presented on the ECBS. The ECBS has so far issued 93 documents on recommendations or guidelines. Of these, 63 documents are vaccine specific, 12 are general documents that apply to all vaccines, 10 are general documents that apply to both vaccines and biotherapeutics, and a further 8 are specific to biotherapeutic products. The ECBS also adopts guidance documents on blood products and in vitro diagnostics, as well as measurement standards that are essential for vaccine development. Eight collaborating centres are working on standards for biologicals, and other centres worldwide are working on regulatory issues. New written standards approved by the ECBS in the period 2016–2018 include those that relate to maternal immunization and

the labelling of influenza vaccines, Ebola vaccines, human challenge trials, and hepatitis E vaccines. Measurement standards being considered for adoption by the ECBS in 2018 included the seventh international standard for rabies vaccine and the first international standard for meningococcal serogroup W and Y polysaccharide, as well as standards for the evaluation of blood products.

The ECBS sees the purpose of its guidelines as providing key principles for the evaluation of biologicals, as a basis for setting national requirements and for WHO prequalification. At the same time, the standards must leave space for NRAs to formulate additional or more specific requirements. Standards should also be living documents that will be developed further, in line with the progress in scientific knowledge and experience. WHO assists with the implementation of the guidelines into regulatory and manufacturing practices, through global, regional and national workshops involving regulators, manufacturers and other relevant experts, plus training workshops and advisory groups. It is, however, important to take account of the guidance issued by other bodies; WHO's intention is to complement them, not to create a conflict. Among the strategic issues faced by the ECBS are standardization in the context of priority pathogens for public health emergencies; the need for amendments or revision of recommendations for international standards and reference preparations; the standardization of advanced therapies; and regulatory convergence.

The Expert Committee noted the update.

2.1.4 Expert Committee – selection and use of the *WHO Model List of Essential Medicines*

Ms Bernadette Cappello reported that the EML Expert Committee meets every 2 years to update the EML (*2*) and the *WHO Model List of Essential Medicines for Children* (*5*). The next meeting of the EML Expert Committee will be held from 1 to 5 April 2019. Close collaboration with WHO technical departments/programme areas take place to ensure the EML and WHO treatment guidelines are aligned, where appropriate. At the time of the meeting, the application period was currently open and would remain so until early December 2018. Anticipated applications included the following:

- antibiotics for infectious syndromes that were not considered in the comprehensive review of antibiotics in the EML in 2017 (typhoid [enteric] fever, surgical prophylaxis, oral/dental infections);
- medicines for the treatment of multiple myeloma;
- biological disease-modifying medicines (anti-tumour necrosis factor) for chronic inflammatory conditions (e.g. rheumatoid arthritis, inflammatory bowel diseases);
- immunotherapy medicines for treatment of multiple sclerosis;

- fixed-dose combination dual anti-hypertensives formulations;
- methylphenidate for attention deficit hyperactivity disorder;
- review of novel oral anticoagulants.

The full agenda will be finalized following closure of the application period. The Innovation, Access and Use (IAU) team looks forward to being able to update the ECSPP next year on the recommendations made by the EML Expert Committee.

The Expert Committee noted the update.

2.1.5 Antimicrobial resistance

Dr Verica Ivanovska presented on AMR. The IAU team within the Essential Medicines and Health Products department has a number of ongoing activities in order to achieve the objectives of the WHO *Global action plan on antimicrobial resistance* (*6*) by optimizing the use of antibiotics in humans. To support the identification of priorities for research and development (R&D) on AMR, WHO updated the report on *Antibacterial agents in clinical development* in 2018 (*7*), reporting three new antibiotics with marketing authorization in the past year, granted by the United States Food and Drug Administration (USFDA), and a further 48 new antibiotics in the clinical pipeline. Nevertheless, there are continuing incidences of shortages of antibiotics, and the pipeline is insufficient for the treatment of priority pathogens and tuberculosis (TB).

WHO is currently expanding its work to the preclinical pipeline and, in addition, antifungal treatments are potential candidates for inclusion in the next clinical pipeline review. Target product profiles are to be developed for selected priority AMR pathogens, with R&D roadmaps for priority pathogens in the future.

To further support the *Global framework for development and stewardship to combat antimicrobial resistance* (*8*), WHO, in partnership with the Food and Agriculture Organization of the United Nations (FAO), International Organization of Employers (IOE) and UN Environment, held the Second Member States' and Partners' Consultation in October 2018.

A *Model List of Essential In Vitro Diagnostics* (*9*) was released in May 2018, containing a limited number of in vitro diagnostics, while the next update in 2019 is expected to include additional in vitro diagnostics for infectious diseases, noncommunicable diseases and AMR. Members of the Expert Committee were also informed that the first global *WHO report on surveillance of antibiotic consumption* (*10*) would be launched in November 2018, while a WHO protocol for point prevalence surveys on measuring antibiotic use in hospitals would also be released by the end of the year. Efforts to promote a more appropriate use of antibiotics, referred to as antibiotic stewardship, have

included the development of advocacy materials and a practical toolkit on how to perform stewardship programmes in hospitals in low- and middle-income countries. Additionally, as part of national action plans for AMR, a number of countries have asked for WHO support in relation to the safe disposal of antibiotics, and WHO activities will be planned accordingly.

The Expert Committee noted the update.

2.1.6 International Conference of Drug Regulatory Authorities

Dr Samvel Azatyan presented on the ICDRA, whose conferences have been held biannually since 1980 with the aim of promoting exchange of regulatory information on medical products and collaborative approaches to issues of common concern.

The ICDRA's main objectives are to promote collaboration between NRAs, to reach a consensus on matters of common interest, facilitate timely and adequate exchange of information, and discuss issues of international relevance. Much of the ICDRA meeting dealt with regulatory collaboration, convergence and harmonization, with a great deal of emphasis on regional collaboration and networks.

The 18th ICDRA took place in Dublin, Ireland, from 5 to 7 September 2018, with more than 400 participants attending.

The theme was "Smart safety surveillance (3S): building sustainable pharmacovigilance systems, maintaining public confidence and enabling access to innovative treatments". 3S is about expanding and streamlining pharmacovigilance systems, focusing initially on the safety of priority medicines and vaccines. It encourages strong regulatory systems along the product life-cycle. The proposition of 3S is to build sustainable pharmacovigilance systems, maintain public confidence and enable access to innovative treatments.

The 18th ICDRA addressed a number of issues of common interest for regulators worldwide, such as enabling access to innovative medical products, the benchmarking of regulatory systems, facilitated registration pathways, regulation of clinical trials, and so on. The recommendations of the 18th ICDRA will be published in the journal *WHO Drug Information*.

The Expert Committee noted the update.

2.2 International collaboration

2.2.1 International Atomic Energy Agency

Dr João Alberto Osso Junior outlined the International Atomic Energy Agency (IAEA) mandate, which describes the agency's purpose of seeking "to accelerate and enlarge the contribution of atomic energy to peace, health and prosperity throughout the world".

The IAEA has three pillars: safeguards and verification; safety and security; and science and technology. Within the latter area are projects related to the production of medical radioisotopes and radiopharmaceuticals. Education in these areas include e-learning and training courses on the regulatory aspects of radiopharmaceutical production. Radiopharmaceuticals raise complex issues that make regulation a complex matter. The IAEA has publications on quality control in the production of radiopharmaceuticals, and two technical meetings held in 2015 and 2017 on regulation and radiopharmaceuticals resulted in recommendations on regulations, guidelines, education and training, and communications. The IAEA is planning another meeting to determine whether the GMP for radiopharmaceuticals adopted by the ECSPP in 2003 would need to be revised to respond to recent developments.

The IAEA also runs technical cooperation projects on radiopharmaceuticals, and a working group of the Nuclear Community on Radiopharmaceuticals has been formed. Collaboration between WHO and the IAEA was described as being vital. Work is gathering momentum to revise the general monograph on radiopharmaceuticals and to identify/update monographs on radiopharmaceuticals. An international symposium on trends in radiopharmaceuticals is planned for 2019 at the IAEA headquarters in Vienna, Austria, and will include the regulation of radiopharmaceuticals.

The Expert Committee noted the update.

2.2.2 Pharmacopoeial Discussion Group

Dr Andrea Lodi, Head of Laboratory at the European Directorate for the Quality of Medicines and Healthcare (EDQM), summarized the 2018 meeting of the Pharmacopoeial Discussion Group (PDG) on behalf of the European Pharmacopoeia. Four excipient monographs were harmonized during the meeting, bringing the number of harmonized monographs to 46 out of 60 in the workplan. The harmonization of several other monographs is under way. Twenty-eight out of 31 general chapters were harmonized. The next meeting of the PDG is scheduled to take place in Tokyo, Japan, in October 2019.

The Expert Committee noted the update.

2.2.3 United Nations Children's Fund

Dr Peter Svarrer Jakobsen gave an overview of the work of UNICEF, whose principal supply goal is "Every child survives and thrives". The total procurement value of supplies purchased by UNICEF is US$ 2.342 billion, with US$ 1.317 billion of that spent on vaccines and US$ 164.2 million spent on medicines. UNICEF has plans to publish the names of all its suppliers – both international and local. The list of countries from which UNICEF obtains supplies is headed by India. UNICEF applies its own QA system but, for the procurement of

medicines, the agency follows WHO's guidance in the *Model quality assurance system for procurement agencies* (*11*). Dr Jakobsen mentioned that the interagency questionnaire was under revision by the various agencies. All procurement of medical products is centralized in the UNICEF Supply Division, so that country offices cannot procure medicines directly unless they apply for, and are granted, a specific exception.

UNICEF carries out a full technical evaluation of all products that do not comply with WHO prequalification, USFDA's tentative approval, the Global Fund Expert Review Panel, the European Medicines Agency Article 58 (*12*), or products registered by stringent regulatory authorities (excluding "for export only"). UNICEF has its own warehouse in Copenhagen, Denmark, and carries out frequent GMP inspections – some 180 were conducted in the period 2014–2017. There is an annual inspection plan, with annual sampling and testing, and about 40–50 inspections are carried out each year. During the period 2014–2017, 26 manufacturers were found to be GMP-noncompliant. UNICEF relies on WHO's prequalification of vaccines and products for HIV, malaria and TB, and joint inspections are carried out with WHO, the International Committee of the Red Cross, and Médecins sans Frontières. UNICEF is also a partner to the Pharmaceutical Inspection Cooperation Scheme (PIC/S). Inspection reports are shared with international partners by UNICEF, and GMP reports and information from partners are used to prioritize GMP inspections.

In the closed session of the ECSPP meeting, the members of the Expert Committee suggested that the WHO Secretariat contacts the Interagency Pharmaceutical Coordination Group with regard to possible maintenance of the questionnaire published in the *Model quality assurance system for procurement agencies* (*11*).

The Expert Committee noted the update.

3. Quality assurance – collaboration initiatives

3.1 International meetings of world pharmacopoeias

Dr Sabine Kopp presented on the above topic. There are currently 56 pharmacopoeias around the world, whose core mission is to protect public health by creating and making available public standards to help ensure the quality of medicines. The Vietnamese Pharmacopoeia hosted the Ninth International Meeting of World Pharmacopoeias (IMWP) in Da Nang, Viet Nam, in April 2018. Thirteen national, regional and international pharmacopoeias, representing 50 pharmacopoeial authorities around the world, were present. The meeting was chaired by the Vietnamese Pharmacopoeia and co-chaired by representatives from the Brazilian and Japanese Pharmacopoeias.

Since 2012, the IMWP has been convened by WHO, with the first eight meetings focusing on the development of good pharmacopoeial practices. The 2018 meeting focused on creating new collaboration models and improving the sharing of information. Among other developments, participants agreed to establish a network with a pharmacopoeial alert system to exchange information on problems detected with products covered by monographs that necessitate urgent action by a pharmacopeia. The delegations also agreed to use the annual IMWP as a discussion forum to inform each other of recent challenges and to share solutions found. The new synergies resulting from the good pharmacopoeial practices will reduce potential duplication and enhance international efforts to enable patients to be treated with safe quality medicines all around the world. A working group was created, which started to prepare a white paper on the role of pharmacopoeias.

The Expert Committee noted the report.

3.2 Inspection guidelines and good practices

3.2.1 Revision of *WHO good manufacturing practices for sterile pharmaceutical products*

Dr Joey Gouws reported that, as a follow-up to the recommendation of the ECSPP, the WHO Secretariat pursues efforts towards an efficient collaboration with the European Union (EU) and the PIC/S in the revision process for *WHO good manufacturing practices for sterile pharmaceutical products* (*13*). It is considered that a harmonized text would be beneficial to the authorities and manufacturers, would save resources and, thus, would ultimately help patients to have better access to quality medicines. WHO therefore widely circulated the new proposal developed by the EU and PIC/S, with input from WHO, in order to obtain feedback and comments on the suggested revision. The newly revised text will be circulated again for comments.

The manufacture of sterile medical products covers a wide range of product types (sterile active substance through to finished dosage form), batch sizes (single unit to multiple units), processes (from highly automated systems to manual processes), primary packaging materials and technologies (such as biotechnology, classical small molecule manufacturing, and closed systems). This revised annex would provide general guidance that should be used for all sterile medical products and sterile active substances, via adaptation, using the principles of quality risk management to ensure that microbial, particulate and pyrogen contamination associated with microbes is prevented in the final product.

Between May 2015 and November 2017, there was a great deal of communications and follow-up between the PIC/S, the EU and WHO, including an official exchange of letters with the chairperson of PIC/S to explore cooperation towards convergence on new guidance in data integrity and revision of *WHO good manufacturing practices for sterile pharmaceutical products* (*13*). During the drafting process of the GMP text for sterile products, input was provided by the PQT-inspection group. A meeting on GMP from 29 June to 1 July 2015 recommended collaboration with the PIC/S on the update and new guidance, including risk classification, practices for data and record management and for GMP for sterile products. The proposal was presented to the 52nd meeting of the Expert Committee that took place in October 2017, for advice. A period of public consultation followed between December 2017 and March 2018. The compilation of comments and revision of the draft began in April 2018. It is anticipated that a revised text will be presented to the ECSPP in October 2019.

The Expert Committee noted the update.

3.2.2 *Good manufacturing practices for biotherapeutic products*

Dr Dianliang Lei reported on a collaboration between the PIC/S and WHO on GMP for biotherapeutic products. He informed members of the Expert Committee that WHO's advice on *Good manufacturing practices for biological products* (*14*) was first developed in 1992 and revised in 2015 following a consultation process. The guidance is widely used by regulators and is mandatory for medicine and vaccine prequalification programmes. Recent implementation workshops were held in Thailand in 2017 and the Republic of Korea in 2018. An Association of Southeast Asian Nations (ASEAN) workshop on GMP for biologicals and biosimilars was held in August 2018 in Viet Nam, and the Republic of Korea hosted an international symposium on GMP for biologicals in September 2018. WHO GMP for biologicals was the main topic of this workshop and symposium.

Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products (ATMPs) – such as gene therapy medicinal products,

somatic cell therapy medicinal products and tissue-engineered products – were already adopted by the EU in 2017 (*15*). The PIC/S is also in the process of incorporating advice on ATMPs in its guidance on manufacture of biological medicinal products for human use. Since ATMPs are very diverse, detailed guidance cannot be given for every product but guidance must emphasize the need for a thorough risk assessment of the process, identifying risks to patients, risks of cross-contamination and elements to consider in the application for marketing authorization. ATMPs can be defined largely by reference to their method of manufacture.

As yet, WHO has no plans or resources to develop a specific WHO GMP for ATMPs by the ECBS, but will continue to monitor the use of the EU's GMP for ATMPs and the development of the PIC/S GMP for ATMPs.

The Expert Committee noted the reports.

4. Nomenclature, terminology and databases

4.1 International Nonproprietary Names for pharmaceutical substances

Dr Raffaella Balocco presented on the above topic. Lists of International Nonproprietary Names (INNs) are published in the journal *WHO Drug Information*, as well as in a cumulative list. Members of the Expert Committee were shown the range of WHO INN publications. The number of INNs published annually has doubled in the past 10 years, with the list of new names headed by biological monoclonal antibodies. Some of the more recent stems and substems allocated to biologicals and chemicals were shown. Statistics on the 120th list of proposed INNs, with 124 additional names, were presented. It comprised 35% monoclonal antibodies, 40% of which are chemicals. Sometimes it is not evident how to develop names for substance types that did not exist 10 years ago. There are four options for devising INNs in such new groups of substances, for example, variations of prefixes and infixes, since many substances are almost identical.

The School of International Nonpropietary Names will go live in 2019. The platform has been developed and will be open access, with freely downloadable training materials. The school will also include a module dedicated to biologicals.

A questionnaire was circulated to Member States on INN-related issues, such as whether or not pharma substances are named using INNs, and questions on the brand names, and whether or not they are part of the marketing authorization process. On the issue of inventing new names, similarities are searched for. INNs are not too difficult but brand names are complex, as there is no international standard.

The Expert Committee noted the report.

4.2 Quality assurance terminology

Dr Sabine Kopp stated that all the terms and definitions included in the guidelines adopted to date by the ECSPP have been updated in the Quality Assurance of Medicines Terminology Database, which is posted on the WHO website under "MQA".

The Expert Committee noted the update.

4.3 Guidelines and guidance texts adopted by the Expert Committee

Dr Sabine Kopp gave an update on this topic. The guidelines developed by WHO are prepared through a global consultative process involving WHO Member States, national authorities and international agencies, in consultation with the

EAP, with specialists from industry, national institutions, nongovernmental organizations, and so forth. The draft guidelines are evaluated during the meetings of the ECSPP and, if found suitable, adopted as international standards. Dr Kopp gave an overview of the MQA website (*16*). All QA guidelines and *The International Pharmacopoeia* (*1*) were included on the new CD-ROMs and USB memory sticks, which were distributed to all members of the Expert Committee.

The MQA web page links to all current WHO QA guidelines for medicines, which are grouped into "Development", "Production", "Quality control", "Inspections", "Distribution" and "Other regulatory guidelines". The guidelines under development or for comment are found under "Current projects".

The Expert Committee noted the update.

5. Prequalification of priority essential medicines and active pharmaceutical ingredients

5.1 Update on the prequalification of medicines

Dr Joey Gouws gave an update on the prequalification of medicines. Prequalification is a response to the request from Member States and procurement agencies for quality-assured health products. The PQT creates and applies QA mechanisms. Members of the Expert Committee were provided with a description of the process of prequalification from the initial expression of interest (EOI). The PQT uses standards adopted by the Expert Committee to carry out its work. So far, 612 products have been prequalified, as have 127 APIs. The average length of time taken to complete the prequalification process is around 270 days. A range of supporting documentation must be submitted in support of prequalification but a new online platform is being developed so that applicants can, in future, upload their submissions online. To ensure adequate funding for the programme, a new fee structure has been implemented, modelled on the practices of regulatory authorities around the world. Members of the Expert Committee noted that prequalification could potentially be expanded to other workstreams, such as diabetes treatments and cancer products.

5.2 Update on the prequalification of active pharmaceutical ingredients

Ms Helena Martin-Ballestero presented on behalf of Dr Anthony Fake. Manufacturers of APIs participate in the WHO prequalification procedure, either in support of a finished pharmaceutical product (FPP), for which prequalification is being sought, or via the standalone API prequalification procedure.

Some 127 APIs are currently prequalified and a further 42 are under assessment for prequalification. In addition, a further 69 API master files (APIMFs) have been accepted in the APIMF procedure, while a further 14 are under assessment. Of some 200 APIMFs submitted to the PQT, two thirds now support a prequalified API, thus ensuring both the quality of the API used in the FPP and also the GMP status of the API manufacturer.

The number of applications received and the applications for prequalification remain encouragingly constant, indicating a continued interest in this procedure. Measures are being taken to reduce the time this process takes, and deadlines for manufacturers' responses (6 months for the first round of questions, and up to 3 months for subsequent rounds) were introduced in 2018. The voluntary application of the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3D

guidance for APIs (*17*) was introduced in May 2018. Work is ongoing to introduce a new database system to cover all prequalification groups and will include a portal for users to upload and download submissions, letters and other documents.

The Expert Committee noted the update.

6. Quality control – prequalification and WHO monitoring projects

6.1 Update on the prequalification of quality control laboratories

Dr Luther Gwaza gave a presentation on behalf of Mr Rutendo Kuwana. Five new laboratories have been prequalified in 2018. Overall, there are 49 prequalified quality control laboratories and 44 are still in the pipeline, some for a long time now. The large number in the pipeline also includes a number that have been inspected but have not managed to improve their standards to WHO Prequalification (PQ) level.

To support the national quality control laboratories, WHO has organized technical assistances (7 in 2018) and peer audits (3 in 2018).

There was a discussion of the Expert Committee with regard to the procedure related to the laboratories in the pipeline.

6.2 Update on WHO quality monitoring projects

The project that is currently ongoing is the survey of selected antibiotics and antimalarial medicines circulating in six African countries. This is carried out together with WHO colleagues from the Safety and Vigilance team. There are three main survey objectives:

1. to establish the quality of selected essential medicines;
2. to improve the understanding of substandard and falsified medical products and contribute to gathering information on AMR;
3. to assess the suitability of near-infrared field and laboratory tools.

The Expert Committee noted the reports.

7. Quality control – national laboratories

7.1 External Quality Assurance Assessment Scheme

Dr Herbert Schmidt presented an update on the ongoing activities of the WHO External Quality Assurance Assessment Scheme (EQAAS), a proficiency testing scheme that provides laboratories with an objective means of assessing and demonstrating the reliability of the data they produce. Consequently, participation in EQAAS provides independent verification of the competence of a laboratory and shows commitment to the maintenance and improvement of performance. Proficiency testing covers the entire performance of a laboratory, from reception and storage of samples, the experimental work in the laboratory, the interpretation of data, and transcription of the data and conclusions onto the reporting sheets. Failure at any stage also reflects on the competence of the laboratory, and a report on an EQAAS study cannot be modified if the laboratory discovers such failure after receiving the first preliminary report. Comments from the laboratories are added to the final report, but tables, figures and conclusions are not modified unless the data submitted by the laboratory have been mistyped by WHO. EQAAS is open to any laboratory that wishes to undertake the testing, and not only prequalified laboratories.

EQAAS Phase 8 consisted of two studies. The aim of study 8.1 was to assess the performance of laboratories with regard to the determination of assay of a given API by liquid chromatography. Laboratories received one vial containing 175 mg of the testing sample (clindamycin hydrochloride) and one vial containing 175 mg of clindamycin hydrochloride RS. Their task was to determine the content of the latter according to the method described in the monograph on clindamycin hydrochloride in *The International Pharmacopoeia* (*1*).

Thirty-five laboratories submitted results for this study. Thirty reported satisfactory results, while five reported either unsatisfactory or doubtful results. These five laboratories were informed that they need to investigate their procedures, while one of them was additionally asked to improve its performance.

In study 8.2, the 35 laboratories were asked to determine the content of impurity B (clindamycin B) and impurity C (7-epiclindamycin) in the sample provided to them, according to the liquid chromatography method that was described in the monograph on clindamycin hydrochloride of *The International Pharmacopoeia* (*1*). While the majority of laboratories again performed satisfactorily, nine were informed of the need to investigate their procedures and seven of those were called on to take action to improve their performance.

The Expert Committee noted the report. The Expert Committee also recommended that the WHO Secretariat investigate a possible means of encouraging more laboratories to participate in the scheme, especially those that are involved in the prequalification process.

This ended the open session.

8. Quality control – specifications and tests: *The International Pharmacopoeia*

8.1 Update

Dr Herbert Schmidt gave an update on *The International Pharmacopoeia* (*1*). The eighth edition (2018) of *The International Pharmacopoeia* is now available online on the WHO website, on CD-ROM and, for the first time, on USB memory sticks. Based on decisions taken at the 52nd meeting of the ECSPP in 2017, new and revised texts were introduced for 40 monographs on pharmaceutical substances, 13 monographs on dosage forms and one method of analysis. As part of the activities to replace mercury salts in titrations of halide salts of weak bases, alternative titrations, either with perchloric acid in anhydrous acetic acid or with sodium hydroxide in alcoholic media, were introduced in 31 monographs. The new text on capillary electrophoresis is based on the internationally harmonized texts developed by the PDG.

8.2 Workplan 2018–2019

Members of the Expert Committee received a workplan listing 38 product monographs and 22 API monographs proposed for high-priority development for *The International Pharmacopoeia* (see Table 1). The proposals were based on a survey to identify medicines that are listed in the EML (*2*) or invitations to submit an EOI for prequalification but that are not yet subject to a monograph in the current British Pharmacopoeia, European Pharmacopoeia, Japanese Pharmacopoeia or United States Pharmacopeia. The survey also included the APIs contained in the evaluated medicines. In addition, eight monographs were identified for omission, as the corresponding medicines are no longer mentioned in the EML or in guidelines from WHO disease programmes.

Table 1
Monographs proposed for high-priority development for *The International Pharmacopoeia* with high priority

Active pharmaceutical ingredient	Finished dosage forms
	abacavir and lamivudine dispersible tablets
	abacavir dispersible tablets
	amphotericin B liposomal complex for injection
	artemether and lumefantrine dispersible tablets

Table 1 *continued*

Active pharmaceutical ingredient	Finished dosage forms
Piperaquine phosphate	artenimol and piperaquine phosphate tablets
	artesunate and amodiaquine tablets
	artesunate and mefloquine tablets
Pyronaridine tetraphosphate	artesunate and pyronaridine tablets
	artesunate rectal capsules
	atazanavir and ritonavir tablets
Bedaquiline	bedaquiline tablets
Daclatasvir hydrochloride	daclastavir tablets
Darunavir	darunavir tablets
Dasabuvir sodium	dasabuvir tablets
Delamanid	delamanid tablets
Dolutegravir	dolutegravir tablets
Entecavir	entecavir oral solution
	estradiol cypionate and medroxyprogesterone acetate injection
Itraconazole	itraconazole capsules
Ledipasvir	ledipasvir and sofosbuvir tablets
Linezolid	linezolid powder for suspension
	linezolid tablets
Mifepristone	mifepristone tablets
Miltefosin	miltefosine capsules
	morphine sulfate granules (slow-release; to mix with water)
	nevirapine dispersible tablets
	norethisterone enantate injection
Ombitasvir	ombitasvir, paritaprevir and ritonavir tablets
	oseltamivir powder for oral suspension

Table 1 *continued*

Active pharmaceutical ingredient	Finished dosage forms
p-aminosalicylic acid (sodium salt) (aminosalicylate sodium)	p-aminosalicylic acid granules for oral solution (aminosalicylate sodium granules for oral solution)
Paritaprevir	
	paromomycin sulfate for intramuscular injection
	pyrazinamide dispersible tablets
Raltegravir	raltegravir tablets
Rifapentine	rifapentine tablets
Sofosbuvir; velpatasvir	sofosbuvir and velpatasvir tablets
	sofosbuvir tablets
Ulipristal acetate	ulipristal acetate tablets
	zidovudine dispersible tablets

The Expert Committee adopted the workplan 2018–2019 for *The International Pharmacopoeia* as presented.

8.3 Procedure for the development, revision and omission of monographs and other texts for *The International Pharmacopoeia*

Dr Herbert Schmidt presented on this topic. The revision of the procedure was drafted in March 2018 and discussed at the informal consultation in May 2018. The aim was to incorporate decisions of previous Expert Committee meetings and to expedite the development and release of International Chemical Reference Substances (ICRS), to ensure that newly published monographs can be used without delay, in accordance with the request from the Expert Committee at its 52nd meeting in October 2017. The revised procedure would require that potential donors of candidate materials should be contacted before the adoption of the monograph, to ascertain the availability of suitable materials. After adoption of a monograph (and before its publication), establishment reports of already established ICRS should be reviewed, to evaluate whether the intended uses as declared in the leaflets are still valid or whether they need to be amended or revised. During the year, newly established ICRS would be released by the ICRS Board and these releases would be confirmed by the ECSPP at its annual meeting.

As decided at the 51st meeting of the ECSPP, omitted monographs would be transferred to a publicly accessible archive section on the WHO website. Any ICRS referred to in omitted monographs should be removed from the ICRS catalogue 1 year after the monograph has been transferred to the archive.

The Expert Committee noted the report, and took note that the revised procedure would be sent out for public consultation and submitted to the Expert Committee at its next meeting in October 2019.

8.4 General policy – transition from microbiological to physicochemical assays in monographs on capreomycin active pharmaceutical ingredient and products

A concept paper on the transitioning of capreomycin was drafted in early 2017 and was discussed at the informal consultation on New Medicines, Quality Control and Laboratory Standards in May 2018, before being circulated for public consultation from May to July 2017. In October 2017, the Expert Committee recommended that a working group that had been established at the informal consultation should assess the situation and advise on the next steps. Initial investigations of the working group:

1. compared national capreomycin reference substances, focusing on assessing whether or not the omission of capreomycin in the WHO International Standards for Antibiotics had led to divergent national capreomycin standards for microbiological assays;
2. began a landscape analysis of capreomycin APIs and products on the global market, looking at whether or not the composition of capreomycin in products on the market differs significantly.

While these investigations have yielded initial results, the informal consultation on New Medicines, Quality Control and Laboratory Standards in May 2018 concluded that more information would be needed in order to evaluate the results. Consequently, additional capreomycin products from the international market will need to be analysed, in order to complete the landscape analysis.

The Expert Committee took note of the update.

8.5 General chapters

8.5.1 Limit test for heavy metals

Professor John Miller introduced a proposal to revise chapter 2.2.3 entitled *Limit test for heavy metals*.

The *Guideline for elemental impurities Q3D* (*17*), published by the ICH includes a process on how to assess and control elemental impurities in FPPs,

using the principles of risk assessment. Regulatory authorities may decide whether or not to apply this ICH guideline for assessing elemental impurities. If the ICH Q3D guideline is implemented, pharmaceutical substances will no longer be required to comply with the limit test for heavy metals. Consequently, in order to take account of this situation, a draft was prepared in November 2017 for a revision to the text of *The International Pharmacopoeia*. The draft was discussed at the informal consultation on New Medicines, Quality Control and Laboratory Standards in May 2018 and was subsequently revised on the basis of feedback received, with the revised draft being sent out for public consultation from August to September 2018. Feedback from this public consultation was then incorporated and the draft was presented to the Expert Committee for discussion.

Further changes to the text were proposed:

1. to add a new procedure for the preparation of the test solution – namely procedure 5, a closed-vessel microwave digestion that should be used as an alternative, particularly for procedures 3 and 4 employing ignition techniques;
2. to replace the reagent hydrogen sulfide R by thioacetamide R;
3. to align parts of text to the corresponding text included in the *European Pharmacopoeia*, thereby keeping and further simplifying the structure of the existing text.

The Expert Committee discussed the proposal to revise the chapter 2.2.3 *Limit test for heavy metals* and adopted the revised chapter.

8.5.2 Polymorphism

The draft text of a proposed chapter on polymorphism, to be included in the "Supplementary information" section of *The International Pharmacopoeia* under "Notes for guidance", was submitted to the Expert Committee for consideration. Originally drafted in March 2017, the proposed chapter was discussed at the informal consultation on Quality Control Laboratory Tools and Specifications for Medicines in May 2017 and sent out for public consultation from July to September 2017, before being presented to the Expert Committee in October 2017. Following comments from members of the Expert Committee, a first revised draft of the chapter was completed in March 2018 and was discussed at the consultation on Screening Technology, Sampling and Specifications for Medicines in May 2018. It was noted that the aim of the proposed chapter is to provide a brief overview of the terminology associated with crystal polymorphism; some analytical techniques commonly used to characterize polymorphs; the relevance of polymorphism for APIs and FPPs; and the control strategies for polymorphism employed by *The International Pharmacopoeia*.

The Expert Committee discussed the text as presented, as well as the comments received. Since the previous public consultation had resulted in a large number of comments, it was further agreed to send the document out for another round of public consultation and to submit it to the 54th meeting of the ECSPP in October 2019.

8.5.3 Dissolution test for solid oral dosage forms

A revision of the text on the dissolution test for solid oral dosage forms was drafted in January 2018, sent out for public consultation from February to March 2018, and then discussed at the consultation on Quality Control Laboratory Tools and Specifications for Medicine in May 2018. Changes to the text were proposed, to align the text to the internationally harmonized texts developed by the PDG. In addition, it was proposed to add a further buffer to the section of the chapter that is not part of the PDG text, and to revise the requirements for the qualification of dissolution testers by introducing the concept of an "enhanced mechanical calibration".

The Expert Committee adopted the chapter, subject to the changes agreed.

8.5.4 General notice: solubility

The experts participating at the informal discussion in May 2018 discussed the possibility of harmonizing the temperature at which solubility studies have to be performed. The information given under "Solubility" in monographs was presented to the Expert Committee for information. This is not regarded as an analytical requirement, as a need to harmonize the text in *The International Pharmacopoeia* was not identified by the informal consultation.

The Expert Committee noted the report and agreed that no change in *The International Pharmacopoeia* was required.

8.6 Specifications and draft monographs for medicines, including paediatric and radiopharmaceutical medicines

8.6.1 Medicines for maternal, newborn, child and adolescent health

Estradiol valerate

A draft monograph on estradiol valerate was presented to the Expert Committee, with a proposal for inclusion in *The International Pharmacopoeia*. The first draft was received from the collaborating laboratory in June 2018 and a draft revision was sent out for public consultation from July to August 2018.

The Expert Committee adopted the monograph, subject to the changes proposed.

Estradiol valerate and norethisterone enantate injection

The draft monograph on estradiol valerate and norethisterone enantate injection was proposed for inclusion in *The International Pharmacopoeia*. The proposed methods and specifications were based on a submission from a manufacturer and upon laboratory investigations. In September 2018, specifications and samples were submitted to WHO and a first draft was prepared for submission to the Expert Committee.

The Expert Committee agreed that the monograph should be further circulated for public consultation.

Ethinylestradiol

A proposal was introduced to revise the monograph on ethinylestradiol by replacing the existing thin-layer chromatography (TLC) method to test for related substances with a high-performance liquid chromatography (HPLC) method, by adding an alternative assay method, adding an alternative identity test C by HPLC and revising the identity test B by TLC, and by adding a transparency list to the monograph. A revision of the monograph was prepared in September 2018 and presented to the Expert Committee.

The Expert Committee adopted the monograph, subject to its finalization by a small group of experts.

Norethisterone enantate

Norethisterone enantate injection

The first draft of the proposed monograph on norethisterone enantate was received from the collaborating laboratory in June 2017 and a revised draft was sent out for public consultation from July to September 2017. The draft was then presented to the meeting of the Expert Committee in October 2017 and further revised on the basis of comments received during the public consultation and the meeting of the ECSPP. Further discussion followed, during the consultation on Screening Technology, Sampling and Specification for Medicines in May 2018. The document was submitted for information and discussion.

The draft of a new monograph on norethisterone enantate injection was first prepared in early 2017 and sent out for public consultation from July to September 2017. The draft was discussed by the Expert Committee in October 2017 and at the consultation on Screening Technology, Sampling and Specification for Medicines in May 2018. Laboratory investigations are ongoing. The document was therefore submitted for information and discussion.

The Expert Committee discussed the monographs and took note of the progress made.

8.6.2 Antimalarial medicines

Pyrimethamine

Pyrimethamine tablets

The first drafts of the monographs on pyrimethamine and pyrimethamine tablets were received from the collaborating laboratory in January 2017 and discussed at the consultation on Screening Technology, Sampling and Specifications for Medicines in May 2017. The drafts were subsequently revised in September 2017 and submitted to the Expert Committee for comments in October 2017. This was followed by public consultation on both drafts from November 2017 to January 2018 and discussion at the consultation on Screening Technology, Sampling and Specifications for Medicines in May 2018. Additional laboratory investigations are ongoing. An interim laboratory report and revised draft monographs were presented for comments at the 53rd meeting of the ECSPP.

The Expert Committee noted the report and the progress made in the development of the two monographs, which would be circulated for additional public consultation.

8.6.3 Antituberculosis medicines

Levofloxacin

Levofloxacin tablets

Experts had suggested revision of the monographs on levofloxacin and levofloxacin tablets. The proposed monographs were drafted in March 2017 and were discussed at the informal consultation on Quality Control Laboratory Tools and Specifications for Medicines in May 2017, before being presented to the Expert Committee in October 2017. Laboratory investigations to verify the suitability of the methods and specifications were carried out between March 2017 and October 2018 and the draft monographs on levofloxacin and levofloxacin tablets were reviewed by the Expert Committee. It was noted that the monographs would require public consultation before being submitted at the 54th meeting of the Expert Committee in October 2019 for potential adoption.

The Expert Committee proposed some changes to the monographs and noted the report.

Moxifloxacin hydrochloride

Moxifloxacin tablets

The draft monographs on moxifloxacin hydrochloride and moxifloxacin tablets were completed in March 2016. Laboratory investigations were carried out to verify and validate the analytical provision between March 2016 and October 2017. The drafts were then discussed at the informal consultation on Quality

Control Laboratory Tools and Specifications for Medicines held in May 2016 and were presented to the 52nd meeting of the ECSPP in October 2017. The Expert Committee adopted the monographs in 2017, subject to a further round of consultation. The drafts were then sent out for public consultation between January and March 2018 and the manufacturer proposed the inclusion of a test and a limit for the moxifloxacin enantiomer in the API monograph. The comments were discussed at the information consultation in May 2018 and the experts advised that the comments should be taken into consideration and that a test for the enantiomer should be included.

The Expert Committee endorsed the proposal to include the proposed changes to the monograph previously adopted at the 52nd ECSPP, subject to further expert review. The Expert Committee released the use of moxifloxacin for system suitability chemical reference substance (CRS) established by the EDQM.

8.6.4 Antiviral medicines including antiretrovirals

Daclatasvir dihydrochloride

Daclatasvir tablets

The first drafts of the daclatasvir dihydrochloride and daclatasvir tablets monographs were received from a collaborating laboratory in March 2018 and both were discussed at the consultation on Quality Control Laboratory Tools and Specifications for Medicines in May 2018. Revisions of the drafts were then sent out for public consultation from June to August 2018.

The Expert Committee adopted the monographs, subject to a further round of review by a small group of experts.

Dolutegravir sodium

Dolutegravir tablets

Draft monographs on dolutegravir sodium and dolutegravir tablets were received from a collaborating laboratory in August 2018.

The Expert Committee noted the progress in developing the monographs.

Ritonavir

Ritonavir tablets

Ritonavir oral solution

Proposals for the revision of monographs on ritonavir and ritonavir tablets and for a new monograph on ritonavir oral solution were discussed by the Expert

Committee in October 2017 and at informal consultations on Quality Control Laboratory Tools and Specifications for Medicines in both May 2017 and May 2018. Laboratory investigations are continuing and the monographs are to be sent out for public consultation. The drafts were submitted to the 53rd meeting of the ECSPP for discussion, as appropriate. The revisions are being carried out in collaboration with the British Pharmacopoeia, with specifications being based on more samples from more regions of the world, and with efforts to align the specifications with those of other pharmacopoeias.

The Expert Committee noted the progress made in developing the monographs.

Sofosbuvir

Sofosbuvir tablets

The Expert Committee received a concept note for the monographs on sofosbuvir and sofosbuvir tablets. The concept note included an overview of the chemical and physical properties of sofosbuvir, a draft proposal for the sofosbuvir monograph, and a draft proposal for the sofosbuvir tablets, in each case followed by comments and additional information.

The Expert Committee noted the progress made in developing the monographs.

8.6.5 Medicines for tropical diseases

Albendazole

The monograph on albendazole chewable tablets was published 2015 and included an assay and test for related substances by HPLC. However, the monograph on albendazole was not revised at the same time and still includes the test for related substances by TLC. Consequently, a revision of the monograph on albendazole was proposed and the Expert Committee was informed that the revision would include the replacement of the TLC test for related substances with an HPLC method, the addition of the information that the substance shows polymorphism (with a subsequent change in the identity test), the addition of a test on "clarity and colour of solution", an updating of the style of the monograph, and several minor additional changes. The revised draft was completed in February 2018 and was discussed at the consultation on Screening Technology, Sampling and Specification for Medicines in May 2018. Laboratory investigations were ongoing and a public consultation was planned.

The Expert Committee adopted the monograph, subject to its finalization by a small group of experts, and released the use of albendazole for system suitability CRS (established by the EDQM) for this monograph.

Ivermectin

Ivermectin tablets

Draft monographs on both ivermectin and ivermectin tablets were proposed for inclusion in *The International Pharmacopoeia*. Both monographs were drafted at the end of 2016 and laboratory investigations were carried out to develop, optimize, verify or validate the proposed analytical tests and specifications between May 2017 and March 2018. The monographs were then discussed at a consultation on Screening, Technology, Sampling and Specifications for Medicines in May 2018 and the revised drafts were sent out for public consultation from June to August 2018.

The Expert Committee adopted the monographs.

8.6.6 Ophthalmological and dermatological medicines

Tetracycline hydrochloride

Revision of the current monograph on tetracycline hydrochloride was proposed, in order to replace titration using mercuric acetate (assay method A) and microbiological assay (assay method B) and to revise the test for related substances/transparency list. The first draft of the revision was received from the collaborating laboratory in September 2017 and was presented to the 52nd meeting of the ECSPP in October 2017. It was further discussed at the consultation on Screening Technology, Sampling and Specifications for Medicines in May 2018.

The Expert Committee adopted the monograph, subject to further review by a small group of experts.

9. Quality control – international reference materials

9.1 Update on International Chemical Reference Substances, including the report of the custodial centre of the dedicated ECSPP subgroup on the International Chemical Reference Substances

Dr Herbert Schmidt and Dr Andrea Lodi presented on the above topic. The annual report of the custodial centre was published at the end of March 2018. Since the last meeting of the 52nd ECSPP in October 2017, the ICRS Board had released standards on the following:

- trimethoprim ICRS 2
- mebendazole ICRS 2
- sulfamethoxazole ICRS 2
- capreomycin sulfate for identification ICRS 1
- cycloserine ICRS 1
- methylthioniunium chloride ICRS 1
- ritonavir ICRS 3
- clindamycin hydrochloride ICRS 1.

In 2017, the 52nd meeting of the ECSPP requested consideration of ways to expedite the development and release of ICRS in order to ensure that monographs newly published in *The International Pharmacopoeia* could be used without delay. Proposals for doing this were discussed under the agenda item on the "Procedure for the development, revision and omission of monographs". The WHO Secretariat expressed its gratitude to:

- EDQM (the custodian centre for ICRS) for establishing, storing and distributing the ICRS and for providing guidance and support to primary standards;
- the ICRS Board for reviewing the establishment reports and releasing the ICRS;
- the collaborating laboratories for participating in collaborative trials to determine the assigned content.

The Expert Committee noted the report and confirmed the release of the stated ICRS.

10. General policy – chemistry

10.1 Revision of guidance on representation of graphic formulae

Dr Sabine Kopp drew attention to a working document on the graphic representation of pharmaceutical substances to replace the current existing guidance text published in 1996. The document was circulated and comments had been received. It was proposed to establish a working group to review the document, with the intention of presenting a version for adoption at the 54th meeting of the ECSPP in October 2019.

The Expert Committee noted the update.

11. Quality assurance – good manufacturing practices and inspection

11.1 Interpretation of *Guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems*

WHO published the first edition of the *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* in 2006 (*18*). After consideration of the comments and recommendations received through a public consultation over a number of years, the Expert Committee agreed at its 52nd meeting held in October 2017 that these guidelines, as amended, should be adopted as Part 1. This document (Part 1) consists of GMP recommendations for heating, ventilation and air conditioning (HVAC) systems for non-sterile products (*19*). The Expert Committee further agreed that Part 1 should be supplemented by an additional document (Part 2) that will reflect the interpretation of the recommendations in Part 1.

The proposed additional document (*Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of* Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products) was prepared by a consultant from January to February 2018 and circulated for public comments in February 2018. The proposed Part 2 contains non-binding examples, drawings, technical representations and interpretation in support of Part 1. It is intended as a basic and explanatory guide for use by pharmaceutical manufacturers and GMP inspectors. It is not intended to be prescriptive in specifying requirements and design parameters but attempts to facilitate a harmonized understanding of expectations for HVAC systems for manufacturers of non-sterile products. Comments and feedback were consolidated in May 2018 and the working document was discussed during an informal consultation on GXP for Medicines and Inspection Tools in July 2018, after which it was circulated for further public consultation in August 2018. Comments and feedback received after this second round of public consultation were incorporated in September 2018, prior to submission for consideration by the Expert Committee in October 2018.

The Expert Committee emphasized that both Parts 1 and 2 focus on good practices for HVAC systems for non-sterile products and that these were not intended as enforceable criteria for the design or review of HVAC systems for other dosage forms. Some of the principles referred to in these parts may, however, be considered in the HVAC system design and approach for, for instance, APIs or sterile products.

The Expert Committee adopted *Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. Part 2: Interpretation of* Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products (Annex 2).

11.2 Good manufacturing practices for validation

11.2.1 General main text

Validation is an essential part of good practices, including GMP and good clinical practices, and is therefore an element of the pharmaceutical quality system. Validation incorporates qualification and should be applied over the life-cycle of a product, process, method or system.

WHO published *Supplementary guidelines on good manufacturing practices: validation* in 2006 (*20*). The main text of these guidelines is supported by several appendices, listed as follows:

- Appendix 1: Validation of heating, ventilation and air-conditioning systems;
- Appendix 2: Validation of water systems for pharmaceutical use;
- Appendix 3: Cleaning validation;
- Appendix 4: Analytical method validation;
- Appendix 5: Validation of computerized systems;
- Appendix 6: Qualification of systems and equipment;
- Appendix 7: Non-sterile process validation.

However, the need for a revision was identified and draft documents were circulated for comment over recent years. For example, the appendix on *Non-sterile process validation* (Appendix 7) was revised in 2013 and was subsequently adopted by the Expert Committee at its 49th meeting in October 2014. The revised main text was adopted by the 51st meeting of the Expert Committee in 2016 but was not published, since the remaining appendices (which were to be published as part of the series together with the main text) were still under review.

The main text included in the document presented to the Expert Committee at its 53rd meeting in October 2018 constituted the general principles of the new guidance on validation. The principles that are applied in the revised documents include:

1. the execution of qualification and validation should be in compliance with regulatory expectations;

2. quality must be designed and built into the product;
3. quality cannot be inspected or tested into the product;
4. principles of quality risk management should be applied in determining the need, scope and extent of qualification and validation;
5. ongoing review should take place, to ensure that the qualified or validated state is maintained and opportunities for continuing improvement are identified.

During the 53rd meeting of the ECSPP, the validation documents were considered as a set of guidelines on validation, covering the general principles of qualification and validation in the main part, with the principles applied to cleaning, computerized systems, equipment, utilities and analytical methods in the appendices.

The Expert Committee discussed the appendices that were still under review.

11.2.2 Analytical procedure validation

In view of the trends in validation, there was a discussion of the proposed need for revision of the guideline on *Analytical method validation* (Appendix 4 in reference (*20*)) during an informal consultation on Data Management, Bioequivalence, GMP and Medicines Inspection from June to July 2015. A draft proposal for revision of the main text of the *Supplementary guidelines on good manufacturing practices: validation* (*20*) and several appendices was prepared by specialists, in collaboration with PQT inspections, based on the feedback received during the informal consultation and from PQT inspections, with draft proposals developed on the various topics by specialists, as identified in the individual working documents. A presentation on progress was subsequently made to the 50th meeting of the ECSPP in October 2015. Discussion at the informal consultation on Good Practices for Health Products, Manufacture and Inspection in April 2016 provided feedback for a further revision in May 2016, which was then circulated for public consultation in June 2016. Comments received fed into a further revision, which was then presented at the 51st meeting of the ECSPP in October 2016. Feedback and changes proposed were reviewed by an analytical chemist, from May to June 2018, and the text was further discussed at an informal consultation on GMP and Inspection Tools in July 2018, followed by further revision and review.

After discussion, the document *Analytical procedure validation* was adopted by the Expert Committee, subject to a review of the comments received by a subgroup (Annex 3, Appendix 4).

11.2.3 Validation of computerized systems

The working document on *validation of computerized systems*, is Appendix 5 to the main text on validation (Annex 3). The text of the draft appendix followed a similar review and revision process to that of the main text and other appendices. Following a presentation to the 51st meeting of the ECSPP in October 2016, the public consultation between October 2016 and April 2017 resulted in more than 400 comments, which were evaluated and prioritized by the German Inspectors' Expert Group on Computerized Systems ("EFG 11 – Computergestützte Systeme").

There was further discussion at the informal consultation on Good Practices for Health Products, Manufacture and Inspection in April 2017 and the resulting large amount of feedback and comments led to major restructuring and reworking with the assistance of experts and PQT inspections. The revised working document was circulated for review in June 2018 and comments received were consolidated in July 2018. The revised document was then discussed at the WHO consultation on Good Practices for Health Products, Manufacture and Inspection in July 2018, and was further revised during the same month, before being sent out for another round of public consultation from July to October 2018. The latest comments received were compiled prior to the draft being presented to the Expert Committee in October 2018. Issues raised and discussed in the meeting included cybersecurity, data security, backup and legacy systems.

The Expert Committee adopted the text, subject to the changes discussed (Annex 3, Appendix 5).

11.2.4 Qualification

Appendix 6 to the main text on validation (Annex 3) was entitled *Validation on qualification of systems, utilities and equipment* and was presented as a working document to the Expert Committee, following a series of rounds of consultation, discussion and revision to the other documents in the series. The Expert Committee noted the change in the title of the document to "qualification"; that the document was still under consultation; and that only a limited number of comments had been received to date.

After further discussion, the document on qualification was adopted by the Expert Committee, subject to a review of the comments received by a subgroup and with the title changed to *Guidelines on qualification* (Annex 3, Appendix 6).

In summary, the Expert Committee noted that the status of the set of validation guidelines was adopted and will be part of this report as follows; it also recommended that the Appendix on *Cleaning validation* be opened for revision, to be updated and brought in line with new developments:

- Annex 3, main text: *Good manufacturing practices: guidelines on validation* (adopted during the 51st meeting of the ECSPP)
- Annex 3, Appendix 1. *Validation of heating, ventilation and air-conditioning systems* (as cross-reference to TRS 1010, Annex 8 (*19*))
- Annex 3, Appendix 2. *Validation of water systems for pharmaceutical use* (as published in TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (*21*))
- Annex 3, Appendix 3. *Cleaning validation* (as published in TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (*21*))
- Annex 3, Appendix 4. *Analytical procedure validation* (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Annex 3, Appendix 5. *Validation of computerized systems* (adopted, subject to the changes discussed by the Expert Committee)
- Annex 3, Appendix 6. *Guidelines on qualification* (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Annex 3, Appendix 7. *Non-sterile process validation* (as published in TRS 992, Annex 3, 2015 (*22*)).

11.3 Update on review of existing WHO inspection guidance, including *Guidelines for inspection of drug distribution channels* and *Quality system requirements for national good manufacturing practice inspectorates*

During the informal consultation on Regulatory Guidance for Multisource Products in July 2016, participants considered that a number of WHO guidance documents, published as annexes to the WHO TRS, need to be updated. The Expert Committee confirmed the need for updating at its meeting in October 2016 and the WHO Secretariat reviewed the documents to prioritize the review. The 53rd meeting of the Expert Committee in 2018 was informed that three guidance documents were considered top priority for revision. These were: *Guidelines on import procedures for pharmaceutical products* (1996) (*23*); *Guidelines for inspection of drug distribution channels* (1999) (*24*); and *Quality system requirements for national good manufacturing practice inspectorates* (2002) (*25*).

For the update of the *Guidelines on import procedures*, see Section 12.1.

11.3.1 Guidelines for inspection of drug distribution channels

During the consultation on Good Practices for Health Products Manufacture and Inspection in July 2018, the WHO Secretariat presented a detailed analysis, considering that the *Guidelines for inspection of drug distribution channels* (*24*) provide general information on the training and qualification that inspectors involved in the verification and validation of distribution channels for medical products should have. The WHO Secretariat further proposed that these guidelines become redundant, considering that the content is planned for inclusion in the next update of the *Quality system requirements for national good manufacturing practice inspectorates* (*25*). However, the experts attending the meeting on Good Practices for Health Products Manufacture and Inspection in July 2018 strongly recommended maintaining the *Guidelines for inspection of drug distribution channels* (*24*).

The Expert Committee recommended consolidation of the *Good storage practices* and *Good distribution practices* for pharmaceutical products and the elements of good distribution channel guidance into one document.

11.3.2 Quality system requirements for national good manufacturing practice inspectorates

The WHO guidance on *Quality system requirements for national good manufacturing practice inspectorates* (*25*) defines basic requirements that apply to quality systems for the operation of inspection services within NRAs concerned with GMP inspections. In October 2016, the ECSPP confirmed the need to update this guidance. In 2018, the WHO Secretariat proposed to begin revision of this document, in collaboration with the PQ inspection team and in line with *Quality system requirements for pharmaceutical inspectorates from the Pharmaceutical Inspection Co-operation Scheme* (PIC/S) (*26*).

The Expert Committee recommended that this document be revised to cover GXP and suggested that consideration should be given for expansion so as to include good distribution practices and possibly elements of good clinical practice.

11.4 Update and recommendations from inspectors' meeting, including on good manufacturing practices and environmental issues

The discussion on AMR includes areas such as the production of antibiotics (APIs and FPPs) and related waste management. In this connection, the question has been raised as to whether or not the environmental challenges cannot be better addressed in GMP texts. While GMP are intended to control the manufacture of medicines and do not focus on environmental aspects, they

do include issues related to the protection of the environment and of workers. If fully implemented, GMP should therefore prevent waste of all sorts appearing in the environment.

The WHO Secretariat sought the Expert Committee's opinions on the need for revision of GMP to address the environmental protection from emissions when manufacturing pharmaceutical products, and the role of GMP inspectors in environmental protection and AMR control.

It was noted that this would probably increase inspectors' burdens; environmental protection was perceived to be outside the scope of GMP, which is quality-driven; and there is a lack of inspectors trained in environmental control; a lack of legal power for NRAs to enforce measures relating to the environment; and a lack of provisions for environmental protection in Member States' national legislation.

A pilot project on AMR and environmental control enforced through GMP was viewed as a possibility to start focused surveillance, beginning with a few antibiotics, such as those identified by the WHO Expert Committee on the Selection and Use of Essential Medicines as the antibiotics "RESERVE" group.

The Expert Committee:

1. **acknowledged the concern about AMR and supported the preparation of a text on points to be considered in relation to prevention of AMR. This could include reference to the role that inspectors can play during inspections;**
2. **considered that the pilot project was outside the scope of the mandate of this Expert Committee and recommended that the WHO Secretariat investigate collaboration between responsible agencies and Member States in this regard and report on this at the next meeting of the ECSPP in 2019.**

11.5 Inquiry regarding production of "water for injection"

In recent years, several pharmacopoeias have adopted revised monographs on water for injection (WFI), allowing production by non-distillation technologies. Until now, the production of WFI in many countries has been limited to distillation only. The monograph revisions in a number of pharmacopoeias were the result of extensive consultations with stakeholders and now allow production of WFI by a purification process equivalent to distillation – such as reverse osmosis – coupled with appropriate techniques.

During the 52nd meeting of the ECSPP in October 2017, members of the Expert Committee recommended that the WHO Secretariat should collect feedback on whether or not to revise the WHO specifications and GMP in relation to the production of WFI. In light of this, feedback was sought on

whether or not the WHO specifications and GMP text(s) should be revised in relation to the production of WFI, allowing other purification processes and, if yes, whether details on additional requirements should be added, and, if so, which requirements these should be. A working document for public inquiry was circulated in March 2018 and comments received were consolidated in April 2018. The issue was discussed at an informal consultation on Screening Technologies, Sampling and Specifications for Medicines held in May 2018 and then again during an informal consultation on GMP and Inspection Tools held in July 2018. Comments and feedback were then consolidated before presentation of the document and all comments to the Expert Committee in October 2018.

The Expert Committee discussed and agreed that the monograph in *The International Pharmacopoeia, Water for injections* (*27*) and *WHO good manufacturing processes: water for pharmaceutical use* (*21*) be revised to allow different technologies for production of WFI other than distillation.

11.6 Proposal for good chromatography practices

The WHO Secretariat received a recommendation from a member of the EAP to develop new guidance for good chromatography practices. The reasons provided for this proposal are that, in recent years, a number of warning letters, import alerts, and noncompliance notifications were issued by inspectorates as a result of data-integrity problems in chromatography. Such a guideline could assist inspectors in NRAs to better understand what the problems are, and also to ensure that industry understands the regulatory expectation in good chromatography practices. A document on good chromatographic practices would help to support inspectors in identifying, and helping to avoid, lapses in chromatographic data.

The Expert Committee endorsed the proposal for development of a document on *good chromatography practices*.

12. Quality assurance – distribution and supply chain

12.1 Guidelines on import procedures for medical products

A proposal for revision of the WHO *Guidelines on import procedures for pharmaceutical products* (*23*) was made during the consultation on Good Practices for Health Products Manufacture and Inspection in April 2017, and the proposal was subsequently presented to the 52nd meeting of the ECSPP in October 2017. A draft for revision was prepared in February 2018 and was reviewed by a member of the EAP in April 2018. The draft was finalized and sent out for public consultation from May to June 2018 and comments were consolidated in July 2018. The working document was discussed during the informal consultation on Good Practices for Health Products Manufacture and Inspection in the same month, and the title was revised to *Guidelines on import procedures for medical products*, to bring it in line with WHO terminology. Comments from the consultation were incorporated and the draft was then mailed out for public consultation from August to September 2018, after which comments were consolidated.

The draft presented to the Expert Committee included changes introduced as the result of the latest round of consultation. Members of the Expert Committee were asked for their comments on a number of issues. It was pointed out that the title of the document had been changed to include the term "medical products" instead of "pharmaceutical products", to bring the document into line with recent developments. This change was also reflected throughout the text of the document. The term "medical products" is defined in the document as "A term that includes medicines, vaccines, diagnostics and medical devices".

The Expert Committee adopted the document, subject to the changes proposed (Annex 5).

12.2 Update on review of existing WHO guidance, procedures and operational documents for pharmaceutical procurement

12.2.1 New guidance on shelf-life for supply and procurement of medicines

The Expert Committee was informed of the existence of different guidance with regard to the shelf-life of products purchased and supplied by procurement agencies. In considering the differences in recommendations and the problems experienced by procurement agencies, it was proposed that a WHO policy guidance be developed on the rationale and criteria for an acceptable remaining shelf-life for procurement and importation of medicines, and for appropriate management of stockpiled medicines. During their discussion, members of the Expert Committee noted considerable global differences in the acceptability of the shelf-life of medicine donations. A need was recognized for a clear explanation of terms such as "shelf-life" and "expiry".

The Expert Committee endorsed the proposal to develop WHO guidance on the rationale and criteria for an acceptable remaining shelf-life for procurement and importation of medicines, and for appropriate management of stockpiled medicines.

12.2.2 Update of listing of stability conditions for WHO Member States

The guidance on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* was published in 2009 (*28*), and was recently updated in in 2018 (*29*). The aim of these regulatory guidelines is to outline the core stability data package required for the registration of APIs and FPPs. The guidelines include cross-reference to the series of related documents published by the ICH and other WHO guidelines. On the basis of the interlinkages when developing these guidelines, the ICH parties withdrew one of their guidance texts (Q1F) and published a reference to the WHO guidelines on their website, which has now been updated to include the newly published text.

The updated guidance on *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (*29*), published in 2018, no longer includes the annex on Stability conditions for WHO Member States, which was published together with the previous version of the WHO guidance on stability testing in 2009 (*28*). The list is currently updated whenever a notification is received from an NRA, with the most recent change being made in August 2018. The Expert Committee was therefore informed of a proposal to make a more systematic update of this list, especially with regard to the information extrapolated from the literature. The systematic review of updating the list, entitled *Stability conditions for WHO Member States*, would include web-based searches on the NRA websites, communication with the NRAs to verify and amend data as necessary, and replacement of information provided by the International Federation of Pharmaceutical Manufacturers and Associations on the basis of literature data and publications. The document would be produced as a stand-alone living publication rather than as an annex to an old guideline.

The Expert Committee endorsed the proposal to continually update and maintain the list currently titled *Stability conditions for WHO Member States* as a stand-alone living publication.

13. Regulatory guidance and model schemes

13.1 Proposal to waive in vivo bioequivalence requirements for medicines included in the *WHO Model List of Essential Medicines*

As part of its 2006 guidance on the waiving of bioequivalence requirements for immediate-release oral solid dosage forms in the EML, WHO provided a list of APIs that are eligible for biowaiver (*30*). In 2016, the Expert Committee recommended the WHO Secretariat revise this list of APIs on the basis of verified laboratory data to promote access to quality multisource (generic) essential medicines. In 2017, the Expert Committee endorsed the proposed approach to conducting equilibrium solubility studies, to provide an important step towards a Biopharmaceutics Classification System (BCS)-based classification that is the framework supporting the biowaiver approach. Following the recommendation from the Expert Committee, the WHO Secretariat led a multicentre biowaiver pilot project to:

1. develop a new protocol to conduct equilibrium solubility experiments on APIs and a template for reporting the test results;
2. determine, using a harmonized approach as detailed in the WHO protocol, the solubility profiles of three APIs prioritized in collaboration with WHO Prequalification Team-Medicines and contained in medicines in the EML;
3. based on the equilibrium solubility test results, classify according to the BCS the APIs in a new revised *WHO biowaiver list*.

The first set of APIs for the new revised *WHO biowaiver* list was presented to the Expert Committee for comments.

The Expert Committee reviewed and accepted this first set of APIs as shown in Table 2, including the explanatory notes.

Table 2
The first set of active pharmaceutical ingredients for the new revised *WHO biowaiver list*

API contained in medicines in the EML	Therapeutic area	Indication	Highest therapeutic dose [mg]	BCS class[a]	Eligible for biowaiver	PQ EOI[b] / PQ
Tenofovir disoproxil fumarate	Anti-infectives	HIV	300 mg	I/III	Yes	Yes[c]

Table 2 *continued*

API contained in medicines in the EML	Therapeutic area	Indication	Highest therapeutic dose [mg]	BCS class[a]	Eligible for biowaiver	PQ EOI[b] / PQ
Dolutegravir	Anti-infectives	HIV	50 mg	II/IV	No	Yes[d]
Ethionamide	Anti-infectives	TB	15–20 mg/kg	II/IV	No	Yes[e]

API: active pharmaceutical ingredient; BCS: Biopharmaceutics Classification System; EML: *WHO Model List of Essential Medicines*; EOI: expression of interest; PQ: prequalification.

[a] According to the WHO guidelines, *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (WHO TRS No. 1003, Annex 6, 2017), APIs belonging to Class I and III are eligible for biowaiver. The present solubility characterization is deemed sufficient to provide an indication of whether an API is eligible for biowaiver or not. Once experimental absorption/permeability data are available, the exact BCS class attribution will be possible.

[b] Expression of interest for prequalification.

Note: for exemption from an in vivo bioequivalence study, an immediate-release, multisource product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to those of the reference product. The excipients used in the formulation must be considered, together with a risk-based approach in terms of the therapeutic index and clinical indications.

Two potential approaches were presented to the Expert Committee in order to move from the pilot to the full phase, namely experimental and regulatory pathways.

13.1.1 Experimental pathway

The experimental pathway involves generation of ad hoc experimental test results for biowaiver purposes, according to the WHO criteria to accept biowaiver and the established protocol (*31*):

1. collaboration with manufactures/pharmaceutical companies. Individual companies or international associations of companies/manufacturers could be asked to provide to WHO, for regulatory purposes, equilibrium solubility data measured against WHO standards and methodology (described in the WHO protocol);
2. collaboration with university/state laboratories at two levels:
   a. university/state laboratories could perform the equilibrium solubility tests, as in the Biowaiver Pilot Project;
   b. university/state laboratories could verify the equilibrium solubility results produced by manufacturers in a systematic or in a case-by-case approach (such as for borderline results).

13.1.2 Regulatory pathway

The regulatory pathway involves cooperation with international regulators/agencies to share the outcome of the BCS-based classification for APIs (selecting those in the EML) and, most importantly, the data underpinning such classification.

The proposed pathways can be combined. In future, when the BCS-based classification of APIs in the EML is completed, a systematic classification can be considered for new entries in the EML.

13.1.3 Prioritization exercise

A prioritization exercise has been conducted on APIs contained in medicines in the EML, considering country needs and criteria, such as:

- dosage forms;
- therapeutic use;
- inclusion in the EOI for PQ;
- previous classifications;
- their use in WHO projects and programmes.

The two lists that follow were drafted and proposed to the Expert Committee for the experimental and regulatory pathways respectively:

List of active pharmaceutical ingredients proposed for Biopharmaceutics Classification System-based classification (experimental pathway)

1. aciclovir (antiviral)
2. amoxicillin trihydrate (antibacterial)
3. azithromycin (antibacterial)
4. codeine phosphate (central nervous system)
5. bedaquidine (multidrug-resistant TB)
6. cefixime (antibacterials)
7. daclatasvir (hepatitis C)
8. darunavir (HIV)
9. efavirenz (HIV)
10. furosemide (cardiovascular)
11. methyldopa (pregnancy-induced hypertension)
12. primaquine (malaria)
13. pyrimethamine (malaria)

14. rifampicin (TB)
15. raltegravir potassium (HIV)

List of active pharmaceutical ingredients proposed for classification through the regulatory pathway

1. capecitabine (antineoplastic)
2. dasatinib (antineoplastic)
3. emtricitabine/tenofovir disoproxil (antiretroviral)
4. entecavir (antihepatitis)
5. imatinib (antineoplastics)
6. ledipasvir + sofosbuvir (antiviral)
7. oseltamivir (antiviral)
8. voriconazole (antifungal)

The Expert Committee endorsed the following three points, namely:

1. **the revised *WHO biowaiver list* (see above);**
2. **the WHO *Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (Annex 4);**
3. **the WHO Secretariat's proposal on the APIs to be classified for the next phase, based on the criteria outlined above.**

13.2 WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

Dr Sabine Kopp and Dr Samvel Azatyan presented on the above topic. WHO's *Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* is an international voluntary agreement to provide assurance to countries taking part in the scheme about the quality of pharmaceutical products moving in international commerce. The primary document of the scheme is the certificate of a pharmaceutical product. The 52nd meeting of the Expert Committee in 2017 was informed about the current situation of the scheme, including the fact that, at its 43rd meeting in 2008, the Expert Committee recommended that the scheme should be revised in line with recent developments. In 2017, the Expert Committee recommended that the WHO Secretariat should prepare a proposal for revision of the scheme for public consultation. The draft working document, which includes the proposed revision of the scheme, was duly prepared and was discussed during an informal

consultation in May 2018. The working document was circulated for public consultation and was also presented during a workshop held at the pre-ICDRA meeting and further presented to the 18th ICDRA held in Dublin, Ireland, in September 2018. The ICDRA recommended that the scheme should be updated by WHO and made a number of suggestions, particularly in view of the increasing use of electronic documentation.

The Expert Committee recommended that a small group of regulators be convened to review the recommendations and comments received, with the view to a revision of the document. It was the Expert Committee's view that this document is of a technical nature and it suggested that the WHO Secretariat explores the possibilities for the formal process of adoption of the revised text.

13.3 Good practice guidance document on implementing the collaborative procedures

Dr Luther Gwaza and Dr Milan Smid presented on the above topic. The need for collaboration and reliance to achieve effective regulation of medical products is well recognized. The *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* (*32*) and the *Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities* (*33*) have been implemented for this purpose. Experience with the implementation of these two procedures has shown that clear procedures for the regulatory authorities are critical. At its 52nd meeting, the Expert Committee had discussed a concept paper and the proposed outline of this guideline prepared in consultation with the focal persons participating in the collaborative registration procedures. The aim of the guideline is to support a NRA in making effective use of facilitated pathways for registration and post-registration management of medical products and supplement other guidelines promoting reliance-based approaches. The documents and tools informing the guideline had been developed and discussed at several annual meetings organized for the focal persons participating in the collaborative registration procedures since 2014. A consolidated version following the discussion of the concept note by the Expert Committee was developed and discussed at the Joint Meeting on Regulatory Guidance for Multisource Products with MQA and the WHO PQT assessment team in May 2018. Revised drafts were posted for public comment on the WHO website in August and September 2018. The text was further revised and presented to the Expert Committee at its 53rd meeting in 2018, together with the comments received.

The Expert Committee adopted the guideline, subject to the amendments agreed (Annex 6).

13.4 Guidance document to support and facilitate the implementation of quality management systems for national regulatory authorities

Dr Claudia Alfonso presented on the above topic. Work has continued, following endorsement by the Expert Committee at the 52nd meeting of the ECSPP in October 2017, to merge the principles of quality management systems with those of good regulatory practices. A quality management system is an effective tool for ensuring compliance with good regulatory principles for developing and implementing rules and regulations. The document outlines the principles of good regulatory practice – legality, impartiality, consistency, proportionality, flexibility, effectiveness, efficiency, clarity and transparency – and it shows how they may be applied to the regulation of medical products for human use.

A number of workshops – most recently in Tunis in December 2017 and followed by a series of WebEx meetings between April and September 2018 – have encouraged brainstorming on needs and methods for improvement in a variety of NRAs. A number of NRAs have put forward examples of both from their own experience. The Expert Committee acknowledged the extensive work that has gone into the guidelines. In the first quarter of 2019, a public consultation is planned to obtain further input, followed by a face-to-face consultation to address the comments and produce the next draft. It is expected that the final draft of the guidelines will be presented to the Expert Committee at its 54th meeting in October 2019.

The Expert Committee noted the report.

13.5 Good regulatory practices

The Expert Committee was briefed on the development of *Good regulatory practices: guidelines for national regulatory authorities for medical products*. The Expert Committee was advised that the draft document was to be revised and sent out for consultation.

The Expert Committee noted the update.

14. Miscellaneous

14.1 Update of WHO/UNFPA prequalification guidance for contraceptive devices and condoms

Ms Seloi Mogatle and Dr William Potter from the United Nations Population Fund (UNFPA) gave an update on the prequalification guidance for contraceptive devices and condoms. The UNFPA had contacted WHO to inquire how best to start a process to update the relevant texts that were adopted by the ECSPP and published in 2008 (*34*, *35*). The Expert Committee agreed on the importance of updating these materials in view of the changes in the contraceptive field globally over the previous decade. The two organizations committed to work together to bring the documents up to date. It was suggested by UNFPA to separate out the current procedure for condoms to include the following aspects:

1. prequalification guidance for contraceptive devices;
2. prequalification programme for male latex condom and annexes;
3. technical specification for male latex condom and annexes;
4. male latex condom prequalification inspection aide memoire;
5. condom quality assurance and annexes;
6. guidance on testing male latex condoms;
7. condom storage and transportation;
8. post-market surveillance of condoms;
9. public assessment reports for contraceptive devices – condoms and intrauterine devices.

UNFPA also raised the issue of specifications for lubricants (both water-based and silicon-based), which needs to be considered when developing the new guidelines.

The Expert Committee supported the development of the relevant documents for prequalification of condoms in consultation with the WHO Secretariat and their preparation for public consultation and took note that they will be reported back to the Expert Committee.

15. 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 by enabling access to quality medical products. She thanked all for their active participation and contributions. Dr Sabine Kopp thanked all members of the Expert Committee 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.

16. Summary and recommendations

The WHO ECSPP advises the Director-General of WHO in the area of medicines quality assurance. The Expert Committee oversees the maintenance of *The International Pharmacopoeia* (*1*) 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 Expert Committee's guidance documents are developed through a broad consensus-building process, including an iterative public consultation phase. Representatives from international organizations, state actors, non-state actors, pharmacopoeias and relevant WHO departments are invited to the Expert Committee's annual meetings, to provide updates and input to the Committee's discussions.

At its 53rd meeting held from 22 to 26 October 2018 in Geneva, Switzerland, the Expert Committee heard updates on cross-cutting issues from other WHO bodies, including the ECBS, the Expert Committee on the Selection and Use of Essential Medicines, local manufacturing, the programme working to combat AMR, the Member State mechanism on substandard and falsified medical products, the INN programme and the RSS unit. Updates were also presented by partner organizations, including UNICEF and the PDG and by the IAEA.

Progress updates on quality control activities were presented by the EDQM as the custodian centre in charge of ICRS for use with monographs of the *The International Pharmacopoeia* (*1*). Briefings were also provided on the outcomes of the Ninth International Meeting of World Pharmacopoeias, which was co-hosted by WHO and Viet Nam, and on the results of proficiency testing studies conducted in Phase 8 of the WHO EQAAS.

Progress updates were provided on prequalification of medicines, APIs 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* (*1*). The Expert Committee adopted 9 guidelines and 12 pharmacopoeial texts (2 general chapters, 10 new and revised monographs), and confirmed the release of 8 new ICRS established by the custodian centre for ICRS and two for use in connection with *The International Pharmacopoeia*.

The decisions and recommendations made by the Expert Committee at its 53rd meeting in 2018 are listed next.

The following guidelines and decisions were adopted and recommended for use:

1. *Procedure for the development of World Health Organization medicines quality assurance guidelines* (Annex 1) (*new*)
2. *Interpretation of* Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products (Annex 2) (*new*)
3. *Good manufacturing practice: guidelines on validation*:
   - General main text (Annex 3) (*revision*)
   - *Analytical procedure validation* (Annex 3 – Appendix 4) (*revision*)
   - *Validation of computerized systems* (Annex 3 – Appendix 5) (*revision*)
   - *Guidelines on qualification* (Annex 3 – Appendix 6) (*revision*)
4. Proposal to waive in vivo bioequivalence requirements for medicines included in the EML – set of priorities agreed
5. Pilot study 3 of new API data and classifications confirmed
6. *Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (Annex 4) (*new*)
7. *Guidelines on import procedures for medical products* (Annex 5) (*revision*)
8. *Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products* (Annex 6) (*new*)

For inclusion in *The International Pharmacopoeia*

The following general texts were adopted by the Expert Committee:

- Workplan 2018–2019

General chapters

- *2.2.3 Limit test for heavy metals (revision)*
- *5.5 Dissolution test for solid oral dosage forms (revision)*

Monographs

For medicines for maternal, newborn, child and adolescent health

- estradiol valerate

- ethinylestradiol

For antituberculosis medicines

- moxifloxacin hydrochloride
- moxifloxacin tablets

For antiviral medicines, including antiretroviral medicines

- daclatasvir dihydrochloride
- daclatasvir tablets

For medicines for tropical diseases

- albendazole (*revision*)
- ivermectin
- ivermectin tablets

For ophthalmological and dermatological medicines

- Tetracycline hydrochloride (*revision*)

International Chemical Reference Substances

The Expert Committee confirmed the release of the following ICRS that have been newly characterized by the EDQM, the custodian centre:

- trimethoprim ICRS 2
- mebendazole ICRS 2
- sulfamethoxazole ICRS 2
- capreomycin sulfate for identification ICRS 1
- cycloserine ICRS 1
- methylthioniunium chloride ICRS 1
- ritonavir ICRS 3
- clindamycin hydrochloride ICRS 1.

The Expert Committee also authorized the following reference substances, established by the EDQM for use according to the respective monographs in *The International Pharmacopoeia*.

- moxifloxacin for system suitability CRS
- albendazole for system suitability CRS

Recommendations

The Expert Committee made the recommendations listed below in the various QA-related areas. Progress on the suggested actions will be reported to the Expert Committee at its 54th meeting in October 2019.

The Committee recommended that the Secretariat, in collaboration with experts as appropriate, should take the actions listed next.

The International Pharmacopoeia

- Continue development of monographs, general methods and texts and general supplementary information, including radiopharmaceutical monographs developed by the IAEA, in accordance with the workplan and as decided at the meeting

Quality control – national laboratories

- Continue offering the EQAAS, including to those laboratories participating in the prequalification process

Good manufacturing practices and related areas

- Develop a revised text for the "cleaning validation", to bring it in line with new developments
- Develop a new comprehensive text on *Good distribution practices*, including the elements of WHO *Good storage practices* (*36*) and other related guidance texts, such as the *Guidelines for inspection of drug distribution channels* (*24*)
- Develop a new text on *Quality system requirements for national GMP inspectorates*
- Develop a document, e.g. as "points to consider", on environmental aspects relating to manufacturing for the prevention of AMR, to possibly include the role of inspectors
- For water for injection: update the current monograph in *The International Pharmacopoeia* on WFI and the related GMP text, to allow other technologies for production of WFI in addition to distillation
- Develop a new text on *Good chromatography practices*

Distribution

- Initiate the development of new guidance on the determination of shelf-life requirements for the supply and procurement of medicines

Regulatory mechanisms

- Continue the updating process for the *WHO certification scheme on the quality of pharmaceutical products moving in international commerce*, with a subgroup and active involvement of Member States
- Continue the drafting of the guidance document to support and facilitate the implementation of quality management systems for national regulatory authorities
- Continue the development of good regulatory practices
- Start the next phase of the WHO Biowaiver Project, on the BCS-based classification of the second set of APIs from the EML, in accordance with the newly adopted criteria for setting priorities, using the regulatory and experimental pathways
- Update the listing of stability conditions required for marketing authorizations in WHO Member States

Other

- Update the WHO/UNFPA guidance texts serving the prequalification of condoms, in close collaboration with colleagues in WHO and UNFPA
- Continue the revision of the *Guidance on representation of graphic formulae for medicines*
- Continue to provide the database of terms and definitions covered by this Expert Committee on the WHO website

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Annex 1

Procedure for the development of World Health Organization medicines quality assurance guidelines

1. Introduction

The process described in this annex is designed to ensure wide consultation and transparency when developing the World Health Organization (WHO) norms and standards for medicines quality assurance for WHO's Member States. These quality assurance (QA) guidelines include good practice quality guidelines and regulations (GXPs) and technical regulatory guidance. The steps outlined in Section 3 are designed to ensure that these texts are made available in a timely manner. These QA guidelines are developed and maintained up to date under the aegis of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), in line with WHO rules and procedures governing expert committees, adopted by WHO Member States. The steps involved in the development of specifications and monographs for inclusion in *The International Pharmacopoeia* (*1*) are addressed separately (*2*–*4*).

QA guidelines are the recognized WHO technical standards to support the whole life-cycle of medical products, from development through to production (for example, good manufacturing practices, quality control, inspectorate guidelines), marketing authorization (for example, stability and bioequivalence) and distribution (good distribution practices), up to the post-marketing phase (for example, WHO *Guidelines on the conduct of surveys of the quality of medicines* (5) and *WHO guidance on testing of "suspect" falsified medicines* (*6*)).

To reflect the constant technical progress in pharmaceutical development, production, regulatory science and quality control, it is crucial that QA guidelines and guidance texts are kept up to date, that they reflect science, and that the WHO procedures to elaborate or review them are flexible enough to allow rapid interventions by regulators, while maintaining a rigorous public consultation process with all stakeholders.

QA guidelines provide an important element of the quality dimension for the medical products (included on the basis of their efficacy and safety) in the WHO *Model List of Essential Medicines* (*7*) and in WHO treatment guidelines. Major WHO programmes, such as the Prequalification Team-Medicines, and others managed by partner organizations, such as the United Nations Children's Fund and The Global Fund to Fight AIDS, Tuberculosis and Malaria, rely heavily upon the quality specifications set out in *The International Pharmacopoeia* (*1*) and in the QA guidelines.

2. Purpose and scope

The primary objective of this guidance document is to establish a standardized policy when developing new QA guidelines. By increasing transparency and communication, the aim is to involve a wide range and a large number of stakeholders able to bring different perspectives to common issues.

In addition, the transparency and promotion of internationally standardized practices could improve the cooperation between national regulatory authorities and stakeholders, when developing quality standards leading to an optimization of resources on a global scale and reducing duplication of work.

3. Development of guidelines

QA guidelines are developed following recommendations by WHO governing bodies (such as, the Executive Board and the World Health Assembly), the International Conference of Drug Regulatory Authorities, the ECSPP, international organizations and United Nations agencies and other WHO programmes and activities, or in response to major public health needs, and are thereafter adopted by the ECSPP. The procedural steps to follow when developing new QA guidance are outlined in the list that follows.

- *Phase 1*: search for information on the identified QA topic available in the public domain.
- *Phase 2*: identify relevant expert(s) in that field, applying conflict-of-interest screening.
- *Phase 3*: contact the experts who are suitable for the task, sharing the relevant WHO confidentiality rules and policy. Confirm the core team of experts, who can be internal and/or external to WHO. The group of core experts is coordinated by the WHO Secretariat.
- *Phase 4*: make arrangements with the expert(s) for developing the first draft text of the QA guideline.
- *Phase 5*: follow the ECSPP consultative process – circulate widely for public consultation; this will last for a period of between 8 and 12 weeks, depending on the topic.
- *Phase 6*: collect and collate the comments received during the global consultation process.
- *Phase 7*: discuss and review the comments received during the consultation process, in the ECSPP meetings and in an informal consultation with experts and specialists.
- *Phase 8*: incorporate all changes agreed during the discussion in the ECSPP meeting leading to adoption, together with any editorial corrections. Present the final text to the ECSPP for possible formal adoption.
- *Phase 9*: if no consensus is reached by the ECSPP, repeat phases 5–8 until the agreed draft is suitable for adoption.

- *Phase 10*: when consensus is reached, the guidance is adopted by the ECSPP and included as an annex in the meeting report. It is recommended by the WHO Director-General to Member States as new WHO guidelines, GXP guidance, and so on.

The different steps leading to the development of a new WHO QA guideline for medicines are reported in the note "Schedule for the adoption process" outlining the development history of a text from its draft to its adoption, which is included in each working document that is circulated and posted on the Medicine Quality Assurance website for comments.

4. The WHO Technical Report Series

In accordance with the WHO rules and procedures, the Secretariat publishes the QA guidelines adopted by the ECSPP in WHO's Technical Report Series, after every meeting of the ECSPP. The ECSPP report includes all the newly adopted guidelines, including GXPs and regulatory guidance texts. It provides recommendations to the WHO Director-General and to WHO Member States. The report is presented to WHO governing bodies (such as the Executive Board) for final comments, endorsement and implementation by Member States. The report of the ECSPP therefore constitutes WHO technical guidance in medicine quality assurance and regulatory matters.

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Annex 2

Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products

Part 2: Interpretation of *Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products*

Background

The World Health Organization (WHO) published the first edition of its *Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* in 2006 (*1*).

Having considered various comments and the recommendations through public consultation over several years, the WHO Expert Committee on Specifications for Pharmaceutical Preparations agreed, during its Fifty-first meeting held in October 2017, that the *Supplementary guidelines for good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms* guidelines, as amended, be adopted as Part 1 (*2*).

It was agreed that Part 1 consists of guidelines that contain recommendations on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile products, and further agreed that Part 1 be supported by an additional document that reflects the interpretation of the recommendations in Part 1.

This document is Part 2 and will be considered for adoption as such after consultation.

1. Introduction and scope

This document represents Part 2 of the guidelines for good manufacturing practices (GMP) for heating, ventilation and air-conditioning (HVAC) systems. It contains non-binding examples, drawings, technical representations and interpretation in support of Part 1 of the HVAC systems guidelines (*2*).

It is intended to be a basic and explanatory guide for use by pharmaceutical manufacturers and GMP inspectors. It is not intended to be prescriptive in specifying requirements and design parameters but it attempts to facilitate a harmonized understanding of expectations for HVAC systems for manufacturers and regulators of non-sterile products.

Part 1 and Part 2 focus on good practices for HVAC systems for non-sterile products. Where applicable, some of the principles referred to may be considered in the HVAC design and approach for other dosage forms. These two documents are, however, not intended to be used as criteria for the design or review of HVAC systems for, for example, active pharmaceutical ingredients or sterile products.

Other relevant national and international standards, as applicable, should be considered when Part 1 and Part 2 are used. These include, but are not limited to, current publications such as ISO 14644 (*3*) and American Society of Heating and Air-Conditioning Engineers (ASHRAE) standards.

In general, HVAC systems can play an important role in facilitating a suitable environment for the manufacture of quality pharmaceutical products. Therefore, careful consideration should be given to their design. When designing an HVAC system, careful consideration should also be given to the building design and layout of areas, as these may influence the decision and design relating to, for example, the number of air-handling units (AHUs), components in AHUs, room pressure, pressure differentials, pressure cascades, levels of filtration, humidification, dehumidification, and heating and cooling of air. These may, in turn, have an impact on the quality of materials and products, as well as the functioning of equipment and instruments.

The conditions of areas should be defined and should be appropriate for storage, manufacture and use, as appropriate, of equipment, instruments, materials and products. It should further ensure that comfortable conditions are maintained for operators.

2. Risk assessment and design

2.1 Risk assessment

In line with the current approach in GMP, risk identification should be done for utilities such as HVAC systems. A science-based, comprehensive exercise of risk assessment should be used to determine risks related to possible failure of

the HVAC system and AHUs (including their components and subcomponents). An appropriate risk-assessment tool, such as failure modes and effects analysis or fault tree analysis, should be selected. Controls should be identified to eliminate the risks, or minimize the risk to an acceptable level. For example, the effect of failure of one or more AHUs in the HVAC system; failure of dust-extraction systems; or failure of AHU components such as filters, heating coils, cooling coils and fans should be assessed, and appropriate controls should be identified and implemented.

For more information on risk assessment, refer to the current WHO [World Health Organization] *guidelines on quality risk management* (*4*).

2.2 Design parameters

Manufacturers should define the design parameters of the HVAC system, to ensure appropriate operation and functioning of the system, which is needed for all the areas. Special consideration should be given to the required conditions for storage, manufacture and handling of materials and products, equipment and instrument functioning, personnel (operator) requirements and contamination control.

3. Glossary

For definitions and abbreviations, see Part 1 (*2*).

4. Premises

4.1 Premises design

Both the architectural design of the building and that of the HVAC system should be carefully considered when attempting to achieve the general objectives of preventing contamination and cross-contamination and ensuring an appropriate environment for the production and control of pharmaceutical products. It is important to ensure that the required environmental conditions, cleanliness and containment are achieved and maintained.

The infiltration of contamination from outside air should be minimized by the use of appropriate filtration, room pressure differentials and airlocks. Manufacturing facilities should normally be maintained at a positive pressure relative to the outside, to limit the ingress of contaminants. Where facilities are to be maintained at negative pressures relative to the ambient pressure, special precautions should be taken to avoid ingress and egress of contaminant.

Risks of contamination should be controlled, especially in the case of potent contaminants, to ensure protection of materials, products, operators and the environment.

Where necessary, air locks, change rooms and pass-through hatches may be considered and provided with effective ventilation and filtered air. Special attention should be given to door design, as gaps between doors and floors, doors opening into low-pressure areas, and sliding doors can result in changes in the pressure differential between areas. An interlocking system and a visual and/or audible warning system may be used, where required, to prevent opening of more than one door at a time where required.

In addition to the design of the premises, general controls should be in place to ensure protection of materials, products and personnel. The HVAC system can play a role in achieving this objective. Where identified, areas should be maintained within defined limits for temperature, relative humidity, and viable and non-viable particles. To ensure that the clean area is maintained at the defined limits, areas are normally classified. When classifying the area, the manufacturer should state whether the classification is for the "as built", "at rest" or "in operation" condition. For details, including definitions, see ISO 14644 (*3*).

Manufacturers may use different terms when classifying areas, including Grade A, B, C, D, or ISO 7, ISO 8, or Level 1, Level 2 or others (*5*) (see Table A2.1). When classifying an area, the class selected should be defined and described (see also Section 7).

Table A2.1
Examples of area classification (*5*)

Level	Example of area
Level 1	General area with normal housekeeping and maintenance, where there is no potential for product contamination, e.g. warehousing
Level 2	Protected area in which steps are taken to protect the pharmaceutical starting material or product from direct or indirect contamination or degradation, e.g. secondary packing, warehousing, first-stage change rooms
Level 3	Controlled area in which specific environmental conditions are defined, controlled and monitored, to prevent contamination or degradation of the pharmaceutical starting material or product, e.g. where product, starting materials and components are exposed to the room environment; plus equipment wash and storage areas for equipment product contact parts

The following describes approaches (with illustrations by means of diagrams) of different room arrangements and room pressures.

4.2 Weighing/dispensing and sampling areas

A room for weighing (e.g. dispensing of materials) should be of appropriate design (for examples, see Figs A2.1 and A2.2). It is often advantageous to have several rooms associated with the weighing activity. These may include a pre-weighing staging area, personnel airlock, material airlock, weighing area with a containment booth, post-weighing staging area, washing area and provision for waste removal. The HVAC system for such areas should ensure that the areas have at least the same area classification as other production areas where materials and products are exposed to the environment, logical flow of material and personnel, and an appropriate number of AHUs, as well as appropriate pressure differentials, containment, dust control, and rate of air exchange.

The objective of having a booth in a weighing room is to provide dust containment and operator protection. For example, the dust generated at the weighing location should be extracted through a perforated worktop, thus protecting the operator from dust inhalation, but at the same time protecting the material and product from contamination by the operator by means of the vertical airflow stream. The airflow velocity should be such that it does not disrupt the sensitivity of balances.

Fig. A2.1
Example of a weighing area

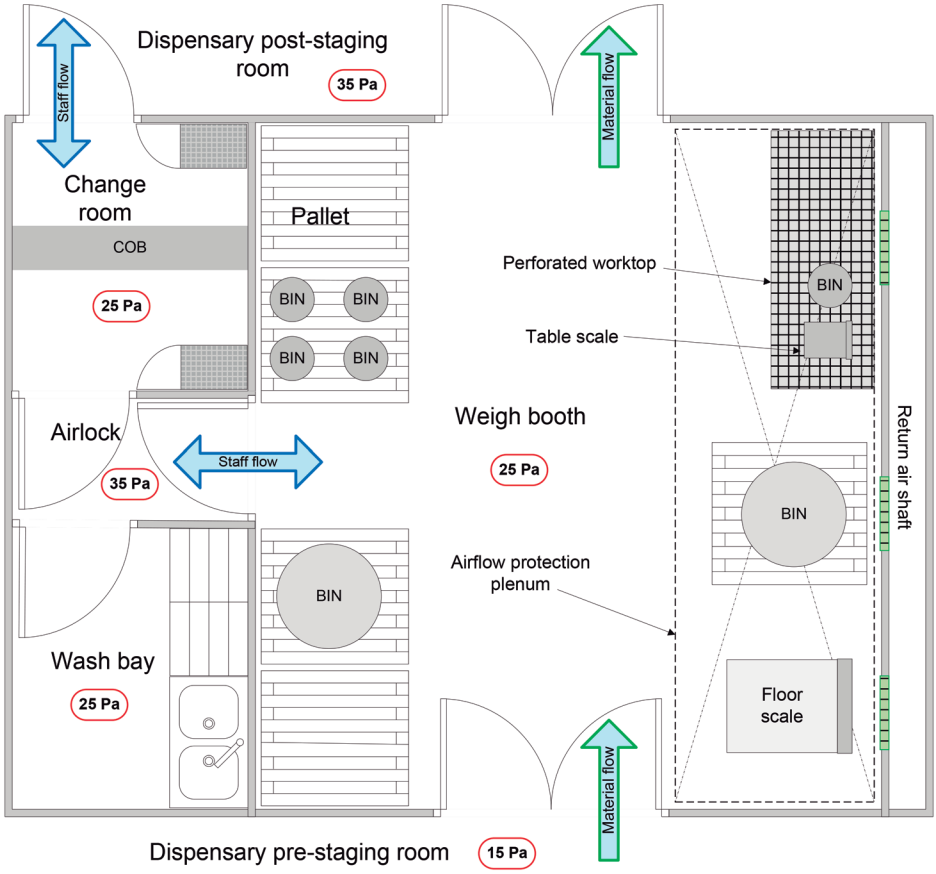


Fig. A2.2
Examples of weighing areas

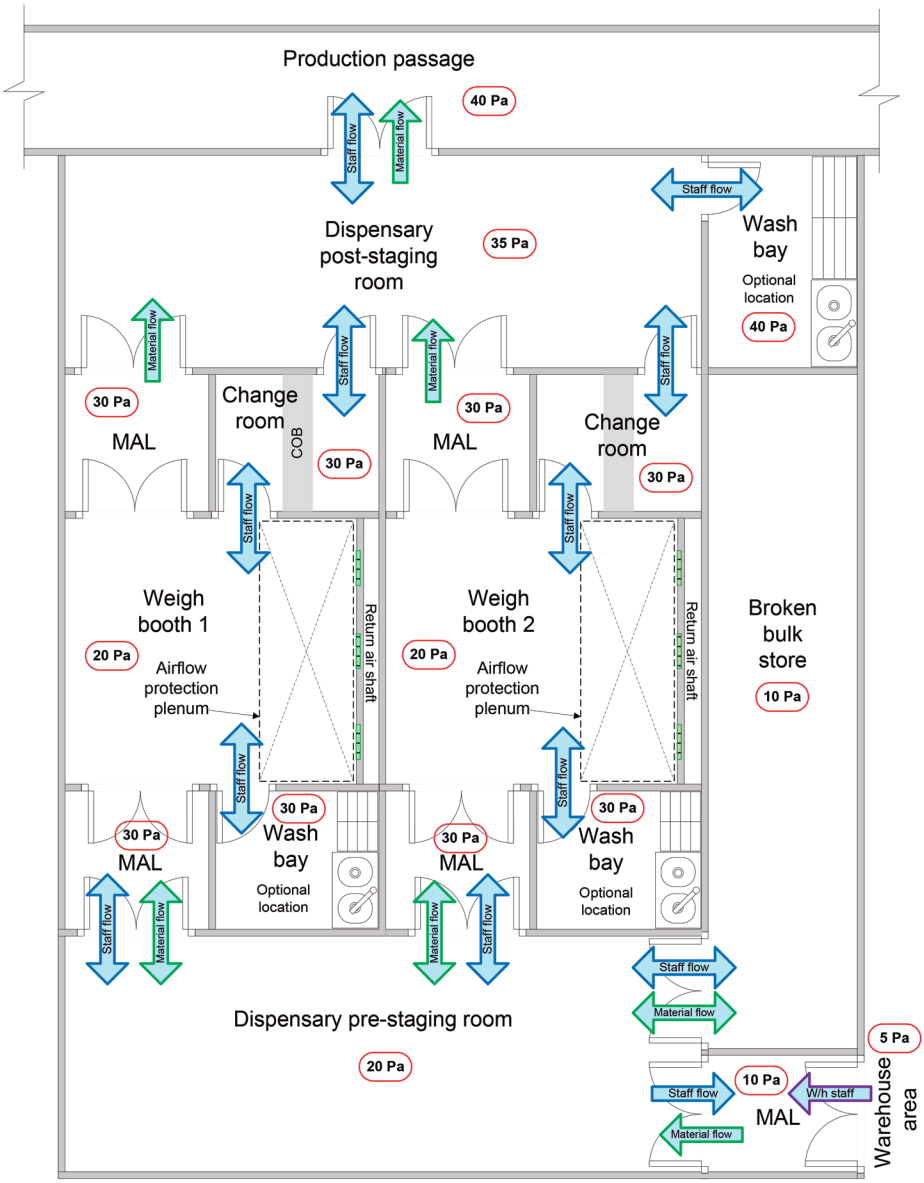
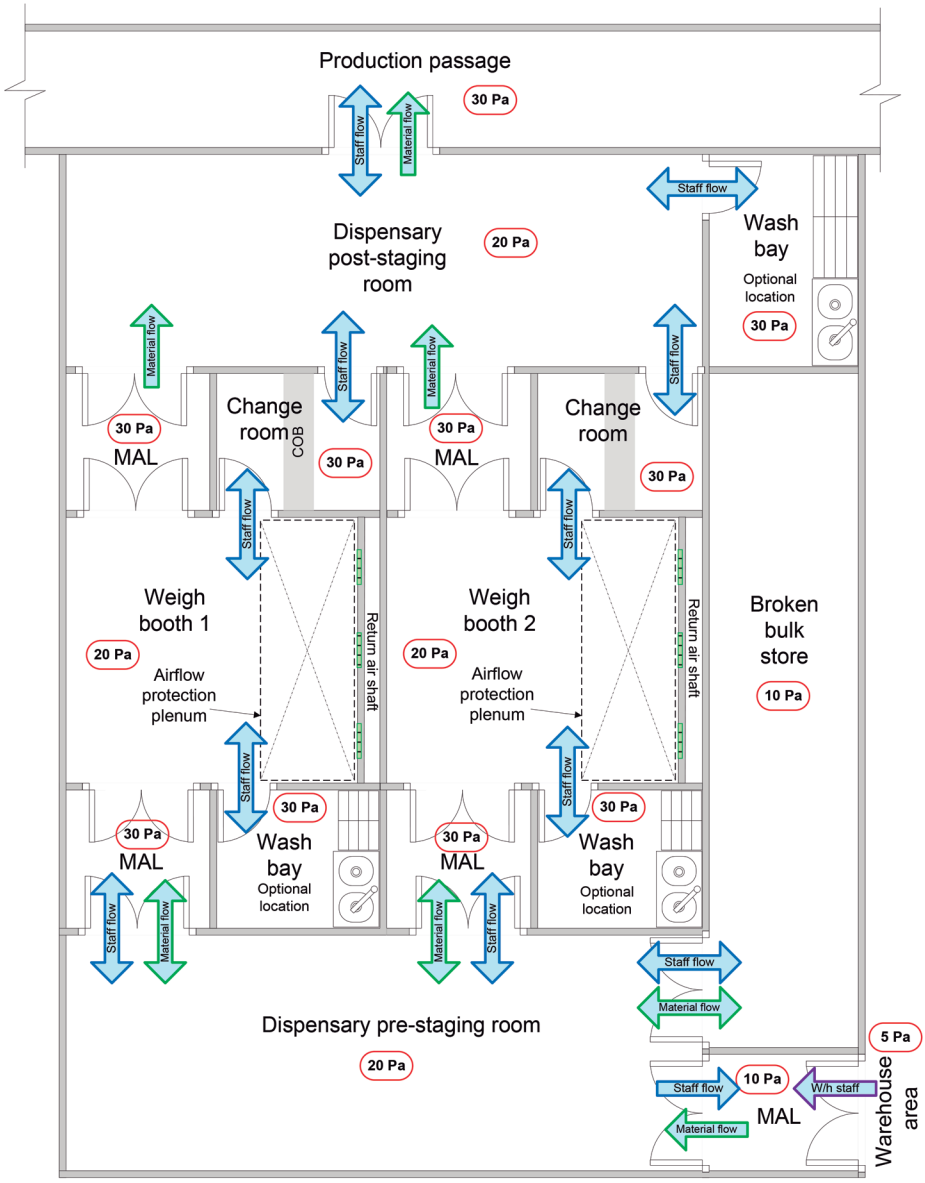


Fig A2.2 *continued*

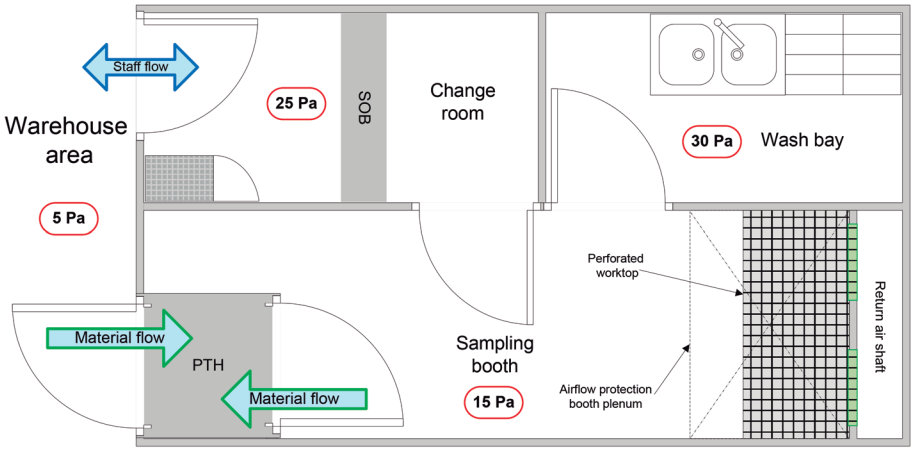


Note that the adjacent room pressures impact on determining the dispensary pressures.
COB: cross-over bench; MAL: material airlock; W/h: warehouse.

Similar aspects may be considered when designing a sampling area, as materials and primary components may be exposed to the environment during sampling (for examples, see Figs A2.3 and A2.4).

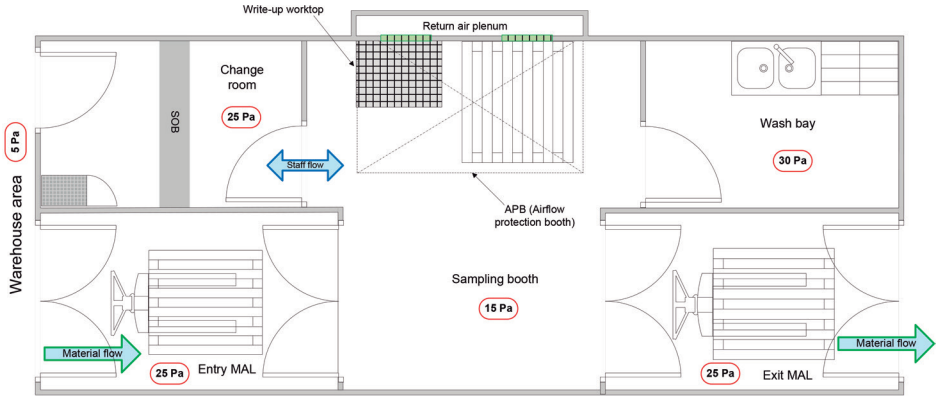
Sampling of materials such as starting materials, primary packaging materials and products, should be carried out in the same environmental conditions that are required for further processing of the product.

Fig. A2.3
Example of a sampling area



PTH: pass-through hatch.

Fig. A2.4
Example of a sampling area



MAL: material airlock.

A clean corridor concept is usually recommended for non-sterile oral solid-dosage form production areas, where there is then a higher pressure in the corridor compared to airlocks or production rooms. This is to facilitate containment of dust and contaminants that may have been generated in production rooms (see also the principles mentioned in the text on weighing/dispensing and sampling areas) (for an example, see Fig. A2.5).

To further support containment, consideration may also be given to having material airlocks (MALs) and personnel airlocks (PALs), where needed, for entry and exit of processing areas (for an example, see Fig. A2.6). Appropriately designed airlocks can assist in ensuring containment. Additional controls, such as pressure differentials between areas, an appropriate number of air changes in an area, and sufficient filtration of air, should be in place. The use of airlocks assists in ensuring containment; however, other means may be considered to achieve this objective, such as closed systems and pressure gradients between adjacent areas.

Fig. A2.5
Example of a change room and some production areas

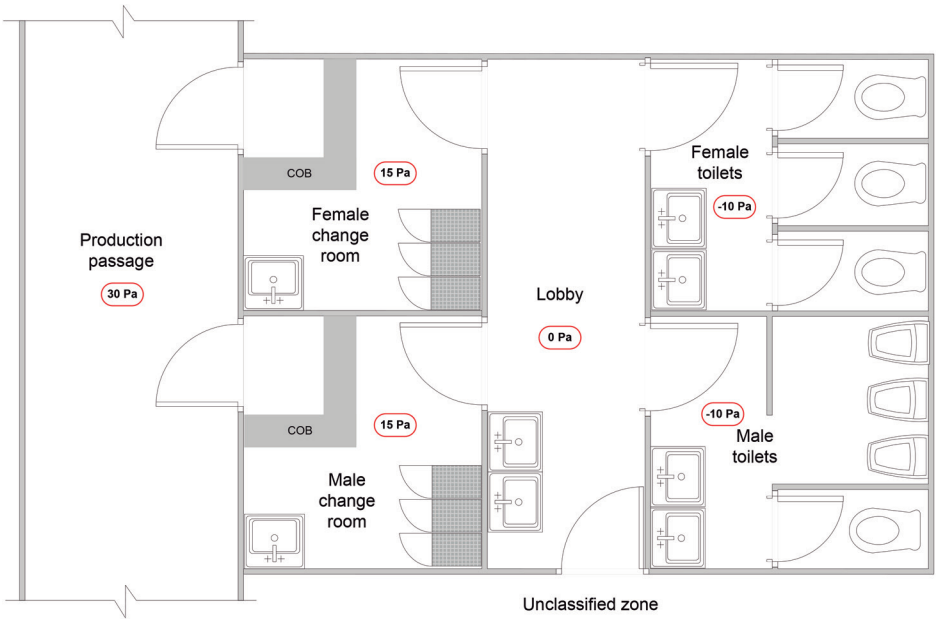
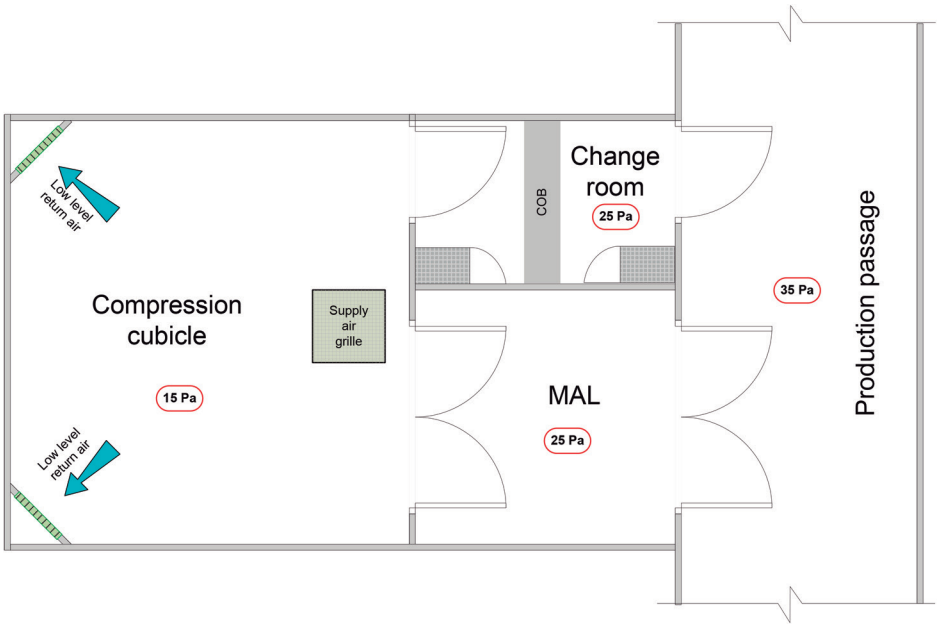
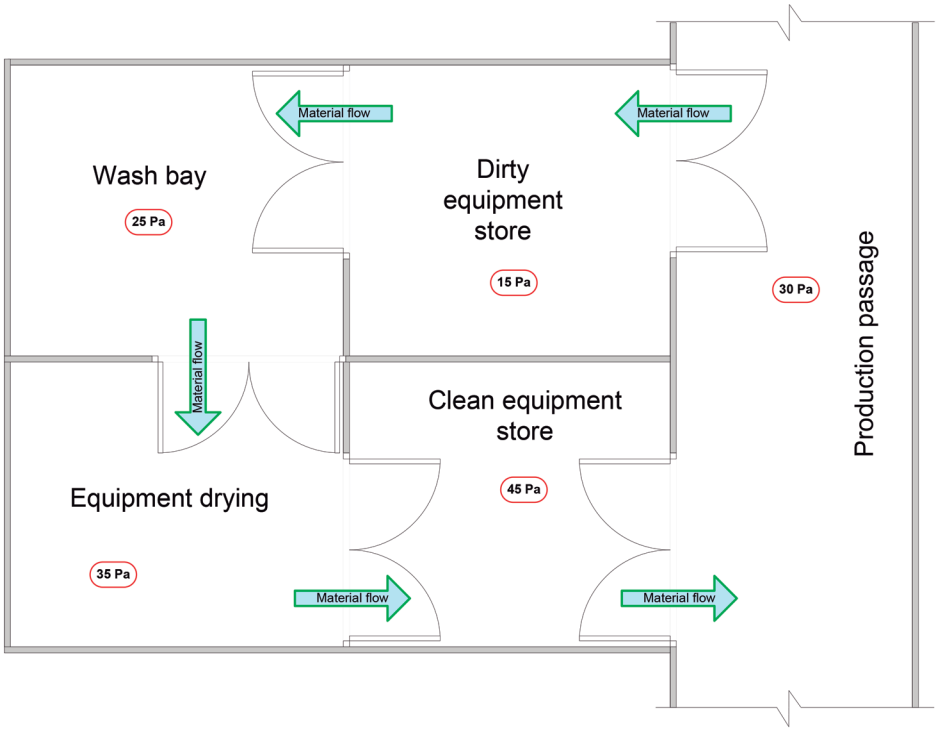


Fig. A2.6
Example of a compression cubicle with material (MAL) and personnel (PAL) airlocks (also used as an area to change garments)



Washing areas should be designed and used in such a manner that equipment and components will not be re-contaminated after cleaning. The system supplying and extracting air from the area(s) should be suitably designed to ensure that this objective is achieved. Principles that may be considered include (but are not limited to) filtration of air, pressure differentials between areas, air changes per hour and airflow directions (for an example, see Fig. A2.7).

Fig. A2.7
Example of a washing area



5. Design of HVAC systems and components

The HVAC system should be appropriately designed, taking into consideration the design of the facility, with various rooms or areas for storage of materials and in-process materials or products, processing, and movement of materials, products and personnel. The required cleanliness classification should be achieved, as well as other parameters, such as air filtration, airflow velocity, air volumes, pressure differentials, temperature, relative humidity, viable and non-viable particle counts and containment. Conditions and limits should be specified, based on need. Manufacturers should determine and define limits for these. These should be realistic, appropriate and scientifically justifiable at rest, in operation and as built at the time of design. In determining these, relevant factors and risks should be considered, including but not limited to possible failures of AHUs, seasonal variations, properties and types of materials and products, numbers of personnel and risks of cross-contamination.

Other aspects, such as the number of AHUs, dust-collecting or dust-extraction systems, the need for recirculation of air, percentage of fresh air (in

the case of recirculated air) and the level of filtration of air should be defined by the manufacturer when considering the design of the facility and activities in different areas and rooms.

Manufacturers should maintain schematic drawings of the HVAC system, AHUs and components. These should reflect the initial design and installation, as well as the current situation. Changes made during the life-cycle of the system should be reflected in change-control records and qualification protocols and reports, as appropriate.

The components selected in an HVAC system should be of sufficient capacity to ensure that the design objectives are met (e.g. for heating, cooling, humidification, dehumidification, airflow volumes), taking impacting factors into consideration, such as loss of air due to leakage and seasonal variations. Materials for construction of components, and their placement, should be such that these do not become the source of contamination. For example, components should not shed particles and the sequence of components should be logical; for example, filters should be placed in such a manner that any possible contaminants generated in the system can be retained by filters and not be introduced into the production area.

To prevent contamination of areas, components such as ventilation dampers, filters and other services should be accessible from outside the manufacturing areas (such as service corridors).

The overall design should be such that there is no possibility of undesired, unfiltered air or contaminants entering manufacturing areas.

5.1 Containment

Manufacturers should ensure that appropriate measures are taken to contain product dust in a manufacturing area, thus preventing or minimizing the risk of contamination of other areas and possible cross-contamination. In some cases, it may be advisable to have airlocks or pass-through hatches between rooms or areas. In addition, sufficient dilution, pressure differentials (recommended minimum values of 5 Pa) and airflow directions can further support containment in an area.

5.2 Cleanliness

Areas should be maintained at the defined levels of cleanliness and classifications. The HVAC system can support this through, for example, appropriate levels of filtration of air, dilution and dust removal. Equipment, containers, personnel and other related components should be appropriately located or placed in areas so as not to obstruct airflow and the effectiveness of the HVAC system.

Recontamination should be prevented by ensuring that movement of material and personnel is within the same area classification and not back

and forth between areas of different classification. Where such back-and-forth movement is unavoidable, appropriate controls should be identified and implemented, to ensure that moving from a higher class to a lower-classified area and back to a higher-classified area will not result in contaminants being brought into the cleaner classified area.

5.3 Automated monitoring systems

The performance of the HVAC system achieving and maintaining the desired results for parameters such as temperature, relative humidity, airflow and pressure differential should be carefully controlled and monitored. This is to ensure that there is no departure from these limits during manufacturing. Monitoring systems should be in place to ensure that the system operates within its design limits. Manual or automated (computerized) systems may be used.

Automated monitoring systems may provide possibilities for ongoing monitoring with better assurance of compliance with the defined limits. Where these automated systems are considered to be good practice (GXP) systems, these should be appropriately validated. The scope and extent of validation of the computerized system should be determined, justifiable and appropriately executed. This includes, but is not limited to, access and privileges to the software, setting of limits, monitoring and acknowledging alarms, audit trails, controls, and reporting.

5.4 Switching off air-handling units

It is recommended that the HVAC system be operational on an ongoing basis. Where a manufacturer decides to use energy-saving modes or switch some selected AHUs off at specified intervals, such as overnight, at weekends or for extended periods of time, care should be taken to ensure that materials and products are not affected. In such cases, the decision, procedures and records should be sufficiently documented and should include risk assessment, standard operating procedures, records and validation. This includes procedures and records for the start-up and shut-down sequence of AHUs.

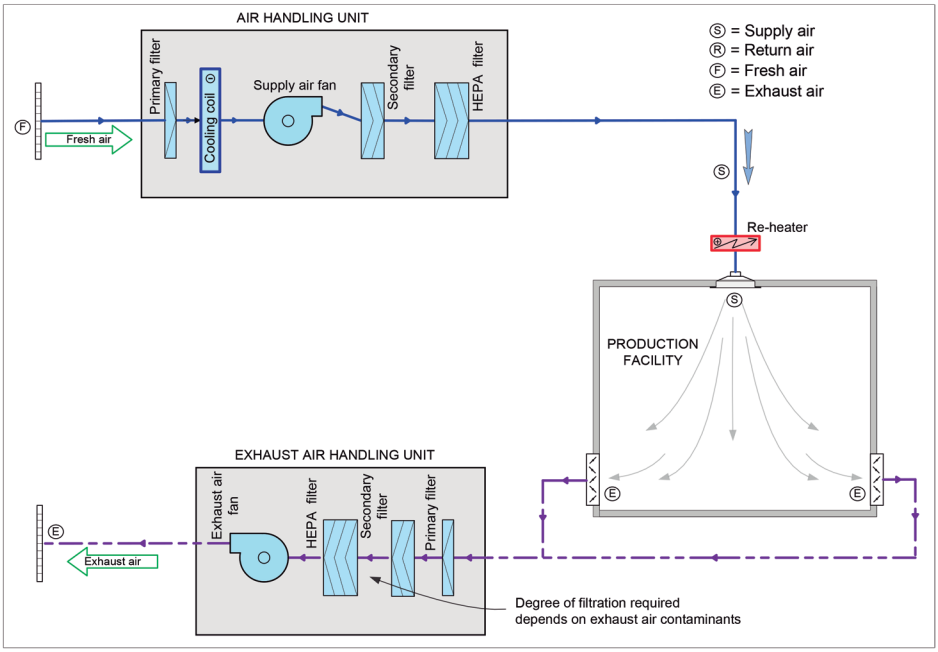
6. Full fresh air systems and recirculation systems

Manufacturers may select to have full fresh air systems (for an example, see Fig. A2.8) or recirculate treated air supplied to production areas (in a full fresh air system, no air is recirculated; in recirculation systems, a defined percentage of the air is recirculated). In both cases, the air supplied to the production areas should be appropriately treated, to ensure that the environmental conditions specified are met and that the risks for contamination and cross-contamination are controlled.

Manufacturers using recirculation systems should determine the percentage of fresh air to be supplied to the relevant manufacturing areas, as required by national and international standards. This volume of air should be verified during qualification.

In both scenarios, appropriate levels of filtration should be applied, to prevent contamination and cross-contamination. Manufacturers should ensure that when high-efficiency particulate air (HEPA) filters are used, these are appropriately installed, not damaged and thus suitable for the intended use (see tests described in Section 12).

Fig. A2.8
Example of a full fresh air system



HEPA: high-efficiency particulate air filter.

7. Air filtration, airflow direction and pressure differentials

Effective ventilation and appropriate levels of filtration are recommended in basic GMP guidelines. Manufacturers should determine which classes of filters should be used in ensuring that contaminants from outside are not introduced into manufacturing areas and that where recirculation systems are used, filtration of recirculated air is carried out effectively, to ensure that there is no risk of cross-

contamination. Where different products are manufactured in different rooms in the same facility at the same time, appropriate controls should be in place to ensure containment and prevention of contamination and cross-contamination.

Filters selected for air filtration should be determined and specified. When a manufacturer chooses to install HEPA filters to achieve the desired degree of filtration of air, these filters may be placed in the AHU, or may be installed terminally near the supply grille.

Filters have an impact on the cleanroom class or level of protection. The different levels of protection and recommended filter grades are presented in Table A2.2.

Table A2.2
Levels of protection and recommended filtration (*5*)

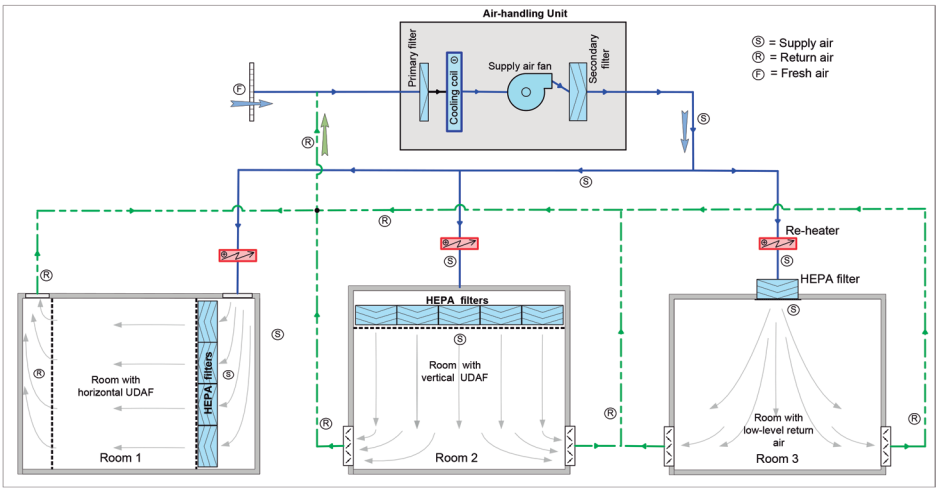
Level of protection	Recommended filtration
Level 1	Primary filters only (e.g. EN 779 G4 filters)
Level 2	Protected areas operating on 100% outside air: primary plus secondary filters (e.g. EN 779 G4 plus F8 or F9 filters)
Level 3	Production facility operating on recirculated plus ambient air, where potential for cross-contamination exists: primary plus secondary plus tertiary filters (e.g. EN 779 G4 plus F8 plus EN 1822 H13 filters; for full fresh air system, without recirculation, G4 and F8 or F9 filters are acceptable)

The number of air changes or air-exchange rates should be sufficient. A guidance value is between 6 and 20 air changes per hour. Manufacturers should also establish how much time it takes for a room that is out of its classification to return within the specified class. This is often referred to as clean-up or recovery time. A guidance time period for clean-up or recovery is about 15–20 minutes.

Airflow directions should be specified and proven to promote containment and not be adversely affected or obstructed by equipment, utilities, containers or personnel. The location of supply and return or exhaust air grilles should facilitate appropriate airflow directions in an area.

Fig. A2.9 is a schematic diagram of an example of an air-handling system serving rooms with horizontal directional flow, vertical directional flow and turbulent flow, for rooms 3, 4 and 5, respectively. In these rooms, the HEPA filters are indicated to have been placed terminally mounted in the rooms and not in the AHU. Whenever HEPA filters are terminally mounted, it can assist with preventing cross-contamination from room to room in the event of a fan failure.

Fig. A2.9
Example of horizontal airflow, vertical flow and turbulent flow



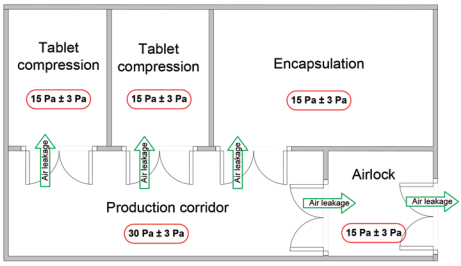
UDAF: unidirectional airflow.

The pressure differential should be of sufficient magnitude to ensure containment and prevention of flow reversal, but should not be so high as to create turbulence problems. It is suggested that pressure differentials of between 5 Pa and 20 Pa be considered. Where the design pressure differential is too low and tolerances are at opposite extremities, a flow reversal can take place. There should be no risk of overlap in the acceptable operating range, for example, 5 Pa to 15 Pa in one room and 15 Pa to 30 Pa in an adjacent room, resulting in failure of the pressure cascade (for examples, see Fig. A2.10). The upper and lower limits for pressure differentials between areas in a facility should be defined by the manufacturer. Where there are interleading rooms, the limits should be appropriate to ensure that there is no overlap in actual values, as this may result in loss in pressure differential between areas and even reversal of air flow.

Cumulative tolerances for the instruments measuring pressure differential should not cause a situation where an undetected reversal of airflow is possible. This can be accomplished by setting the limits such that there is no overlap in the differential between adjacent rooms at the extremes of acceptable tolerances, or by using a common reference point such as the corridor outside of a suite of rooms.

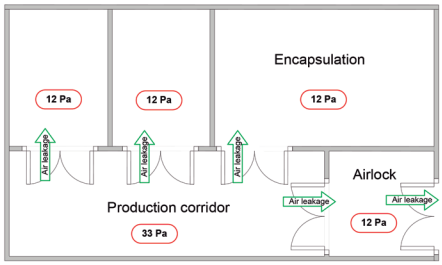
The pressure control and monitoring devices used should be calibrated and, where possible, be linked to an alarm system set according to the determined levels.

Fig. A2.10
Examples of pressure cascades

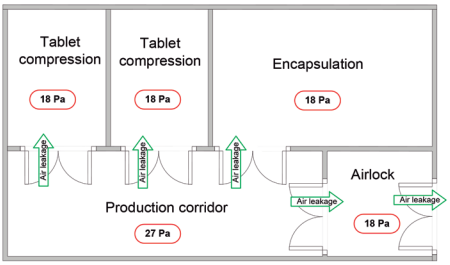


Design condition (15 Pa pressure differential)

Image of room pressure gauge indicating colour-coded normal, alert & action parameters



Maximum differential (21 Pa pressure differential)



Minimum differential (9 Pa pressure differential)

7.1 Airlocks

Airlocks with different pressure cascade regimes include the cascade airlock, sink airlock and bubble airlock:

- *cascade airlock*: higher pressure on one side of the airlock and lower pressure on the other (for an example, see Fig. A2.11);
- *sink airlock*: lower pressure inside the airlock and higher pressure on both outer sides (for an example, see Fig. A2.12);
- *bubble airlock*: higher pressure inside the airlock and lower pressure on both outer sides (for an example, see Fig. A2.13).

Fig. A2.11
Example of a cascade airlock: in most cases, the internal pressure of the airlock is not critical; the pressure differential between the two outer sides is the important criterion

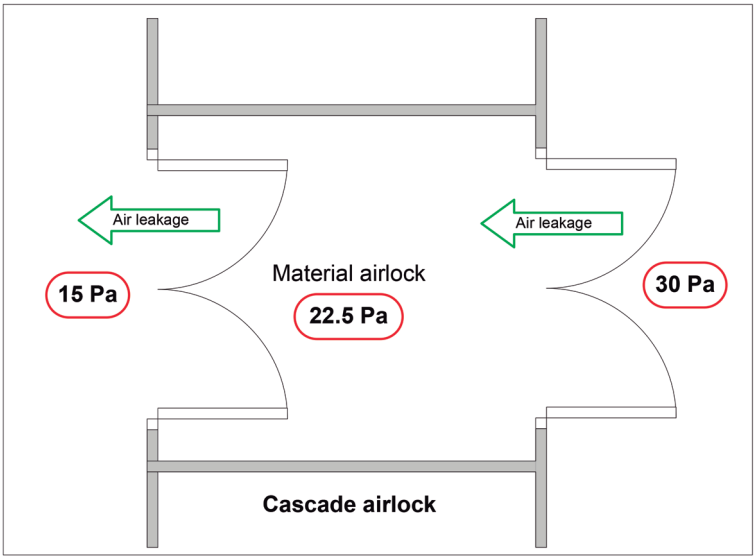


Fig. A2.12
Example of a sink airlock

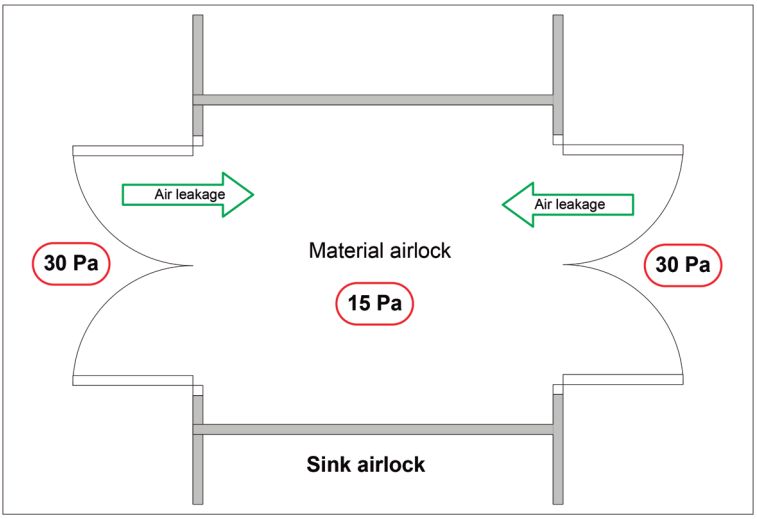
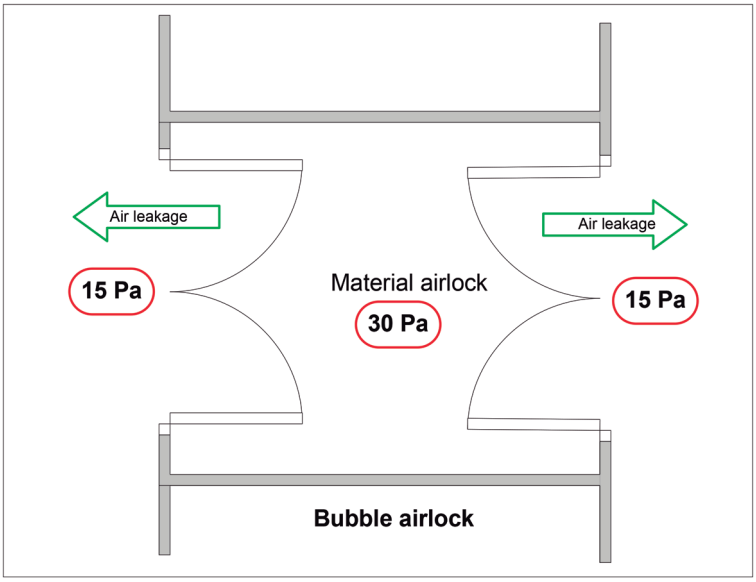


Fig. A2.13
Example of a bubble airlock



Note: The diagrams above and the differential pressures shown here are for illustration purposes only. Pressures indicated in these examples are absolute pressures, whereas the local pressure indication would most likely be the pressure differential from room to room.

Additional controls should be identified through risk identification and risk assessment. For example, where possible, personnel should not move between different areas during production (such as compression rooms and in process control laboratories), unless there is no risk of contamination of other areas. Personnel often become sources of contamination, as they may carry dust from one area to another. Controls may include airlocks or gowning procedures.

8. Temperature and relative humidity

Manufacturers should set appropriate upper and lower limits for temperature and relative humidity for different areas. The required storage conditions specified for the materials and products should be considered when the limits are defined. The HVAC system should be designed in such a manner that these limits can be achieved and maintained through all seasons.

Systems for dehumidification or humidification require special considerations, owing to their contamination risk (e.g. condensate formation, bacterial and fungal contamination, contaminated steam and risks when using

mobile systems between different areas). Chemicals such as corrosion inhibitors or chelating agents, which could have a detrimental effect on the product, should not be added to the boiler system. Humidification systems should be well drained. No condensate should accumulate in air-handling systems. Other humidification appliances such as evaporative systems, atomizers and water mist sprays, should not be used, because of the potential risk of microbial contamination. Air filters should not be installed immediately downstream of humidifiers, as moisture on the filters could lead to bacterial growth. Cold surfaces should be insulated to prevent condensation within the clean area or on air-handling components. Chemical driers using silica gel or lithium chloride are acceptable, provided they do not become sources of contamination.

9. Dust, vapour and fume control

Manufacturers should ensure that dust-generated vapours and fumes are effectively removed from the manufacturing areas. Extraction or collecting systems should be designed and qualified to demonstrate this. Sufficient air velocity should be maintained in such systems to effectively remove dust and vapours.

A dust extractor should normally not serve different rooms where different products can be processed at the same time, owing to the risks such as backflow or flow from room to room, resulting in possible contamination and cross-contamination.

Wherever possible, dust or vapour contamination should be removed at source, that is, as close as possible to the point where the dust is generated. Ducting for dust extraction should be designed with sufficient transfer velocity (determined by the manufacturer, depending on materials and products processed), to ensure that dust is carried away, and does not settle in the ducting (a guidance value is 15–20 m/s). As vapours can be problematic, extraction may be supported by directional airflow to assist in the removal. The density of the vapour should be taken into consideration, with extract grilles at a high level or possibly at both high and low levels.

10. Protection of the environment

Manufacturers should have controls in place to ensure that air from production areas, including contaminated air from equipment such as fluid bed driers, is passed through appropriate levels of filtration, to ensure that the environment is not polluted. Manufacturers should consult national and international environmental legislation.

11. Commissioning

Where manufacturers perform commissioning, this should be clearly documented.

12. Qualification

Manufacturers should consider all stages of qualification for their HVAC systems. This includes, where appropriate, user requirement specification, design qualification, factory acceptance test, site acceptance test, installation qualification, operational qualification and performance qualification. Qualification to be done over the life-cycle of the HVAC system should be described and executed, including, for example, when changes are made to the system.

Validation master plan(s), protocols, reports and source data for tests should be available. The scope and extent of qualification should be determined based on risk assessment. Parameters with limits included in qualification (such as temperature test, airflow direction, viable and non-viable particle counts) should be justified by manufacturers. The procedures followed for the performance of the tests should generally be in line with the standard as described in ISO 14644 (*3*).

Some of the typical HVAC system parameters that should be included in the tests during qualification are listed next and the selection of the parameters should be justified (for examples, see Table A2.3). It is recommended that the tests be done at defined intervals. The tests typically cover:

- 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.

Table A2.3
Considerations for test parameters and procedures

Test parameter	Test procedure	Note
Temperature	ISO 14644 (*3*) and WHO Technical Report Series, No. 961 (*6*)	Adapt ISO tests in case of longer periods, and consider the temperature mapping test as described in WHO Technical Report Series
Relative humidity	ISO 14644 (*3*) and WHO Technical Report Series, No. 961 (*6*)	Adapt ISO tests in case of longer periods, and consider the temperature mapping test as described in WHO Technical Report Series
Pressure differential	ISO 14644 (*3*)	Consider extended periods to show consistency in performance
Airflow volumes	ISO 14644 (*3*)	
Installed filter leakage	ISO 14644 (*3*)	
Particle counts	ISO 14644 (*3*)	
Airflow direction	ISO 14644 (*3*) or company procedure (smoke test)	Ensure a continuous capture of the process, e.g. video, with correct angles to demonstrate air flow direction, and appropriate records and labelling indicating date, time, signatures and area filmed and recorded in a traceable manner
Airflow velocity	ISO 14644 (*3*)	
Recovery	In-house procedure	
Air-change rate		

13. Maintenance

Manufacturers should maintain current documentation for HVAC systems, including operation and maintenance manuals, schematic drawings, procedures and records.

Repairs, maintenance and preventive maintenance (including cleaning, replacement of components, changes, qualification) should be executed in accordance with procedures. Records for these should be maintained for an appropriate time.

References

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2. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 8 (WHO Technical Report Series, No. 1010; http://apps.who.int/medicinedocs/documents/s23455en/s23455en.pdf, accessed 9 February 2019).
3. ISO 14644. Cleanrooms and associated controlled environments. Parts 1–15. Geneva: International Organization for Standardization; 2012–2018 (https://www.iso.org/obp/ui/#search, accessed 14 March 2019).
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5. Good practice guide: heating, ventilation, and air conditioning (HVAC). North Bethesda (MD): International Society for Pharmaceutical Engineering (ISPE); 2009.
6. WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-fifth report. Geneva: World Health Organization; 2011 (WHO Technical Report Series, No. 961; https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1, accessed 8 February 2019).

Annex 3

Good manufacturing practices: guidelines on validation

Background

The need for revision of the published World Health Organization (WHO) *Supplementary guidelines on good manufacturing practices: validation* (*1*) was identified by the Prequalification of Medicines Programme and a first draft document was circulated for comment in early 2013. The focus, at that time, was revision of the appendix on *Non-sterile process validation* (Appendix 7) (*2*), which had been revised and was adopted by the ECSPP at its Forty-ninth meeting in October 2014 (*3*).

The overarching text presented in this annex constitutes the general principles of the new guidance on validation.

The following appendices included in this annex address specific aspects of validation and are intended to complement the general text on validation:

- Appendix 1. Validation of heating, ventilation and air-conditioning systems (as cross-reference to TRS 1010, Annex 8 (*4*))
- Appendix 2. Validation of water systems for pharmaceutical use (as published in TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (*5*)
- Appendix 3. Cleaning validation (as published in TRS and TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (*5*)
- Appendix 4. Analytical procedure validation (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Appendix 5. Validation of computerized systems (adopted, subject to the changes discussed by the Expert Committee)
- Appendix 6. Guidelines on qualification (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Appendix 7. Non-sterile process validation (as published in TRS 992, Annex 3, 2015 (*3*)).

1. Introduction

1.1 Validation is an essential part of good practices, including good manufacturing practices (GMP) (*6*) and good clinical practices (GCP). It is therefore an element of the pharmaceutical quality system. Validation, as a concept, incorporates qualification and should be applied over the life-cycle of, for example, a product, process, method, system, equipment or utility.

1.2 These guidelines cover the general principles of qualification and validation. In addition to the main text, appendices on some validation and qualification activities (such as applied to heating, ventilation and air-conditioning systems, water systems, cleaning, analytical methods, computerized systems, and non-sterile processes) are included.

1.3 The following principles apply:

1. the execution of qualification and validation should be in compliance with regulatory expectations (*7*);
2. quality must be designed and built into the product;
3. quality cannot be inspected or tested into the product;
4. principles of quality risk management (8) should be applied in determining the need, scope and extent of qualification and validation;
5. ongoing review should take place, to ensure that the qualified or validated state is maintained and opportunities for continuing improvement are identified.

1.4 Provision should be made for appropriate resources such as personnel, financing and time to organize, plan and execute qualification and validation.

2. Scope

2.1 These guidelines focus mainly on the overall concept of qualification and validation and are not intended to be prescriptive in specific validation requirements. This document serves as general guidance only and the principles may be considered useful in its application in the production and control of starting materials and finished pharmaceutical products, as well as other areas such as GCP. Although the principles addressed in this guideline are applicable, qualification and validation of specific products, methods, processes and systems, such as bioanalytical methods, and manufacturing

processes for sterile products, may require other considerations and a detailed approach that is beyond the scope of this document.

2.2 There are many factors affecting the different types of validation and it is, therefore, not intended to define and address all aspects related to one particular type of validation here.

2.3 The general text in the main part of these guidelines may be applicable to qualification and validation of premises, equipment, utilities, systems, methods, processes and procedures.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

calibration. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

change control/change management. 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 the system is maintained in a validated state.

cleaning validation. Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

computerized system validation. Confirmation by examination and provision of objective documented evidence that specifications for computerized systems conform to user needs and intended uses, and that all requirements can be consistently fulfilled.

concurrent validation. Validation carried out during routine production of products intended for sale.

design qualification. Documented verification that the proposed design of facilities, systems and equipment is suitable for the intended purpose.

installation qualification. Documented verification that the installations (such as machines equipment and instruments, computer system components, measuring devices, utilities and manufacturing) used in a processor system are appropriately selected and correctly installed, in accordance with established specifications.

operational qualification. Documented verification that the system or subsystem operates as intended over all anticipated operating ranges.

performance qualification. Documented verification that the equipment or system performs consistently and reproducibly within defined specifications and parameters in its normal operating environment (i.e. in the production environment).

process validation. The collection and evaluation of data, throughout the product life-cycle, which provides documented scientific evidence that a process is capable of consistently delivering quality products.

prospective validation. Validation carried out during the development stage, on the basis of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience, to determine whether they may lead to critical situations.

qualification. Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications when properly installed, and/or work correctly and lead to the expected results.

revalidation. Repeated validation of a previously validated system (or a part thereof), to ensure continued compliance with established requirements.

standard operating procedure. An authorized written procedure giving instructions for performing operations that are not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, 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-batch production documentation.

validation. Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

validation master plan. A high-level document that summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's qualification and validation work programme and defines details of and timelines for the work to be performed, including a statement of the responsibilities of those implementing the plan.

validation protocol. A document describing the activities to be performed during validation, including the acceptance criteria.

validation report. A document in which the records, results and evaluation of validation are documented and summarized. It should also contain a conclusion of the outcome of the validation.

verification. The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with established requirements and specifications.

worst case. A condition or set of conditions encompassing the upper and lower processing limits for operating parameters and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily include product or process failure.

4. Relationship between validation and qualification

4.1 In general, qualification and validation follow similar underlying principles. The term "qualification" is normally used, for example, for equipment and utilities, and "validation", for example, for systems, methods and processes.

4.2 Qualification normally precedes validation.

5. Validation

Approaches to qualification and validation

5.1 Manufacturers should organize and plan qualification and validation in a manner that will ensure product quality, safety and efficacy throughout its life-cycle.

5.2 Statistical evaluation should be applied, where appropriate, and provide scientific evidence that, for example, the process, system or other related aspect is appropriately qualified or validated.

5.3 Qualification and validation should be done in accordance with predetermined protocols, and the results appropriately documented, in reports.

5.4 There should be an appropriate and effective quality management system supporting the organization, planning, execution and management of qualification and validation.

5.5 Senior management should ensure that there are sufficient resources to perform validation in a timely manner. Management and persons responsible for quality assurance should be actively involved in the process and authorization of protocols and reports.

5.6 Personnel with appropriate education and experience should be responsible for qualification and validation.

5.7 There should be a specific programme or schedule to support planning and execution of qualification and validation activities.

5.8 Qualification and validation should be performed in a structured way, according to the documented protocols and procedures.

5.9 Qualification and validation (as appropriate), should be performed:

- for new premises, equipment and utilities;
- for new systems, methods, processes and procedures;
- when changes are made, depending on the outcome of risk assessment;
- where necessary or indicated, based on the outcome of periodic review (and may include requalification and revalidation).

5.10 The scope and extent of qualification and validation should be based on knowledge, experience and the outcome of principles of quality risk management, as described in the *WHO guidelines on quality risk management* (*8*).

5.11 Where necessary, worst-case situations or specific challenge tests should be considered for inclusion in the qualification and validation.

6. Documentation

6.1 Documents associated with qualification and validation may include:

- validation master plan;
- standard operating procedures (SOPs);
- specifications;
- protocols and reports;
- risk assessment outcomes;
- process flowcharts;
- operator manuals;
- training records;
- calibration procedures and records;
- sampling plans;
- testing plans and methods;
- statistical methods and results;
- history of qualification and validation;
- plan for ensuring maintaining a validated state including review of validation status.

7. Validation master plan

7.1 A manufacturer should have a validation master plan that reflects the key elements of validation. It should be concise and clear and at least contain reference to/have a short description of the following:

- title page and authorization (approval signatures and dates);
- table of contents;
- abbreviations and glossary;
- validation policy;
- philosophy, intention and approach to validation;
- roles and responsibilities of relevant personnel;
- resources to ensure that qualification and validation are done;
- outsourced services (selection, qualification, management through the life-cycle);
- scope of qualification and validation;
- documentation required in qualification and validation, such as procedures, certificates, protocols and reports;
- premises qualification, such as room verification where appropriate;
- qualification of utilities;
- equipment and instrument qualification;
- process validation;
- cleaning validation;
- personnel qualification (such as analyst qualification);
- analytical method validation;
- computerized system validation;
- establishment of acceptance criteria;
- life-cycle management, including retirement policy;
- requalification and revalidation;
- relationship with other quality management elements;
- validation matrix (such as a table indicating the history and status of qualification and validation on-site);
- retention of qualification and validation documentation;
- deviation management;
- change control;
- risk management principles;

- training;
- references.

7.2 The validation master plan should be reviewed at regular intervals and kept up to date, according to current GMP.

8. Qualification and validation protocols

8.1 There should be qualification and validation protocols describing the qualification and validation to be performed.

8.2 As a minimum, the protocols should be appropriate for the qualification or validation to be executed, and may include the following significant background information:

- a unique document number and version number;
- the objective and scope;
- the site;
- the responsible personnel;
- reference to applicable standard operating procedures;
- equipment or instruments to be used;
- reference to standards, as appropriate;
- the stage of validation or qualification;
- the processes and/or parameters;
- sampling, testing and monitoring requirements;
- stress testing, where appropriate;
- calibration requirements;
- predetermined acceptance criteria for drawing conclusions;
- change control, deviations;
- attachments and reference to attachments, including source data (where relevant);
- archiving and retention.

8.3 There should be a description of the procedure for review, evaluation and interpretation of results, including the application of statistical methods, where appropriate.

8.4 The protocol should be approved by responsible persons, including the quality unit, prior to use. Any changes to a protocol should be approved prior to implementation of the change.

8.5 The protocol should be executed by trained personnel. Records of the training and assessment should be retained.

9. Qualification and validation reports

9.1 There should be written reports on the qualification and validation performed.

9.2 Reports should reflect the protocols and procedures followed and include at least the title and objective of the study; reference to the protocol; reference to the appropriate risk assessment; details of materials, equipment, programmes and cycles used; procedures and test methods; data; changes and deviations; out-of-specification and non-conformance results, with appropriate traceability; and a conclusion.

9.3 Results should be recorded and be in compliance with good data and record management practices (*7*).

9.4 Results should be reviewed, analysed and compared against the predetermined acceptance criteria, interpreted and statistically analysed, where appropriate.

9.5 Results should meet the acceptance criteria. Out-of-specification and out-of-limit results should be documented and investigated according to appropriate procedures. If these are accepted, this should be justified. Where necessary, further studies should be considered.

9.6 The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful, and should make recommendations for future monitoring and setting of alert and action limits, where applicable.

9.7 The departments responsible for the qualification and validation work should approve the completed report.

9.8 When appropriate, the quality assurance department should approve the report. The criteria for approval should be in accordance with the company's quality assurance system.

10. Qualification

10.1 There are different approaches in qualification. The manufacturer should select an appropriate approach for the conduct thereof (see Appendix 6).

10.2 All relevant SOPs for operation, maintenance and calibration should be prepared during qualification.

10.3 Training should be provided to operators, and training records should be maintained.

10.4 Normally, qualification should be completed before process validation is performed.

10.5 The process of qualification should be a logical, systematic process and follow a logical flow from the premises, followed by utilities, equipment, to procedures and processes.

10.6 Stages of qualification should normally start with the preparation of user requirement specifications (URS). Depending on the function and operation of the utility, equipment or system, this is followed by, as appropriate, different stages in qualification such as design qualification (DQ), a factory acceptance test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

10.7 One stage of qualification should be successfully completed before the next stage is initiated. For example, OQ normally follows IQ but, depending on the complexity of the equipment, it may be performed as a combined installation/operation qualification (IOQ). Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

10.8 In some cases, only IQ and OQ may be required, as the correct operation of the equipment, utility or system could be considered to be a sufficient indicator of its performance.

10.9 Major equipment and critical utilities and systems, however, may require URS, DQ, IQ, OQ and PQ.

10.10 Computerized systems, including equipment with software component(s), should be appropriately qualified and validated (see Appendices 5 and 6).

User requirement specifications

10.11 Manufacturers should prepare a document that describes the requirements for the item (such as system(s) for a utility; or equipment) to be sourced.

The requirements may include specifications and should ensure that possible GMP risks are addressed; include technical requirements; and reference associated documentation.

10.12 The URS should be used when selecting the required item from an approved supplier, and to verify suitability throughout the subsequent stages of qualification.

Design qualification

10.13 DQ should provide documented evidence that the design specifications were met and are in accordance with the URS.

Factory acceptance test and site acceptance test

10.14 Where appropriate, FAT and SAT should be performed to verify the suitability of the system at site, prior to the subsequent stages of qualification. This should be appropriately documented.

Installation qualification

10.15 IQ should provide documented evidence that the installation was complete and satisfactory, including supporting utilities, where appropriate.

10.16 The design specifications, including purchase specifications, drawings, manuals, lists of spare parts and vendor details, should be verified during IQ, as should the configuration specifications for the intended operational environment.

10.17 Components installed should be verified, and documented evidence should be provided that components meet specifications, are traceable and are of the appropriate construction material.

10.18 Applicable control and measuring devices, identified through impact or risk assessment, should be calibrated.

Operational qualification

10.19 OQ should provide documented evidence that utilities, systems or equipment operate in accordance with operational specifications.

10.20 Tests should be designed to demonstrate satisfactory operation over the normal operating range, as well as at the limits of its operating conditions. Worst-case conditions may be included in the testing.

10.21 Operation controls, alarms, switches, displays and other operational components should be tested.

10.22 Measurements made in accordance with a statistical approach should be fully described.

Performance qualification

10.23 Normally, PQ should be conducted prior to release of the utilities, systems or equipment. PQ should be performed under conditions simulating the intended use, to provide documented evidence that these can consistently perform in accordance with the specifications under routine use.

Requalification

10.24 Utilities, systems and equipment should be maintained in a qualified state. Any changes made to these should be managed through the change-control procedure. The extent of qualification or requalification as a result of such a change should be determined based on principles of risk management.

10.25 Requalification should be done based on the identified need and risk management principles. Factors such as the frequency of use, breakdowns, results of operation, criticality, preventive maintenance, repairs, calibration, and verification may be considered.

10.26 Requalification should also be considered after cumulative/multiple changes.

10.27 The scope and extent of requalification should be determined when components or parts are replaced.

10.28 Where a system or utility or equipment has not been used for an extended period of time, requalification may have to be considered.

10.29 Where appropriate, periodic requalification may be performed.

11. Revalidation

11.1 Systems should be in place to ensure that procedures, processes and methods remain in a validated state, for example, through periodic review or verification (e.g. in cleaning validation and analytical method validation).

11.2 Revalidation should be done based on the identified need and principles of risk management.

11.3 Any changes made to, for example, procedures, processes and methods, should be managed through the change-control procedure. The extent of validation or revalidation as a result of such a change should be determined based on principles of risk management.

11.4 Where appropriate, periodic revalidation may be performed.

12. Process validation

For recommendations on process validation, see reference (*3*).

13. Change management

13.1 Changes should be controlled in accordance with the appropriate quality management system.

13.2 When a change is initiated, consideration should be given to previous changes and the impact of the cumulative effect of the changes. The scope and extent of qualification and validation should be determined based on risk management principles.

14. Deviation management

14.1 Any deviation during qualification and validation should be appropriately managed (e.g. investigated, evaluated, the impact assessed, and documented) through an appropriate quality management system.

14.2 Corrective actions should be considered.

15. Calibration and verification

15.1 Calibration and verification of equipment, instruments and other devices, as applicable, should be initiated during installation qualification, to ensure that the system operates according to the described specifications and because the calibration status could have been affected during transport and installation.

15.2 Thereafter, it should be performed at regular intervals in accordance with a calibration programme and SOPs.

15.3 Personnel who carry out calibration and preventive maintenance should have appropriate qualification and training.

15.4 A calibration programme should be available and should provide information such as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.

15.5 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration. A valid certificate of calibration should be maintained, which is dated and includes reference to and traceability to, for example, standards used, acceptance limits, uncertainty where applicable, range, calibration due date.

15.6 Calibrated equipment, instruments and other devices should be labelled, coded or otherwise identified, to indicate the status of calibration and the date on which recalibration is due.

15.7 When the equipment, instruments and other devices have not been used for a certain period of time, their function and calibration status should be verified and shown to be satisfactory before use.

15.8 Equipment, instruments and other devices should be calibrated before or on the due date for calibration, to ensure that they are used in a calibrated state.

15.9 Where instruments and devices are identified as critical or non-critical, or impacting and non-impacting for the purpose of calibration, documented evidence of the decision-making process should be available. This should include impact and/or risk assessment.

References

1. 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; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf, accessed 9 February 2019).
2. Appendix 7: Non-sterile process 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; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf, accessed 9 February 2019).
3. Guidelines on good manufacturing practices: validation. Appendix 7: Non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3-TRS992.pdf, accessed 8 February 2019).

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6. World Health Organization. Quality assurance of pharmaceuticals. WHO guidelines, good practices, related regulatory guidance and GXP training materials. CD-ROM, update 2018 (http://digicollection.org/whoqapharm/, accessed 8 February 2019).
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8. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf, accessed 8 February 2019).

Appendix 1

Validation of heating, ventilation and air-conditioning systems

For details on the validation of heating, ventilation and air-conditioning systems, please see:

- Appendix 1: Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 8 (WHO Technical Report Series, No. 1010; http://apps.who.int/medicinedocs/documents/s23455en/s23455en.pdf).

Appendix 2

Validation of water systems for pharmaceutical use

The text of this appendix was previously published as:

- Appendix 2: Validation of water systems for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://www.who.int/medicines/areas/quality_safety/quality_assurance/SupplementaryGMPValidationTRS937Annex4.pdf?ua=1).

For details on the validation of water systems for pharmaceutical use, please see:

- WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; Geneva, World Health Organization 2012 (WHO Technical Report Series, No. 970; http://apps.who.int/medicinedocs/documents/s19464en/s19464en.pdf).

Appendix 3

Cleaning validation

The text of this appendix was previously published as:

- Appendix 3: Cleaning 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; https://www.who.int/medicines/areas/quality_safety/quality_assurance/SupplementaryGMPValidationTRS937Annex4.pdf?ua=1).

1. Principle

1.1 The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharmaceutical starting materials and products.

1.2 Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients [APIs] and excipient residues), residues of cleaning agents, airborne materials, such as dust and particulate matter, lubricants and ancillary material, such as disinfectants, and decomposition residues from:

- product residue breakdown occasioned by, for example, the use of strong acids and alkalis during the cleaning process;
- breakdown products of the detergents, acids and alkalis that may be used as part of the cleaning process.

1.3 Adequate cleaning procedures play an important role in preventing contamination and cross-contamination. Validation of cleaning methods provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its intended use.

1.4 The objective of cleaning validation is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination.

1.5 Cleaning validation is not necessarily required for non-critical cleaning such as that which takes place between batches of the same product (or different lots of the same intermediate in a bulk process), or of floors, walls, the outside of vessels, and following some intermediate steps.

1.6 Cleaning validation should be considered important in multiproduct facilities and should be performed, among others, for equipment, sanitization procedures and garment laundering.

2. Scope

2.1 These guidelines describe the general aspects of cleaning validation, excluding specialized cleaning or inactivation that may be required, for example, for removal of viral or mycoplasmal contaminants in the biological manufacturing industry.

2.2 Normally, cleaning validation would be applicable for critical cleaning such as cleaning between manufacturing of one product and another, of surfaces that come into contact with products, drug products and APIs.

3. General

3.1 There should be written standard operating procedures (SOPs) detailing the cleaning process for equipment and apparatus. The cleaning procedures should be validated.

3.2 The manufacturer should have a cleaning policy and an appropriate procedure for cleaning validation, covering:

- surfaces that come into contact with the product;
- cleaning after product changeover (when one pharmaceutical formulation is being changed for another, completely different, formulation);
- between batches in campaigns (when the same formula is being manufactured over a period of time, and on different days);
- bracketing products for cleaning validation. (This often arises where products contain substances with similar properties [such as solubility] or the same substance in different strengths. An acceptable strategy is to first manufacture the more dilute form [not necessarily the lowest dose] and then the most concentrated form. There are sometimes "families" of products which differ slightly as to actives or excipients.);
- periodic evaluation and revalidation of the number of batches manufactured between cleaning validations.

3.3. At least three consecutive applications of the cleaning procedure should be performed and shown to be successful, to prove that the method is validated.

4. Cleaning validation protocols and reports

Cleaning validation protocols

4.1 Cleaning validation should be described in cleaning validation protocols, which should be formally approved, for example, by the quality control or quality assurance unit.

4.2 In preparing the cleaning validation protocol, the following should be considered:

- disassembly of the system;
- precleaning;
- the cleaning agent, concentration, solution volume, water quality;
- the time and temperature;
- the flow rate, pressure and rinsing;
- the complexity and design of the equipment;
- training of operators;
- the size of the system.

4.3 The cleaning validation protocol should include:

- the objectives of the validation process;
- the people responsible for performing and approving the validation study;
- the description of the equipment to be used, including a list of the equipment, make, model, serial number or other unique code;
- the interval between the end of production and the commencement of the cleaning procedure (the interval may be part of the validation challenge study itself) – the maximum period that equipment may be left dirty before being cleaned, as well as the establishment of the time that should elapse after cleaning and before use;
- the levels of microorganisms (bioburden);
- the cleaning procedures (documented in an existing SOP, including definition of any automated process) to be used for each product, each manufacturing system or each piece of equipment;
- all the equipment used for routine monitoring, for example, conductivity meters, pH meters and total organic carbon analysers;
- the number of cleaning cycles to be performed consecutively;
- the sampling procedures to be used (direct sampling, rinse sampling, in-process monitoring and sampling locations) and the rationale for their use;
- the data on recovery studies (efficiency of the recovery of the sampling technique should be established);
- the analytical methods (specificity and sensitivity). including the limit of detection and the limit of quantification;
- the acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency;

- Documentation of the choice of cleaning agent and approval by the quality unit, which should be scientifically justified on the basis of, for example:
  - the solubility of the materials to be removed;
  - the design and construction of the equipment and surface materials to be cleaned;
  - the safety of the cleaning agent;
  - the ease of removal and detection;
  - the product attributes;
  - the minimum temperature and volume of cleaning agent and rinse solution;
  - the manufacturer's recommendations;
- revalidation requirements.

4.4 Cleaning procedures for products and processes that are very similar do not need to be individually validated. A validation study of the "worst case" may be considered acceptable. There should be a justified validation programme for this approach, referred to as "bracketing", addressing critical issues relating to the selected product, equipment or process.

4.5 Where "bracketing" of products is done, consideration should be given to the type of products and equipment.

4.6 Bracketing by product should be done only when the products concerned are similar in nature or property and will be processed using the same equipment. Identical cleaning procedures should then be used for these products.

4.7 When a representative product is chosen, this should be the one that is most difficult to clean.

4.8 Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300 L, 500 L and 1000 L tanks). An alternative approach may be to validate the smallest and the largest sizes separately.

Cleaning validation reports

4.9 The relevant cleaning records (signed by the operator, checked by production and reviewed by quality assurance) and source data (original results) should be kept. The results of the cleaning validation should be presented in cleaning validation reports stating the outcome and conclusion.

5. Personnel

5.1 Personnel or operators who perform cleaning routinely should be trained and effectively supervised.

6. Equipment

6.1 Normally, only procedures for the cleaning of surfaces of the equipment that come into contact with the product need to be validated. Consideration should be given to "non-contact" parts of the equipment into which product or any process material may migrate. Critical areas should be identified (independently from the method of cleaning), particularly in large systems employing semi-automatic or fully automatic clean-in-place systems.

6.2 Dedicated equipment should be used for products that are difficult to clean, equipment that is difficult to clean, or products with a high safety risk where it is not possible to achieve the required cleaning acceptance limits using a validated cleaning procedure.

6.3 Ideally, there should be one process for cleaning a piece of equipment or system. This will depend on the products being manufactured, whether the cleaning occurs between batches of the same product (as in a large campaign), or whether the cleaning occurs between batches of different products.

6.4 The design of equipment may influence the effectiveness of the cleaning process. Consideration should therefore be given to the design of the equipment when preparing the cleaning validation protocol, for example, V-blenders, transfer pumps or filling lines.

7. Detergents

7.1 Detergents should facilitate the cleaning process and be easily removable. Detergents that have persistent residues, such as cationic detergents, which adhere very strongly to glass and are difficult to remove, should be avoided where possible.

7.2 The composition of the detergent should be known to the manufacturer and its removal during rinsing demonstrated.

7.3 Acceptable limits for detergent residues after cleaning should be defined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.

7.4 Detergents should be released by quality control and, where possible, should meet local food standards or regulations.

8. Microbiology

8.1 The need to include measures to prevent microbial growth and remove contamination where it has occurred should be considered.

8.2 There should be documented evidence to indicate that routine cleaning and storage of equipment does not allow microbial proliferation.

8.3 The period and conditions for storage of unclean equipment before cleaning, and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures.

8.4 Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed to remain in equipment after cleaning.

8.5 Control of the bioburden through adequate cleaning and appropriate storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility, and the control of pyrogens in sterile processing. Equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

9. Sampling

General

9.1 Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, suspensions and bulk drug, or where the drying of residues will directly affect the efficiency of a cleaning procedure.

9.2 Two methods of sampling are considered to be acceptable. These are direct surface sampling and rinse samples. A combination of the two methods is generally the most desirable.

9.3 The practice of resampling should not be used before or during cleaning and operations and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated, because these retests actually document the presence of unacceptable residue and contaminants resulting from an ineffective cleaning process.

Direct surface sampling (direct method)

Note: This method of sampling is the most commonly used and involves taking an inert material (e.g. cotton wool) on the end of a probe (referred to as a "swab") and rubbing it methodically across a surface. The type of sampling material used and its potential impact on the test data is important, as the sampling material may interfere with the test (e.g. the adhesive used in swabs has been found to interfere with the analysis of samples).

9.4 Factors that should be considered include the supplier of the swab, area swabbed, number of swabs used, whether they are wet or dry swabs, swab handling and swabbing technique.

9.5 The location from which the sample is taken should take into consideration the composition of the equipment (e.g. glass or steel) and the location (e.g. blades, tank walls or fittings). Worst-case locations should be considered. The protocol should identify the sampling locations.

9.6 Critical areas, that is, those that are hardest to clean, should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place systems.

9.7 The sampling medium and solvent used should be appropriate to the task.

Rinse samples (indirect method)

Note: This method allows sampling of a large surface, of areas that are inaccessible or that cannot be routinely disassembled, and provides an overall picture. Rinse samples may give sufficient evidence of adequate cleaning where accessibility of equipment parts can preclude direct surface sampling, and may be useful for checking for residues of cleaning agents, for example, detergents.

9.8 Rinse samples should be used in combination with other sampling methods. such as surface sampling.

9.9. There should be evidence that samples are accurately recovered. For example, a recovery of >80% is considered good, >50% reasonable and <50% questionable.

Batch placebo method

Note: This method relies on the manufacture of a placebo batch, which is then checked for carry-over of the previous product. It is an expensive and laborious process. It is difficult to provide assurance that the contaminants will be

dislodged from the equipment surface uniformly. Additionally, if the particles of the contaminant or residue are large enough, they may not be uniformly dispersed in the placebo batch.

9.10 The batch placebo method should be used in conjunction with rinse and/or surface sampling method(s).

9.11 Samples should be taken throughout the process of manufacture. Traces of the preceding products should be sought in these samples. (Note that the sensitivity of the assay may be greatly reduced by dilution of the contaminant.)

10. Analytical methods

10.1 The analytical methods should be validated before the cleaning validation is performed.

10.2 The methods chosen should detect residuals or contaminants specific for the substance(s) being assayed, at an appropriate level of cleanliness (sensitivity).

10.3 Validation of the analytical method should include as appropriate:

- precision, linearity and selectivity (the latter if specific analytes are targeted);
- limit of detection;
- limit of quantitation;
- recovery, by spiking with the analyte;
- reproducibility.

10.4 The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants.

10.5 Suitable methods that are sensitive and specific should be used where possible and may include chromatographic methods (e.g. high pressure liquid chromatography; gas chromatography; and high pressure thin-layer chromatography). Other methods may include (alone or in combination) measurement of total organic carbon, pH, or conductivity; ultraviolet spectroscopy; and enzyme-linked immunosorbent assay.

11. Establishing acceptable limits

Note: uniform distribution of contaminants is not guaranteed.

11.1 The acceptance criteria established for contaminant levels in the sample should be practical, achievable and verifiable. The rationale for the residue limits established should be logical, and based on the knowledge of the materials involved.

11.2 Each situation should be assessed individually. The manner in which limits are established should be carefully considered. In establishing residual limits, it may not be adequate to focus only on the principal reactant, because other chemical variations may be more difficult to remove.

11.3 Where necessary, screening using thin-layer chromatography should be performed in addition to chemical analyses.

11.4 There should be no residue from the previous product, from reaction by-products and degradants, or from the cleaning process itself (e.g. detergents or solvents).

11.5 The limit-setting approach can:

- be product-specific;
- group products into families and choose a worst-case product;
- group products into groups according to risk, for example, very soluble products, products with similar potency, highly toxic, or difficult-to-detect products;
- use different safety factors for different dosage forms, based on physiological response (this method is essential for potent materials).

11.6 Limits may be expressed as a concentration in a subsequent product (parts per million – ppm), limit per surface area (µg/cm2), or in rinse water as ppm.

11.7 The sensitivity of the analytical methods should be defined, to enable reasonable limits to be set.

11.8 The rationale for selecting limits for carry-over of product residues should meet defined criteria.

11.9 The three most commonly used criteria are:

- visually clean: no residue should be visible on equipment after cleaning. Spiking studies should determine the concentration at

which most active ingredients are visible. This criterion may not be suitable for high-potency, low-dosage drugs;

- no more than 10 ppm of one product will appear in another product (basis for heavy metals in starting materials);
- no more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.

11.10 The most stringent of three options should be used.

11.11 Certain allergenic ingredients (e.g. penicillins and cephalosporins) and highly potent material (e.g. anovulent steroids, potent steroids and cytotoxics) should be undetectable by the best available analytical methods. (In practice, this may mean that dedicated manufacturing facilities should be used for the manufacture and processing of such products.)

Appendix 4

Analytical procedure validation

Background

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 4: Analytical method validation. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf).

1. Principle

1.1 This appendix presents some information on the principles and characteristics that should be considered during validation and life-cycle management of analytical procedures. Approaches other than those specified in this appendix may be followed and may be acceptable. Manufacturers should choose the validation protocol and procedures most suitable for testing of their product. Owing to their complex nature, analytical procedures for biological and biotechnological products may, in some cases, be approached differently than is indicated in this document.

1.2 Validation is the documented evidence that the analytical procedure is suitable for its intended purpose.

1.3 Analytical procedures, whether or not they indicate stability, should be validated.

1.4 Analytical procedures should be validated before being used for quality control purposes.

1.5 The recommendations as provided for in good practices (GXP) for pharmaceutical quality control laboratories (*1*), guidance on good data and record management practices (*2*) and guidelines for transfer of technology (*3*) should be followed, where applicable, when analytical procedure validation is organized and planned.

2. General

2.1 There should be specifications (a list of tests, references to analytical procedures and appropriate acceptance criteria) for both materials and products. The tests to be performed should be described in the documentation.

2.2 Acceptance criteria and test methods described in pharmacopoeias ("pharmacopoeial methods"), or suitably developed acceptance criteria or test methods ("non-pharmacopoeial methods"), as approved by the national regulatory authority (NRA), may be used.

2.3 Well-characterized reference standards, with documented suitability for the intended use, should be used in validation studies as well as in analysis.

2.4 The results of analytical procedures should be reliable, that is, attributable, legible, contemporaneous, original, accurate and reproducible.

2.5 The procedure should be followed, to continually assure that it meets the predefined criteria over its life-cycle.

2.6 Trend analysis and risk assessment should be considered at intervals, to ensure that the procedure is appropriate for its intended application.

2.7 Changes to procedures should be managed in accordance with the authorized change-control procedure. When analytical procedures are to be used by another laboratory and method transfer is not possible, the variability of reference standards and other factors, such as changes in the process for synthesis of the drug substance, changes in the composition of the finished product, changes in the analytical procedure, or changes to major pieces of equipment or instruments, should be considered. These should be understood, controlled and, where possible, reduced. Verification or revalidation should be considered, where appropriate.

2.8 The need and scope of verification or degree of revalidation depend on the nature of the change(s) and the outcome of risk assessment.

2.9 There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses ("analyst proficiency") and that the equipment and instruments involved are appropriately qualified.

2.10 The data obtained during procedure validation and verification (including their associated metadata) should be considered covered by GXP requirements and are expected to follow the principles of GXP for data and record management (*2*).

2.11 When computerized systems are used to obtain and process data relating to procedure validation and verification, they should comply with the principles enunciated in *Appendix 5. Validation of computerized systems*.

2.12 Adequate attention should be paid to sample preparation. The description of this step should be as detailed as possible, especially if it can have a significant impact on test results (e.g. particular attention should be paid to details such as sonication time, sonication bath temperature and mixing, conditions of shaking, type of a shaker, and samples where demixing is known to occur). As sample preparation is an integral part of the analytical procedures, this step should be incorporated in the validation experiments as appropriate.

3. Pharmacopoeial methods

3.1 When pharmacopoeial methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (verification – see Section 6).

3.2 Pharmacopoeial methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the product under consideration (no placebo interference).

4. Non-pharmacopoeial methods

4.1 Non-pharmacopoeial methods should be appropriately validated.

5. Procedure validation

5.1 Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.

5.2 Justification should be provided when non-pharmacopoeial methods are used, if pharmacopoeial methods are available.

5.3 Test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, sample preparation, reference standards, the formulae for the calculation of results and system suitability tests.

6. Procedure verification

6.1 Procedure verification consists of partial validation. It should be performed for already validated analytical procedures under the following circumstances:

- when an already validated procedure is used on a product for the first time (e.g. in case of a change in active pharmaceutical ingredient [API] supplier, change in the method of synthesis or after reformulation of a drug product);

- when an already validated procedure is used for the first time in a laboratory that is different from the one that validated the procedure (in some cases, method transfer may be preferable).

6.2 Procedure verification may include only the validation characteristics of relevance to the particular change. The selection of characteristics for verification depends on the procedure and its intended use and should be justified. For instance, in the case of a change in API supplier, the only expected difference would be in the impurity profile or solubility of the API, and therefore, for a procedure for related substances, there should be an appropriate verification that the procedure is able to detect and quantitate all potential impurities, even the late-eluting ones. Specificity should be among the tests considered (see Sections 9 for more detail).

6.3 Procedure verification is suitable in lieu of validation for pharmacopoeial methods.

7. Procedure revalidation

7.1 Procedures should be maintained in a validated state over the life-cycle of the procedure (see point 2.5). Whenever there are changes made to the analytical procedure, the impact assessment should be conducted and revalidation of the procedure should be considered. For example for a high-performance liquid chromatography (HPLC) method, changes requiring revalidation may include (please refer to *The International Pharmacopoeia* (*4*) and other pharmacopoeias for the acceptance limits beyond which revalidation must be performed):

- changes to the mobile phase;
- changes to the column;
- changes to the temperature of the column;
- changes to the concentration/composition of the samples and standards;
- changes to the detector (change in detector type, for example, if going from ultraviolet-visible detection to fluorimetry, or wavelength of detection).

7.2 In the case of repeated system suitability failures or when obtaining doubtful results, an investigation of the root cause should be performed. In the case that the procedure is identified as being the root cause, the appropriate changes should be made and the procedure revalidated.

7.3 Periodic revalidation of analytical procedures should be considered and the interval should be scientifically justifiable.

7.4 It is acceptable for revalidation to include only the validation characteristics of relevance to the particular change and procedure.

8. Method transfer

8.1 During method transfer, documented evidence should be established to prove that a method has equivalent performance when used in a laboratory that is different from the one where it has been validated.

8.2 Generally, it should be performed by comparing a set of results obtained by one laboratory to those obtained by another laboratory to which the method is being transferred.

8.3 The two sets of results should be compared and the differences between them should be within an acceptable range, which is predefined in the transfer protocol.

8.4 Method transfer should be performed before the testing of samples, with a view to obtaining critical data for a dossier, such as process validation or stability studies, or before being applied for routine use.

8.5 A predefined protocol should be followed, which includes at least: a title, objective, scope, responsibilities of the sending unit and the receiving unit; a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any); procedure for the handling of deviations; references; and details of reference samples (starting materials, intermediates and finished products). The protocol should be authorized and dated.

8.6 In the case of independent testing by a separate entity, such as a national quality control testing laboratory that is testing samples on its market, method transfer is not always possible. It is not considered an obligation but may be considered as an optional step when encountering difficulties in applying any particular method. See *WHO guidelines on transfer of technology in pharmaceutical technology* (*3*) for further reference.

9. Characteristics of analytical procedures

9.1 Characteristics that should be considered during validation of analytical procedures include:

- accuracy;
- precision;
- robustness;
- linearity;
- range;
- specificity;
- detection limit;
- quantitation limit.

This list should be considered typical but occasional exceptions should be dealt with on a case-by-case basis.

9.1.1 *Accuracy* is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure, for example, three concentrations/three replicates each.

Note: It is acceptable to use a "spiked" placebo where a known quantity or concentration of a reference standard is used.

9.1.2 *Precision* is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping), and is usually expressed as the standard deviation or relative standard deviation.

Repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure, for example, three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

Intermediate precision expresses within-laboratory variations (usually on different days, with different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.

Reproducibility expresses precision between laboratories.

9.1.3 *Robustness* is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The

results from separate samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase and should show the reliability of an analysis when deliberate variations are made in method parameters.

Factors that can have an effect on robustness when performing chromatographic analysis include:

- stability of the test and standard samples and solutions;
- reagents (e.g. different suppliers);
- different columns (e.g. different lots and/or suppliers);
- variation of extraction time;
- variations of pH;
- variations in mobile-phase composition;
- temperature;
- flow rate.

The variation of extraction time and stability of analytical solutions are of particular importance.

9.1.4 *Linearity* indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used. If linearity is not attainable, a nonlinear model may be used.

9.1.5 *Range* is an expression of the lowest and highest levels of analyte for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. The specified range is normally derived from linearity studies.

9.1.6 *Specificity* (*selectivity*) is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and the assay. The procedures used to demonstrate specificity depend on the intended objective of the analytical procedure.

9.1.7 *Detection limit* (*limit of detection*) is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion.

Approaches may include instrumental or non-instrumental procedures and could include those based on:

- visual evaluation;
- signal-to-noise ratio;
- standard deviation of the response and the slope;
- standard deviation of the blank;
- calibration curve.

9.1.8 *Quantitation limit* (*limit of quantitation*) is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:

- visual evaluation;
- signal-to-noise ratio;
- standard deviation of the response and the slope;
- standard deviation of the blank;
- calibration curve.

9.2 *Characteristics* (*including tests*) that should be considered when using different types of analytical procedures are summarized in Table A3.4.1. More details can be found in the guidelines listed in the Further reading section at the end of this appendix.

Table 3.4.1
Characteristics to consider during analytical validation

Type of analytical procedure		Testing for impurities		
Characteristics	**Identification**	**Quantitative tests**	**Limit tests**	**Assay[a]**
Accuracy	—	+	—	+
Precision				
Repeatability	—	+	—	+
Intermediate precision[b]	—	+	—	+
Specificity	+	+	+	+
Detection limit	—	—[c]	+	—

Table 3.4.1 *continued*

Type of analytical procedure		Testing for impurities		
Characteristics	**Identification**	**Quantitative tests**	**Limit tests**	**Assay[a]**
Quantitation limit	—	+	—	—
Linearity	—	+	—	+
Range	—	+	—	+

— Characteristic is not normally evaluated; + characteristic should normally be evaluated.

[a] dissolution (measurement only) or content/potency.

[b] In cases where a reproducibility study has been performed, intermediate precision is not needed.

[c] May be needed in some cases.

9.3 Statistical analysis used to evaluate validation characteristics against predetermined acceptance criteria should be appropriate for the intended evaluation. Statistical analysis should be performed using appropriately validated software. Alternatively, if validated software is not used, the calculations must be verified to be correct. An appropriate number of samples to provide adequate statistical power and range should be considered.

10. System suitability testing

Note: System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analysed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure being evaluated, for instance, a resolution test for an HPLC procedure.

10.1 System suitability testing should be done as appropriate and defined in the test procedure.

10.2 System suitability runs should include only reference standards or established standards of known concentration, to provide an appropriate comparator for the potential variability of the instrument. The sample material or product under test should not be used as a standard to evaluate the suitability of the system (see *General guidelines for the establishment, maintenance and distribution of chemical reference substances* (*5*)).

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Further reading

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Appendix 5

Validation of computerized systems

Background

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 5: Validation of computerized systems. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf).

1. Introduction and scope

1.1 Computerized systems should be validated in accordance with the principles of quality risk management and the level of validation should be commensurate with the identified risks, complexity and intended use. This guide applies to systems used in good manufacturing practices (GMP) (*1*) but may be extended to systems used in all good practices (GXP) activities, as appropriate.

1.2 The purpose of validation is to confirm that the specifications of a computerized system conform to the user's needs and are fit for intended use, by examination and provision of documented and objective evidence that the particular requirements can be consistently fulfilled. Validation should establish confidence in the accuracy, reliability and consistency in the performance of the system, and should also ensure that all necessary technical and procedural controls are implemented, confirming compliance with good documentation practices for electronic data generated by the system (*1*).

1.3 System elements that need to be considered in validation of a computerized system include computer hardware and software, and related equipment, IT infrastructure and operating system environment, and documentation of procedures and systems, as appropriate, including user manuals. Persons should be appropriately trained and qualified, including but not limited to, developers, end-users, system application administrators, network engineers, database administrators and data managers. Computerized system validation activities should address both system functionality and configuration, as well as any custom-developed elements.

1.4 Computerized systems should be maintained throughout the system life-cycle, in a validated state, with risk-based controls for the operational phase, which may include, but are not limited to, system planning; preparation and verification of standard operating procedures (SOPs) and training programmes; system operation and maintenance, including handling of software and hardware updates; monitoring and review; change management; and incident reporting, followed by system retirement.

1.5 Depending on the types of systems or typical applications, such as process control systems (distributed control system [DCS], programmable logic controller [PLC], supervisory control and data acquisition [SCADA]); laboratory information management systems (LIMS); laboratory instrument control systems; and business systems (enterprise resource planning [ERP], manufacturing resource planning [MRP II]) used by the manufacturer.

Documentation covering, but not limited to, the following information and supporting process should be accessible on-site for review:

- purpose and scope;
- roles and responsibilities;
- validation approach;
- risk management approach;
- approved system requirement/specifications;
- system acceptance criteria;
- supplier selection and assessment;
- configuration management and change-control procedures;
- backup and recovery (application and data);
- error handling and corrective action;
- business continuity plan and disaster recovery;
- maintenance and support;
- data security, including cybersecurity;
- validation deliverables and documentation.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

archiving. Archiving is the process of protecting records from the possibility of being further altered or deleted, and storing these records under the control of independent data management personnel throughout the required retention period. Archived records should include, for example, associated metadata and electronic signatures.

audit trail. The audit trail is a form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for secure recording of life-cycle details, such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record, regardless of its medium, including the "who", "what", "when" and "why" of the action. For example, in a paper record, an audit trail of a change would be documented via a single-line cross-out that allows the original entry to remain legible and documents the initials of the person making the change, the date of the change and the reason for

the change, as required to substantiate and justify the change. In electronic records, secure, computer-generated, time-stamped audit trails should allow for reconstruction of the course of events relating to the creation, modification and deletion of electronic data. Computer-generated audit trails should retain the original entry and document the user identification and the time/date stamp of the action, as well as the reason for the change, as required to substantiate and justify the action. Computer-generated audit trails may include discrete event logs, history files, database queries or reports, or other mechanisms that display events related to the computerized system, specific electronic records or specific data contained within the record.

automatic or live update. A process used to bring up-to-date software and system functionalities in a silent or announced way. More specifically, the update takes place automatically with or without the user's knowledge.

backup. A backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (e.g. in the event of a system crash or corruption of a disk). It is important to note that backup differs from archiving, in that backup copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically overwritten. Such temporary backup copies should not be relied upon as an archiving mechanism.

business continuity plan. A documented plan that defines the ongoing process supported by management and funded to ensure that the necessary steps are taken to identify the impact of potential losses, maintain viable recovery strategies and recovery plans, and assure continuity of services through personnel training, plan testing and maintenance.

cloud based. A model for enabling on-demand network access to a shared pool of configurable computing resources that can be rapidly provisioned and released with minimal management effort or service provider interaction. These computing resources should be appropriately qualified.

computerized system. A computerized system collectively controls the performance and execution of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, for example, manuals and standard operating procedures, as well as personnel interacting with hardware and software.

computerized systems validation. Confirmation by examination and provision of objective and documented evidence that a computerized system's predetermined specifications conform to user needs and intended use and that all requirements can be consistently fulfilled.

commercial off-the-shelf software (COTS). A vendor-supplied software component of a computerized system for which the user cannot claim complete control of the software life-cycle.

configuration management. A discipline applying technical and administrative direction and surveillance to identify and document the functional and physical characteristics of a configuration item, control changes to those characteristics, record and report change processing and implementation status, and verify compliance with specified requirements.

data. All original records and true copies of original records, including source data and metadata, and all subsequent transformations and reports of these data, which are generated or recorded at the time of the GMP activity and allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio or video files or any other media whereby information related to GMP activities is recorded.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable and to which these characteristics of the data are maintained throughout the data life-cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices (*1*).

data life-cycle. All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored, until retirement and disposal. There should be a planned approach to assessing, monitoring and managing the data and the risks to those data, in a manner commensurate with potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the data life-cycle.

disaster recovery. A documented process or set of procedures to recover and protect a business IT infrastructure in any event causing the system to be unavailable. It appropriately defines resources and actions to be taken before, during and after a disaster, to return the system to operational use.

functional specifications. The functional specifications define functions and technological solutions that are specified for the computerized system, based upon technical requirements needed to satisfy user requirements (e.g. specified bandwidth required to meet the user requirement for anticipated system usage).

legacy system. This refers to a mature computer system, programming language, application software, or processes that are used instead of available upgraded versions, and that have not been qualified according to current regulatory requirements.

master data. A single source of business data used across multiple systems, applications and processes and subject to change control to ensure accuracy throughout the data life-cycle.

metadata. Metadata are data about data that provide the contextual information required to understand those data. These include structural and descriptive metadata. Such data describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in weighing, the number 8 is meaningless without metadata, such as, the unit, milligram, gram, kilogram, etc. Other examples of metadata include the time/date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

production environment. For regulated computerized systems, the production environment is the business and computing operating environment in which the computerized system is being used for GMP-regulated purposes.

regression analysis and testing. A documented software verification and validation task to determine the extent of verification and validation analysis and testing that must be repeated when changes are made to any previously examined software component or system.

system life-cycle. The period of time that starts when a computerized system is conceived and ends when the system is retired and decommissioned, taking into consideration regulatory requirements. The system life-cycle typically includes a planning phase; a development phase that includes a design phase and a programming and testing phase; a qualification and release phase that includes a system integration and testing phase; a validation phase; a release phase; an operation and maintenance phase; and, finally, a system retirement phase.

user acceptance testing. Verification of the fully configured computerized system installed in the production environment (or in a test environment equivalent to the production environment) to perform, as intended, in the business process when operated by end-users trained in end-user SOPs that define system use and control. User acceptance testing (UAT) may be a component of the performance qualification (PQ) or a validation step separate from the PQ.

user requirements specification. The user requirements specification (URS), if prepared as a separate document, is a formal document that defines the requirements for use of the computerized system in its intended production environment.

3. Computerized system validation protocols and reports

3.1 A computerized system needs to be validated according to an approved protocol and a final report including results and conclusions, prior to routine use. All validation documentation should be appropriately retained.

Validation protocol

3.2 Validation should be executed in accordance with the validation protocol and applicable written procedures.

3.3 A validation protocol should define the objectives and the validation strategy, including roles and responsibilities and documentation and activities to be performed. The protocol should at least cover the scope, risk management approach, specification, acceptance criteria, testing, review, personnel training and release of the computerized system for GMP use.

3.4 The validation protocol should be tailored to the system type, impact, risks and requirements applicable to the system for which it governs validation activities.

Validation report

3.5 A validation report should be prepared, summarizing system validation activities.

3.6 The report should make reference to the protocol, outline the validation process, and include an evaluation and conclusion of results. Any changes or deviations from the validation protocol and applicable written procedures should be described and assessed, and justification for their acceptance or rejection should be documented. Deviations should be investigated and a root cause determined. A validation report should also include a summary of procedures and training.

3.7 Test results should be recorded, reviewed, analysed and compared against the predetermined acceptance criteria. All critical and major test discrepancies that occurred during the verification/validation testing should be investigated and resolved. If critical and major test discrepancies are accepted after investigation, they should be appropriately justified.

3.8 The conclusion of the report should state whether or not the outcome of the validation was considered successful and should make recommendations for future monitoring where applicable. The report should be approved after appropriately addressing any issue identified during validation, and the system should then be released for routine GMP use.

4. Supplier management

4.1 When third parties (e.g. suppliers, service providers) are used, such as to provide, install, configure, validate, maintain, modify or retain a computerized system or related service, or for data processing or system components, including cloud-based systems, an evaluation of the supplier, supplied system or service, and the supplier's quality systems should be conducted and recorded. The scope and depth of this evaluation should be based upon risk management principles.

4.2 The competence and reliability of a supplier are key factors when selecting a product and/or service provider. Supplier management is an ongoing process that requires periodic assessment and review of the system or service provided. Supplier evaluation activities may include, but are not limited to: completion of a quality-related questionnaire by the supplier; gathering of supplier documentation related to system development, testing and maintenance, including supplier procedures, specifications, system architecture diagrams, test evidence, release notes and other relevant supplier documentation; an on-site audit of the supplier's facilities, which may be conducted based on risk principles to evaluate the supplier's system life-cycle control procedures, practices and documentation.

4.3 A contract should be in place between the manufacturer and the supplier and/or the service provider, defining the roles and responsibilities and quality procedures for both parties, throughout the system life-cycle. The contract acceptor should not pass to a third party any of the work entrusted to her/him under the contract, without the manufacturer's prior evaluation and approval of the arrangements.

5. Requirements specifications

5.1 Requirements specifications should be written to document user requirements and functional or operational requirements and performance requirements. Requirements may be documented in separate user requirements specification (URS) and functional requirements specifications (FRS) documents, or in a combined document.

User requirements specifications

5.2 The authorized URS document, or equivalent, should describe the intended uses of the proposed computerized system and should define critical data and data life-cycle controls that will assure consistent and reliable data throughout the processes by which data are created, processed, transmitted,

reviewed, reported, retained and retrieved and eventually disposed. The URS should be written in a way to ensure that the data will meet regulatory requirements, such as the World Health Organization (WHO) *Guidance on good data and record management practices* (*1*).

5.3 Other aspects to be included in the URS may include, but are not limited to:

- the transaction or data to be entered, processed, reported, stored and retrieved by the system, including any master data and other data considered to be the most critical to system control and data output;
- the flow of data, including that of the business process(es) in which the system will be used, as well as the physical transfer of the data from the system to other systems or network components. Documentation of data flows and data process maps is recommended, to facilitate the assessment and mitigation and control of data integrity risks across the actual, intended data process(es);
- networks and operating system environments that support the data flows;
- the system interfaces with other systems and the overall security;
- the operating program;
- synchronization and security controls of time/date stamps;
- controls of both the application software as well as operating systems, to assure system access only to authorized persons;
- controls to ensure that data will be attributable to unique individuals (e.g. to prohibit use of shared or generic log-in credentials);
- controls to ensure that data related to GMP purposes is legibly and contemporaneously recorded to durable ("permanent") media at the time of each step and event, and controls that enforce the sequencing of each step and event (e.g. controls that prevent alteration or deletion of data in temporary memory in a manner that would not be documented);
- controls that assure that all steps that create, modify or delete electronic data related to GMP purposes will be recorded in independent, computer-generated audit trails or other metadata, or alternate documents that record the "what" (e.g. original entry), "who" (e.g. user ID), "when" (e.g. time/date stamp) and "why" (e.g. reason) of the action;
- backups and the ability to restore the system and data from backups;
- the ability to archive and retrieve the electronic data in a manner that assures that the archive copy preserves the full content of the

original electronic data set, including all metadata needed to fully reconstruct the GMP activity. The archive copy should also preserve the meaning of the original electronic data set;

- input/output checks, including implementation of procedures for the review of original electronic data and metadata, such as audit trails;
- electronic signatures;
- alarms and flags that indicate alarm conditions and invalid and altered data, in order to facilitate detection and a review of these events;
- system documentation, including system specifications documents, user manuals and procedures for system use, data review and system administration;
- system capacity and volume requirements, based upon the predicted system usage and performance requirements;
- performance monitoring of the system;
- controls for orderly system shutdown and recovery;
- business continuity.

5.4 The extent and detail of the requirements should be commensurate with the operational risk and the complexity of the computerized system. User requirements should be specific and phrased in a way that supports their testing or verification within the context of the computerized system.

Functional specifications

5.5 Functional specifications should describe in detail the functions, performance and interfaces of the computerized system, based upon the technical requirements needed to satisfy user requirements, and should be linked to user specifications.

5.6 The functional specifications provide a basis for the system design and configuration specifications. Functional specifications should consider requirements for operation of the computerized system in the intended computing environment, such as functions provided by supplier-provided software, as well as functions required for user business processes that are not met by commercial off-the-shelf software (COTS) functionality, and default configurations that will require custom code development. Network infrastructure requirements should also be taken into account. Each described function should be verifiable.

5.7 Personnel access roles that provide the ability and/or authorization to write, alter or access programs or configuration should be defined and qualified.

There should be appropriate segregation of roles between personnel responsible for the business process and personnel for system administration and maintenance.

6. System design and configuration specifications

6.1 System design and configuration specifications should be developed based on user and functional requirements. Specification of design parameters and configuration settings (separate or combined) should ensure data integrity and compliance with the WHO *Guidance on good data and record management practices* (*1*).

6.2 System design and configuration specifications should provide a high-level system description, as well as an overview of the system's physical and logical architecture, and should map out the system business process and relevant work flows and data flows if these have not already been documented in other requirements specifications documents.

6.3 The system design and configuration specifications may include, as applicable, a software design specification, in case of code development, and configuration specifications of the software application parameters, such as security profiles, audit trail configuration, data libraries and other configurable elements.

6.4 In addition, the system design and configuration specifications may also include, based upon risk, the hardware design and its configuration specifications, as well as that of any supporting network infrastructure.

6.5 System design and configuration specifications should include secure, protected, independent computer-generated audit trails to track configuration changes to critical settings in the system.

7. Design qualification

7.1 Following design qualification (DQ), a review should be conducted to verify that the proposed design and configuration of the system is suitable for its intended purpose and will meet all applicable user and functional specifications.

7.2 It may include a review of supplier documentation, if applicable, and verification that requirements specifications are traceable to proposed design and configuration specifications. The DQ review should be documented.

8. System development and project implementation

8.1 Once the system requirements and the system design and configuration are specified and verified, where applicable, system development activities may begin. The development activities may occur as a dedicated phase following completion of specification of system requirements, design and configuration. Alternatively, development activities may occur iteratively as requirements are specified and verified (such as when prototyping or rapid-development methodologies are employed).

Supplier-provided systems

8.2 For supplier-provided systems, the development controls for the supplier-provided portion of the computerized system should be assessed during the supplier evaluation or supplier qualification. For supplier-provided systems that include custom components (such as custom-coded interfaces or custom report tools) and/or require configuration (such as configuration of security profiles in the software or configuration of the hardware within the network infrastructure), the system should be developed under an appropriate documented quality management system.

Custom-developed systems

8.3 For custom-developed and configurable systems, the system should be developed under an appropriate documented quality system. For these systems or modules, the quality management system controls should include development of code in accordance with documented programing standards, review of code for adherence to programing standards, and design specifications and development testing that may include unit testing and module/integration testing.

8.4 System prototyping and rapid, agile development methodologies may be employed during the system build and development testing phase. There should be an adequate level of documentation of these activities.

Preparation for the system qualification phase

8.5 The system development and build phase should be followed by the system qualification phase. This typically consists of installation, operational and performance testing. The actual qualification required may vary depending on the scope of the validation project, as defined in the validation protocol and based upon a documented and justified risk assessment.

8.6 Prior to the initiation of the system qualification phase, the software program and requirements and specifications documents should be finalized and subsequently managed under formal change control.

8.7 Persons who will be conducting the system qualification should be trained to adhere to the following requirements for system qualification:

- test documentation should be generated to provide evidence of testing;
- test documentation should comply with good documentation practices;
- any discrepancies between actual test results and expected results should be documented and adequately resolved, based upon risk prior to proceeding to subsequent test phases.

9. Installation qualification

9.1 Installation qualification (IQ) – also referred to as installation verification testing – should provide documented evidence that the computerized system, including software and associated hardware, is installed and configured in the intended system test and production environments, according to written specifications.

9.2 The IQ will verify, for example, that the computer hardware on which the software application is installed has the proper firmware and operating system, that all components are present and in the proper condition, and that each component is installed per the manufacturer or developer instructions.

9.3 IQ should include verification that configurable elements of the system are appropriately set as specified. Where appropriate, this could also be done during operational qualification (OQ).

10. Operational qualification

10.1 The OQ – or operational/functional verification testing – should provide documented evidence that software and hardware function as intended over anticipated operating ranges.

10.2 Functional testing should include, based upon risk:

- challenges on the system's ability to do what it should do, including verification that significant alerts and error messages are raised based upon alarm conditions and according to specifications;

- an appropriate degree of testing (such as boundary, range, limit, and nonsense entry testing), to verify that the system appropriately handles erroneous entries or erroneous use.

11. Standard operating procedures and training

11.1 Prior to conducting of the PQ and UAT, and prior to release of the computerized system, there should be adequate written procedures and documents and training programmes created defining system use and control. These may include supplier-provided user manuals as well as SOPs and training programmes developed in house.

11.2 Procedures and training programmes that should be developed include, but are not necessarily limited to:

- system use procedures that address:
  - routine operation and use of the system in the intended business process(es);
  - review of the electronic data and associated metadata (such as audit trails) and how the source electronic records will be reconciled with printouts, if any;
  - mechanisms for signing electronic data;
  - system training requirements prior to being granted system access;
- system administration procedures that address:
  - granting disabling and review of user access and maintaining security controls;
  - backup/restore;
  - archiving/retrieval;
  - disaster recovery and business continuity;
  - change management;
  - incident and problem management;
  - system maintenance.

12. Performance qualification and user acceptance testing

12.1 PQ, which includes UAT, should be conducted to verify the intended system use and administration defined in the URS and DQ, or equivalent document.

12.2 The PQ should be conducted in the live environment (controls for restricted release for GMP use may be necessary) or in a test environment that is functionally equivalent to the live environment in terms of overall software and hardware configuration.

12.3 PQ testing should also include, as applicable, an appropriate degree of stress/load/volume testing, based upon the anticipated system use and performance requirements in the production environment. Such testing may also be performed during OQ if appropriately justified.

12.4 In addition, an appropriate degree of end-to-end or regression testing of the system should be conducted to verify the system performs reliably when system components are integrated in the fully configured system deployed in the production environment.

12.5 UAT should be conducted by system users, to verify the adequacy of the system, use of SOPs and training programmes. The UAT should include verification of the ability to generate and process only valid data within the computerized system, including the ability to efficiently review electronic data and metadata, such as audit trails. SOPs should be finalized and approved upon completion of performance qualification.

Legacy systems

12.6 The continued use of a legacy system should be justified by demonstrating the system continues to be relevant to the GMP process being supported and by ensuring adequate validation of the system (i.e. hardware, software, peripheral devices, networks) has been performed.

12.7 The validation approach to be taken should aim at providing data and information to justify and support the retrospective qualification of the system. It should demonstrate that the system remains in a state of control and is fit for its intended use and, where necessary, it should include an approach for retrospective qualification of the system with relevant evidence.

12.8 A risk assessment should be undertaken to determine the criticality of the system to the process or operation being supported, and a gap analysis should identify the level of completeness of existing qualification documentation (e.g. URS, IQ/OQ/PQ, SOPs) and state of system control, operation and maintenance.

12.9 For legacy systems, development documentation and records appropriate for validation may not be available. Nevertheless, the strategy should be consistent with validation principles where assurance is established, based

on compilation and formal review of the history of use, maintenance, error report and change-control system records. These activities should be based on documented URS. If historical data do not encompass the current range of operating parameters, or if there have been significant changes between past and current practices, then retrospective data would not of themselves support validation of the current system.

12.10 The validation exercise should demonstrate that user requirements and system description have been appropriately established, as well as providing evidence that the system (i.e. hardware, software, peripheral devices, networks, processes) has been qualified and accepted and that GMP requirements are met.

13. System operation and maintenance

Security and access control

13.1 Manufacturers should have systems and procedures in place to ensure data integrity and access control to computerized systems, and these measures should be commensurate with identified risks

13.2 Suitable security measures should be in place to prevent unauthorized entry or manipulation or deletion of data through the application software, as well as in operating system environments in which data may be stored or transmitted. Data should be entered or amended only by persons who are qualified and authorized to do so.

13.3 The activity of entering data, changing or amending incorrect entries, or creating backups should be done in accordance with SOPs.

13.4 Security should extend to devices used to store programs and data. Access to these devices should be controlled.

13.5 Measures for protecting audit trails from alteration or unauthorized deletion should be in place. Procedures for review of audit trails, and when necessary metadata, should define the frequency, roles and responsibilities and nature of these reviews.

13.6 Operation of the system and acquisition of data should be traceable and should identify the persons who made entries and/or changes, approved decisions or performed other critical steps in system use or control.

13.7 Details of user profiles and access rights to systems, networks, servers, computerized systems and software should be documented and reviewed periodically. An up-to-date list on the individual user rights for the

software, individual computer systems and networks should be maintained and subjected to change control. The level of detail should be sufficient to enable computer system validation personnel, as well as IT personnel/any external auditor/inspector, to ascertain that security features of the system and of software used to obtain and process critical data cannot be circumvented.

13.8 All GMP computerized systems, either stand-alone or in a network, should have a system that is commensurate with identified risks for monitoring through an audit trail of events that are relevant. These events should include all elements that need to be monitored to ensure that the integrity (*1*) of the data could not have been compromised without leaving a trace, such as, but not limited to, changes in or deletion of data; changes in dates, times, backups, archives or user access rights; and addition/deletion of users and log-ins, in accordance with WHO *Guidance on good data and record management practices* (*1*). The configuration and archiving of these audit trails should be documented and also be subjected to change control. These audit trails should be system generated, accurate, consistent, secure, available and convertible to a generally intelligible form throughout the retention period, and their generation appropriately qualified.

Operation and maintenance

13.9 Entry of GMP-related data into a computerized system should be verified by an independent authorized person and locked before release for routine use.

13.10 Validated computerized systems should be maintained in a validated state once released to the GMP production environment.

13.11 There should be written procedures governing system operation and maintenance, including, for example:

- performance monitoring;
- change management and configuration management;
- problem/incident management;
- program and data security;
- program and data backup/restore and archiving/retrieval;
- system administration and maintenance;
- data flow and data life-cycle;
- system use and review of electronic data and metadata (such as audit trails);

- personnel training;
- disaster recovery and business continuity;
- availability of replacement parts and technical support;
- periodic re-evaluation.

13.12 Automatic or live updates should be subject to review prior to becoming effective.

Data migration

13.13 Where electronic data are transferred from one system to another, it should be demonstrated that data are not altered during the migration process. Conversion of data to a different format should be considered as data migration. Where data are transferred to another medium, they must be verified as an exact copy, prior to any destruction of the original data.

13.14 Procedures for data migration may vary greatly in complexity, and measures to ensure appropriate transfer of data should be commensurate with identified risks. Migrated data should remain usable and should retain their content and meaning. The value and/or meaning of and links between a system audit trail and electronic signatures should be ensured in a migration process.

Periodic review

13.15 Computerized systems should be periodically reviewed to determine whether the system remains in a validated state or whether there is a need for revalidation. The scope and extent of the revalidation should be determined using a risk-based approach. The review should at least cover:

- system performance and functionality;
- security;
- maintenance;
- review of changes including upgrades;
- review of deviations;
- review of incidents/events (including review of audit trail);
- systems documentation;
- procedures;
- training;
- effectiveness of corrective and preventive action.

13.16 Corrective and preventive action should be taken where indicated as a result of the periodic review.

14. System retirement

14.1 System retirement should be considered as a system life-cycle phase. It should be planned, risk based and documented. If migration or archiving of GMP-relevant data (*1*, *2*) is necessary, the process must be documented.

14.2 Once the computerized system or components are no longer needed, the system or components should be retired and decommissioned, in accordance with established authorized procedures, including a change-control procedure and a formal plan for retirement.

14.3 Records should be archived in a readable form and in a manner that preserves the accessibility, readability and integrity of the data of the source electronic records throughout the required records retention period.

14.4 The outcome of the retirement activities, including traceability of the data and computerized systems, as well as the ability to retrieve the data, should be tested and documented in a report.

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Appendix 6

Guidelines on qualification

Background

There was some confusion regarding the title of this appendix. It was therefore suggested to change the previous title *Validation on qualification of systems, utilities and equipment to Guidelines on qualification*. In this way, the general principles of qualification are addressed, which can be applied for systems, equipment, and so on.

Based on the comments, the general sections on objective and scope were written to make it clear that the guidelines address principles of qualification that can be applied, as appropriate, to premises, systems, utilities and equipment and to include the application of risk management principles.

Moreover, duplication was removed and logical flow of concepts addressed and aligned with international texts and the comments. Discussion of the V Model has been removed, based on the feedback received. In the former published text on qualification (see reference below), protocol formats were included. These protocol formats were extracted from training materials and were intended to serve as examples. In view of the feedback that manufacturers seemingly took them as absolute examples to be used, these examples have been removed in the current version.

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 6: Qualification of systems and equipment. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf).

1. Principle

1.1 In principle, premises, systems, utilities and equipment should be appropriately designed, installed, qualified, operated, cleaned and maintained, to suit their intended purpose.

1.2 Quality management systems should be in place to ensure that these remain in a qualified state throughout their life-cycle.

1.3 Products should be produced and controlled using qualified equipment and instruments.

1.4 Manufacturers who may use an alternative verification framework to achieve qualification should ensure the qualification expectations within these guidelines are satisfied.

2. Scope

2.1 These guidelines describe the general approach to qualification of, for example, premises, systems, utilities and equipment.

2.2 The principles in these guidelines may also be applied to the qualification of instruments, analytical instruments and testing devices, where appropriate.

2.3 These may include, but are not limited to: certain rooms; water purification systems; cleaning systems; heating, ventilation and air-conditioning systems; compressed air systems; gas systems; and steam systems; as well as production equipment and analytical instruments.

2.4 Separate guidelines in this series address other principles in validation, such as process validation and cleaning validation (see Appendices 1–5 and 7).

2.5 The principle should be applied that a qualified state is maintained throughout the life-cycle.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

computerized system. A computerized system collectively controls the performance and execution of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, for example, manuals and standard operating procedures, as well as personnel interacting with hardware and software.

design qualification. Documented evidence that, for example, the premises, supporting systems, utilities and equipment have been designed for their intended purposes and in accordance with the requirements of good manufacturing practices.

factory acceptance test. A test conducted, usually at the vendor's premises, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications.

installation qualification. The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed.

operational qualification. Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

performance qualification. Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters, for prolonged periods.

site acceptance test. A test conducted at the manufacturer's site of use, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications.

user requirements specification. An authorized document that defines the requirements for use of the system, equipment or utility in its intended production environment.

utility. A system consisting of one or more components to form a structure designed to collectively operate, function or perform and provide a service, such as electricity, water, ventilation or other.

4. General

Note: The remainder of the text in these guidelines will refer to utilities and equipment as examples, even though the principles may be applicable to others such as premises and systems.

4.1 The validation master plan, or other relevant document, should specify the policy, organization, planning, scope and stages applied in qualification on site, and should cover, for example, production, quality control and engineering.

4.2 Principles of quality risk management should be applied in qualification. These include:

- a clear understanding of the system and the role it plays in establishing/protecting the process and quality, and all of the potential ways (risks) the process or quality could be impacted by

failures, events, errors, or time/use-based factors (deterioration, out-of-tolerance instruments, wear and tear, and so on);

- defining all of the design, procedural and/or quality system controls required to protect against these potential risks. These controls either mitigate/reduce the risks and/or detect the impact to quality or process, should the risk occur (to ensure the "failure" does not impact final product quality);
- compiling evidence during the design, engineering, commissioning and qualification, to demonstrate that all of these required "controls" have been properly implemented and verified (including "function" where applicable, such as alarms on operating parameters);
- appropriate control and oversight of change once the controls have been verified.

4.3 The scope and extent of qualification and requalification should be determined based on the principles of impact assessment and risk management.

4.4 Qualification should be executed by trained personnel. Training records should be maintained.

4.5 Where appropriate, new premises, systems, utilities and equipment should be subjected to all stages of qualification. This includes the preparation of user requirements specification (URS), design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

4.6 Where it is decided that not all stages of qualification are required, justification should be provided.

4.7 Qualification should be done in accordance with predetermined and approved qualification protocols. The protocol should specify the prerequisites and test details, including acceptance criteria.

4.8 The results of the qualification should be recorded and reflected in qualification reports.

4. 9 A qualification report prepared at the completion of each protocol or stage of qualification (installation/operational/performance) should include, or reference as appropriate, the following:

- test results, including supporting calculations, documentation and raw/original data;
- test failures;

- protocol departures;
- recommendations and justification for issue resolution;
- conclusions.

4.10 There should be a logical sequence for executing qualification, such as premises (rooms), then utilities and equipment.

4.11 Normally, qualification stages should be sequential (e.g. operational qualification should follow after the successful completion of installation qualification). In some cases, different stages of qualification may be executed concurrently. This should be justified and documented in the validation master plan (or qualification protocol).

4.12 Equipment should be released for routine use only once there is documented evidence that the qualification has been successful.

4.13 Certain stages of the qualification may be done by a supplier or a third party, subject to the conditions and responsibilities as defined in writing and agreed between the parties. The contract giver remains responsible to ensure that the qualification is done in accordance with the principles of good manufacturing practices.

4.14 The relevant documentation associated with qualification, including standard operating procedures, specifications and acceptance criteria, certificates and manuals, should be available.

4.15 Utilities and equipment should be maintained in a qualified state and should be periodically reviewed for the need for requalification. Requalification should be considered when changes are made.

5. User requirements specification

5.1 URS documentation should be prepared for, but not limited to, utilities and equipment, as appropriate.

5.2 URS should be used at later stages in qualification, to verify that the purchased and supplied utility or equipment is in accordance with the user's needs.

6. Design qualification

6.1 DQ should demonstrate that the system, as designed, is appropriate for its intended use as defined in the URS.

6.2 A suitable supplier should be selected and approved for the relevant utility or equipment.

7. Factory acceptance test and site acceptance test

7.1 Where a utility or equipment is assembled, or partially assembled at a site other than that of the purchaser or end-user, testing and verification may be done, based on principles of quality risk management, to ensure that it is appropriate, as described in the URS, and ready for dispatch.

7.2 The checks and tests conducted during the factory acceptance test (FAT) should be recorded.

7.3 The acceptability of the assembly and overall status of the utility or equipment should be described in a conclusion of the report for the FAT, prior to shipment.

7.4 Tests, based on principles of quality risk management, may be performed to verify the acceptability of the utility or equipment when it is received at the end-user. This is a site acceptance test (SAT).

7.5 The results of the tests should be evaluated and the outcome of the acceptability of the utility or equipment should be recorded in the conclusion section of the report for the SAT.

8. Installation qualification

8.1 Utilities and equipment should be correctly installed, in an appropriate location.

8.2 There should be documented evidence of the installation. This should be in accordance with the IQ protocol, which contains all the relevant details.

8.3 IQ should include identification and installation verification of relevant components identified (e.g. services, controls and gauges).

8.4 Identified measuring, control and indicating devices, should be calibrated on site, unless otherwise appropriately justified. The calibration should be traceable to national or international standards. Traceable certificates should be available.

8.5 Deviations and non-conformances, including those from URS, DQ and acceptance criteria specified and observed during installation, should be recorded, investigated and corrected or justified.

8.6 The outcome of the IQ should be recorded in the conclusion of the report, before OQ is started.

9. Operational qualification

9.1 Requirements and procedures for operation (or use), calibration, maintenance and cleaning should be prepared before OQ and approved prior to PQ.

9.2 Utilities and equipment should operate correctly and their operation should be verified in accordance with an OQ protocol. OQ normally follows IQ but, depending on the complexity of the utility or equipment, it may be performed as a combined installation/operation qualification (IOQ). This should be justified and documented in the validation master plan (or qualification protocol).

9.3 OQ should include, but is not limited to, the following:

- tests that have been developed from the knowledge of processes, systems and equipment, to ensure the utility or equipment is operating as designed;
- tests over the operating limits.

9.4 Training of operators for the utilities and equipment should be provided and training records maintained.

9.5 Calibration, cleaning, maintenance, training and related tests and results should be verified to be acceptable.

9.6 Deviations and non-conformances observed should be recorded, investigated and corrected or justified.

9.7 The results for the verification of operation should be documented in the OQ report.

9.8 The outcome of the OQ should be recorded in the conclusion of the report, normally before PQ is started.

10. Performance qualification

10.1 PQ should normally follow the successful completion of IQ and OQ. In some cases, it may be appropriate to perform PQ in conjunction with OQ or process validation. This should be justified and documented in the validation master plan (or qualification protocol).

10.2 PQ should include, but is not limited to, the following:

- tests using production materials, qualified substitutes or simulated products proven to have equivalent behaviour under operating conditions, with batch sizes where appropriate;
- tests covering the intended operating range.

10.3 Utilities and equipment should consistently perform in accordance with their design specifications and URS. The performance should be verified in accordance with a PQ protocol.

10.4 There should be records for the PQ (e.g. a PQ report), to indicate the satisfactory performance over a predefined period of time. Manufacturers should justify the period over which PQ is done.

11. Periodic review and requalification

11.1 Utilities and equipment should be maintained in a qualified state throughout the life-cycle of the utility or equipment.

11.2 Utilities and equipment should be reviewed periodically, to confirm that they remain in a qualified state or to determine the need for requalification.

11.3 Where the need for requalification is identified, this should be performed.

11.4 Principles of risk management should be applied in the review and requalification and the possible impact of small changes over a period of time should further be considered (such as, through change control).

11.5 Principles of risk management may include factors such as calibration, verification, maintenance data and other information.

11.6 The qualification status and periodic requalification due dates should be documented, for example, in a qualification matrix, schedule or plan.

11.7 In case a utility or equipment in use is identified that has not been subjected to qualification, a qualification protocol should be prepared where elements of URS, design specifications, operation and performance are verified for acceptability. The outcome of this qualification should be recorded in a report.

Appendix 7

Non sterile process validation

Background

The text of this appendix was previously published as:

- Guidelines on good manufacturing practices: validation. Appendix 7: Non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3-TRS992.pdf).

1. Background and scope

Further to the *Supplementary guidelines on good manufacturing practices: validation*, as published in the World Health Organization (WHO) Technical Report Series (TRS), No. 937 (*1*), additional guidelines to support current approaches to good manufacturing practices (GMP) are published here. These guidelines are intended to further support the concept of process validation linked to principles of quality risk management and quality by design, as described by WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

These guidelines allow for different approaches to process validation. The principles described are mainly applicable to non-sterile finished pharmaceutical dosage forms. Similar approaches may be applicable to active pharmaceutical ingredients (APIs) and sterile products. (See also recommendations in WHO TRS No. 957, Annex 2 (*2*) and WHO TRS No. 961, Annex 6 (*3*).)

A risk-based and life-cycle approach to validation is recommended.

Thorough knowledge of product and process development studies; previous manufacturing experience; and principles of quality risk management are essential in all approaches to process validation, as the focus is now on the life-cycle approach. The life-cycle approach links product and process development, validation of the commercial manufacturing process and maintaining the process in a state of control during routine commercial production. The use of process analytical technology, which may include in line, online and/or at-line controls and monitoring, is recommended, to ensure that a process is in a state of control during manufacture.

2. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

at-line. Measurement where the sample is removed, isolated from, and analysed in close proximity to the process stream.

concurrent validation. Validation carried out during routine production of products intended for sale in exceptional circumstances when data from replicate production runs are unavailable because only a limited number of batches have been produced, batches are produced infrequently or batches are produced by a validated process that has been modified. Individual batches may be evaluated and released before completion of the validation exercise, based on thorough monitoring and testing of the batches.

control strategy. A planned set of controls, derived from current product and process understanding that assures process performance and product quality.

The controls can include parameters and attributes related to API and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

continued process verification. Documented scientific evidence that the process remains in a state of control during commercial manufacture.

critical process parameter. A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and/or controlled to ensure the process produces the desired quality.

critical quality attribute. A physical, chemical, biological or microbiological property or characteristic of materials or products that should be within an appropriate limit, range or distribution to ensure the desired product quality.

in-line. Measurement where the sample is not removed from the process stream: can be invasive or non-invasive.

life-cycle. All phases in the life of a product from the initial development through marketing until the product's discontinuation (*4*).

matrix approach or bracketing. Bracketing is the assessment of a single parameter or variable by identifying the edge(s) of the range of conditions for the parameter or variable and assessing these during validation, to span the possible range of that parameter or variable. For example, bracketing can be applied to process parameters, multiple pieces of identical equipment and/or different size considerations for the same product. The rationale for using this strategy should be justified, documented and approved.

Matrixing involves the assessment of the effect of more than one parameter or variable by using a multidimensional matrix to identify the "worst-case" or "extreme" conditions for a combination of parameters or variables. These conditions are used during validation of the process, rather than validating all possible combinations. Matrixing is typically used when there are significant similarities between products in a product family (e.g. the same product with different strengths in the manufacturing stage or different products with a similar container-closure in the packaging stage). The rationale for using this strategy should be justified, documented and approved.

The use of a matrix approach or bracketing design would not be considered appropriate if it is not possible to demonstrate that the extremes are limited to the batches, products, strengths, container sizes or fills. For those excluded from the exercise, there should be no risk to process capability.

online. Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

pharmaceutical quality system. Management system to direct and control a pharmaceutical company with regard to quality.

process qualification. Process qualification combines the actual facility, utilities, equipment (each now qualified) and the trained personnel with the commercial manufacturing process, control procedures and components to produce commercial batches; confirms the process design; and demonstrates that the commercial manufacturing process performs as expected.

process validation. The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of continuously delivering the finished pharmaceutical product, meeting its predetermined specifications and quality attributes.

quality target product profile (QTPP). A prospectively documented summary of the quality characteristics of a finished pharmaceutical product (FPP) that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the FPP. The QTPP forms the basis of design for the development of the product and typically would include:

- intended use in a clinical setting, route of administration, dosage form, delivery systems;
- dosage strength(s);
- container-closure system;
- therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g. dissolution, aerodynamic performance) appropriate to the FPP dosage form being developed;
- FPP quality criteria (e.g. sterility, purity, stability and drug release) appropriate for the intended marketed product.

real-time release testing. The ability to evaluate and ensure the quality of in-process and/or final product, based on process data, which typically include a valid combination of measured material attributes and process controls.

state of control. A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

3. Introduction

Process validation data should be generated for all products, to demonstrate the adequacy of the manufacturing process. The validation should be carried out in accordance with GMP and data should be held at the manufacturing location whenever possible and should be available for inspection.

Process validation is associated with the collection and evaluation of data throughout the life-cycle of a product – from the process design stage through to commercial production – and provides scientific evidence that a process

is capable of consistently delivering a quality product. A risk-assessment approach should be followed, to determine the scope and extent to which process(es) and starting material variability may affect product quality. The critical steps and critical process parameters should be identified, justified and documented and based on relevant studies carried out during the design stage and on process knowledge, according to the stages of the product life-cycle. During process validation and qualification, the critical process parameters should be monitored. It may be helpful to use a flow diagram depicting all the operations and controls in the process to be validated.

When applying quality risk management to a given operation, the steps preceding and following that operation should also be considered. Amendments to the flow diagram may be made where appropriate, and should be recorded as part of the validation documentation. Manufacturers should ensure that the principles of process validation described in these guidelines are implemented. These cover the phases of validation during process design; scale-up; qualification of premises, utilities and equipment; process performance qualification; and continuous process verification to ensure that the process remains in a state of control.

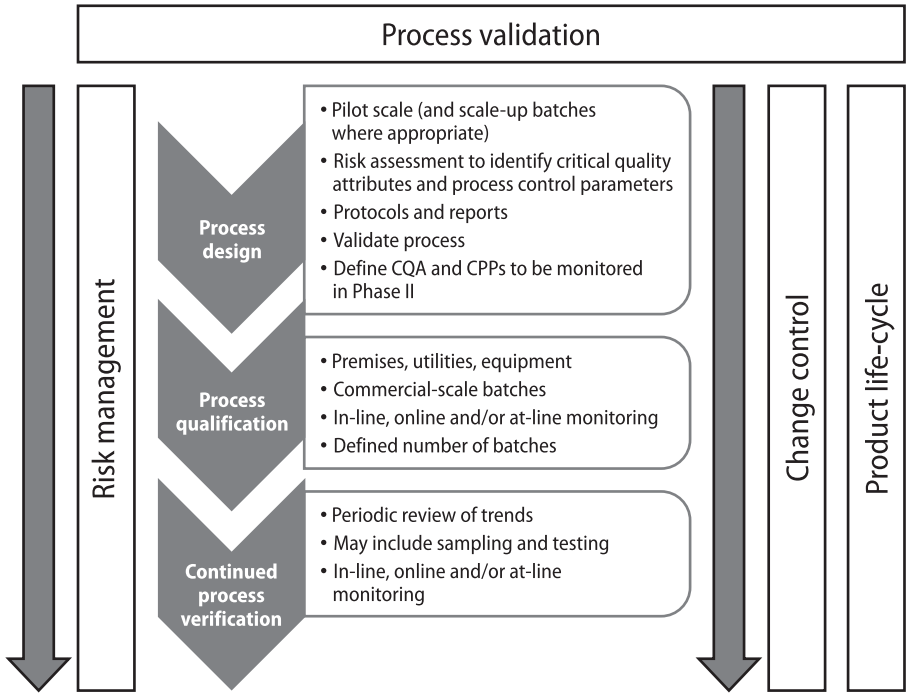
The objectives of process validation include ensuring that:

- the process design is evaluated to show that the process is reproducible, reliable and robust;
- the commercial manufacturing process is defined, monitored and controlled;
- assurance is gained on a continuous basis to show that the process remains in a state of control.

The validation should cover all manufactured strengths of a product, and the extent of validation at each manufacturing site should be based on risk assessment.

A matrix approach or bracketing may be acceptable and should also be based on appropriate risk assessment. There are various approaches to process validation, which include: traditional process validation (consisting of prospective and concurrent validation); process design followed by process qualification and continued process verification; or a combination of traditional process validation and the new approach described in these guidelines. Historical data should be evaluated in cases where there have been changes to the process. Manufacturers should plan to implement the new approach to process validation, which covers process design, process qualification and continued process verification throughout the product life-cycle. Fig. A3.7.1 shows the phases in the new approach to process validation.

Fig. A3.7.1
Phases of process validation



CQA: critical quality attribute; CPPs: critical process parameters.

4. Process design

Under the life-cycle approach, the focus of validation is shifted from commercial-scale batches to development. Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes and a general manufacturing pathway. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

Process design should normally cover design of experiments, process development, the manufacture of products for use in clinical trials, pilot-scale batches and technology transfer. Process design should be verified during product development. Process design should cover aspects for the selection of materials; expected production variation; selection of production technology/process and qualification of the unitary processes that form the manufacturing process as a whole; selection of in-process controls; tests; inspection; and its suitability for the control strategy.

As part of the process validation life-cycle, some process validation studies may be conducted on pilot-scale batches (corresponding to at least 10% or 100 000 units, whichever is the greater) of the production scale. Where the batch size is smaller and/or where the process is tailored to the geometry and capacity of specific equipment, it may be necessary to provide production-scale validation data.

Process qualification and continued process verification should always be linked to process design and be referenced to those specific batches used in studies critical to the development of the product, for example, the batch(es) used for pivotal clinical assessments (biobatch(es)), for example, bioequivalence testing in the case of multisource products, and toxicological studies. The number of batches included in the process design stage of validation should be appropriate and sufficient to include (but not be limited to) the expected variations in starting materials, and confirm the suitability of the equipment and manufacturing technology.

A statistically based design of experiment approach can be helpful during this stage. Processes and results should be appropriately documented. A development report and/or a technology transfer document, formally reviewed and approved by research and development personnel, and formally accepted by manufacturing, engineering and quality personnel, should be prepared. Such a document may include information such as a quality target product profile, desired clinical performance, bills of materials, approved suppliers, finished product specifications and test methods, in-process testing specifications, equipment recommendations, master batch production records, master batch packaging records, stability reports, critical quality attributes, critical process parameters, batch comparisons, data on formulation batches, stability batches, clinical/biobatches and scale-up batches. These documents should be readily available to the manufacturing site. The goal is to design a suitable process for routine commercial manufacturing that can consistently deliver a product that meets its required quality attributes.

5. Process qualification

Personnel, premises, utilities, support systems and equipment should be appropriately qualified before manufacturing processes are validated. Materials, environmental controls, measuring systems, apparatus and methods should be considered during validation. The stages of qualification of equipment may include design, installation, operation and performance of equipment (for more details see reference (*1*)).

Traditionally, three batches have been considered the normal and acceptable number for process validation; however, the number of batches should

be justified and based on a risk assessment that includes, for example, variability of results from the process design stage, variability of materials, product history, where the product is being transferred from and where it will be produced. Manufacturers should define the stage at which the process is considered to be validated and the basis on which that decision was made. The decision should include a justification for the number of batches used based on the complexity and expected variability of the process and critical quality attributes (CQAs).

Successful completion of process performance qualification stage of the life-cycle is required for commercial distribution. A risk assessment should be performed for the change from scale-up to commercial batch size. Process qualification should confirm that scale-up in batch size did not adversely affect the characteristics of the product and that a process that operates within the predefined specified parameters consistently produces a product that meets all its CQAs and control strategy requirements. The process should be verified on commercial-scale batches prior to marketing of the product.

Extensive in-line and/or online and/or at-line controls may be used to monitor process performance and product quality in a timely manner. Results on relevant quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end-points and assessment of CQA and critical process parameter trends. Process analytical technology applications and multivariate statistical process control can be used. Manufacturers are encouraged to implement the new validation approach to ensure that processes are of known and acceptable capability. As full implementation of this approach may take time, the traditional approach of prospective validation and concurrent validation (used infrequently and restricted to the scenarios described in Section 3) may be acceptable in the interim. A combination of elements of the traditional process validation approach and the new continuous process verification approach may be considered appropriate, subject to appropriate controls being in place, based on scientific justification and principles of risk management.

Validation should be done in accordance with process validation protocols. A written protocol is essential for this stage of process validation. The protocol should include or reference at least the following elements:

- the manufacturing conditions, including operating parameters, processing limits and component (raw material) inputs;
- the data to be collected and when and how they will be evaluated;
- the type of testing or monitoring to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step;

- the scientifically justified sampling plan, including sampling points, number of samples and the frequency of sampling for each unit operation and attribute;
- the number of batches for which additional monitoring is proposed;
- status of the validation of analytical methods used in measuring the process, in-process materials and the product;
- a description of the statistical models or tools used;
- review and approval of the protocol by appropriate departments and the quality unit;
- a description of the process;
- details of the equipment and/or facilities to be used (including measuring or recording equipment) together with its calibration status;
- the variables to be monitored, with appropriate justification;
- the samples to be taken
- "who", "where", "when", "how", "how many" and "how much" (sample size);
- the product performance characteristics or attributes to be monitored, together with the test methods;
- the acceptable limits;
- personnel responsibilities;
- details of methods for recording and evaluating results, including statistical analysis. Data should be collected and reviewed against predetermined acceptance criteria and fully documented in process validation reports.

The report should reflect the validation protocol. A dual protocol report can be used; however, such reports must be designed to ensure clarity and sufficient space for recording of results. The outcome should confirm that the acceptance criteria have been met. Any deviations (including abandoned studies) should be explained and justified. The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next phase for confirmation.

6. Continued process verification

Manufacturers should monitor the product quality of commercial batches after completion of process design and process qualification. This will provide evidence that a state of control is maintained throughout the product life-cycle.

The scope and extent of process verification will be influenced by a number of factors, including:

- prior development and knowledge of the manufacturing of similar products and/or processes;
- the extent of process understanding gained from development studies and commercial manufacturing experience;
- the complexity of the product and/or manufacturing process;
- the level of process automation and analytical technologies used;
- for legacy products, with reference to the product life-cycle process, robustness and manufacturing history since the point of commercialization, as appropriate.

Manufacturers should describe the appropriateness and feasibility of the verification strategy (in the protocol), including the process parameters and material attributes that will be monitored, as well as the validated analytical methods that will be employed.

Manufacturers should define:

- the type of testing or monitoring to be performed;
- the acceptance criteria to be applied;
- how the data will be evaluated and the actions to be taken.

Any statistical models or tools used should be described. If continuous processing is employed, the stage at which the commercial process is considered to be validated should be stated, based on the complexity of the process, expected variability and manufacturing experience of the company. Periods of enhanced sampling and monitoring may help to increase process understanding as part of continuous improvement. Information on process trends, such as the quality of incoming materials or components, in process and finished product results and non-conformances, should be collected and assessed to verify the validity of the original process validation or to identify changes to the control strategy required. The scope of continued process verification should be reviewed periodically, and modified if appropriate, throughout the product life-cycle.

7. Change management

Manufacturers should follow change-control procedures when changes are planned to existing systems or processes. The change-control procedure and records should ensure that all aspects are thoroughly documented and approved, including regulatory approval where appropriate (variation).

Sufficient data should be generated to demonstrate that the revised process will result in a product of the desired quality, consistent with approved specifications.

Validation should be considered when changes to production and/or control procedures are planned. Based on risk assessment, changes that may require revalidation could include (but are not limited to):

- changes in the master formula, methods, starting material manufacturer, starting material manufacturing process, excipient manufacturer, excipient manufacturing process;
- changes in the equipment or instruments (e.g. addition of automatic detection systems);
- changes associated with equipment calibrations and the preventive maintenance carried out, which may impact the process;
- production area and support system changes (e.g. rearrangement of areas or a new water-treatment method);
- changes in the manufacturing process (e.g. mixing times, drying temperatures);
- transfer of processes to another site;
- unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data);
- changes to standard operating procedures;
- changes to cleaning and hygiene programmes.

Depending upon the nature of the change being proposed, the change-control process should consider whether existing approved specifications will be adequate to control the product subsequent to implementation of the change.

References

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Further reading

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Annex 4

Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver

1. Scope

The objective of this document is to provide guidance on the design and conduct of equilibrium solubility studies undertaken for the purpose of active pharmaceutical ingredient (API) classification within the Biopharmaceutics Classification System (BCS) (*1*, *2*).

Notably, the definition and guidance given in this document for performing solubility studies apply to APIs and there might be differences in requirement with respect to the conditions for dissolution studies that are applicable to solid finished pharmaceutical products (FPPs).

A study protocol has been developed to provide a harmonized approach when performing solubility studies; however, alternative approaches to determining the solubility of an API, such as phase solubility analysis (*3*), can also be valid if the appropriate test conditions are employed.

The aim of the WHO biowaiver guidance is to reduce the risk of *bioinequivalence* to an acceptable level when granting biowaivers supporting pharmaceutical development. In this context, the solubility, the release from the drug product, and the subsequent absorption phase are considered critical processes underlying the equivalence of the test and reference product.

Equilibrium solubility profiles of APIs contained in medicines in the *WHO Model List of Essential Medicines* (EML) (*4*) can be used in conjunction with absorption/permeability data, FPP dissolution studies, and comparative consideration of FPP excipient content, to enable an informed decision on whether a biowaiver could be granted safely.

2. Experimental considerations

Overall, the API sample should be dissolved/suspended in buffer, then separated by appropriate methods, and the solubilized API concentration measured using a suitable analytical method.

According to the World Health Organization (WHO) definition given in the guidance document *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*5*), an API is considered highly soluble when the highest single therapeutic dose (e.g. the total amount of API administered orally at once), as determined by the relevant regulatory authority, typically defined by the labelling for the innovator product, is soluble in 250 mL or less of aqueous media over the pH range of 1.2–6.8. The pH solubility profile of the API should be determined at 37 ± 1 °C in aqueous media. A minimum of three replicate determinations of solubility at each pH condition is recommended (*5*).

In general, equilibrium solubility experiments should be employed. However, in exceptional cases, for example, where the API is not available in

sufficient quantities; it is prohibitively expensive; or when it is not possible to maintain the pH of the medium with pharmacopoeial buffers, experiments where the highest therapeutic single dose as recommended by the approved label/summary of product characteristics (SmPC) is examined in a 250 mL volume, or a proportionally smaller amount examined in a proportionally smaller volume of buffer, can be considered. As these are equilibrium solubility experiments, small volumes of solubility media may be employed without issue if the available experimental apparatus will permit it.

The source and purity of the API should be reported according to the *Report template for equilibrium solubility experiments for Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* (Appendix 1). Additional characterization of the solid API used in the solubility experiments may be necessary; for example, the solid form of the drug should be confirmed (the crystallinity and polymorphic form). The depth of the characterization will depend on existing knowledge of the solid-state properties of the API in question. For example, if it has been established that the API exists as a single polymorphic form, then less solid-state characterization is necessary.

The "shake flask" method for solubility determination is recommended; a mechanical agitation device should be used (e.g. orbital shaker) and an appropriately validated analytical assay method should also be employed. The device used should be capable of maintaining a temperature of 37 ± 1 °C and an appropriate agitation speed that ensures particle contact with the buffer solution. The agitation speed should be optimized based on the shape of the flask or tube and volume of the liquid, in order to prevent particle agglomeration and ensure particle contact with the diluent. Vortex formation should be avoided. With an optimized agitation rate, it is expected that samples will generally reach equilibrium within 24 hours (*6*). Samples should be collected and analysed at several time points, until equilibrium has been reached.

To address issues such as poor wettability and the tendency of the API to float on the surface of the solubility medium, it may be necessary to include tools such as glass microspheres to aid de-aggregation of the particles with agitation or sonication (*6*). Surfactant should be avoided in equilibrium solubility studies because they would produce biased results. Once wetting is successfully achieved, that is, there are no visible particles floating on the surface or sticking to the container, the solubility experiment should proceed toward equilibrium.

In some circumstances, it can be difficult to obtain true equilibrium solubility, for example, due to excessive material requirements (i.e. very high-solubility, micelle-forming API etc.), long equilibrium times (e.g. slow conversion to a salt form), or poor chemical stability. In these cases, particularly when the compound solubility is very high, it may be appropriate to report a lower solubility limit; that is, the actual solubility is greater than the reported value,

which is still higher than the solubility required to dissolve the highest single therapeutic dose in 250 mL of medium.

3. Buffers for determination of equilibrium solubility

The pH–solubility profile of the API should be determined over the pH range of 1.2–6.8, with the API's solubility classification being based on the lowest solubility measured over this pH range. Measurements should be made in triplicate or more, according to the observed variability, under at least three pH conditions, pH 1.2, 4.5 and 6.8, using for example, 0.1 N HCl test solution or simulated gastric fluid without enzymes – pH 1.2; acetate buffer – pH 4.5; and phosphate buffer – pH 6.8 solution. If there are any known solubility minima for the API in aqueous media within that pH range (for example the pK_a of the API is within the tested pH range of 1.2–6.8), data should also be collected at that pH. Pharmacopoeial buffer solutions are recommended for use in solubility experiments, as reported in Section 3.1. The pH of the buffers should be adjusted at the same temperature as that at which the equilibrium solubility experiments are performed, that is, at 37 ± 1 °C. The pH should be verified after addition of the API and at the end of the experiment, with a calibrated pH meter. If the pH of the buffer changes upon combination with the solute, adjustment of the pH with an appropriate acid or base solution may be sufficient to address the issue, or a buffer with a stronger buffering capacity may be employed. After adjustment of the pH, the solution should be allowed to re-equilibrate for at least one hour before a sample is taken.

3.1 Composition of buffers

Solution pH 1.2, TS (test solution)

Dissolve 2.52 g of sodium chloride R (reagent) in 900 mL of water R, adjust the pH to 1.2 with hydrochloric acid (~70 g/L) TS and dilute to 1000 mL with water R.

Buffer pH 4.5, TS

Dissolve 2.99 g of sodium acetate R in 900 mL of water R, adjust the pH to 4.5 by adding about 14 mL of acetic acid (~120 g/L) TS and dilute to 1000 mL with water R.

Buffer pH 6.8, TS

Dissolve 6.9 g of sodium dihydrogen phosphate R and 0.9 g of sodium hydroxide R in 800 mL of water R, adjust the pH to 6.8 with sodium hydroxide (~80 g/L) TS and dilute to 1000 mL with water R.

Information on the reagents to be used can be found by consulting *The International Pharmacopoeia section on Reagents, test solutions and volumetric solutions* (*7*).

4. Experimental design

The details of the solubility experiment's design should be based on the characteristics of the API under investigation. It is recommended that preliminary testing be conducted to assess the amount of API required and the length of time required for the pivotal solubility experiment.

5. Preliminary assessment of the time to equilibrium and expected solubility

Preliminary estimation of solubility from chemical structure may be used as a starting point, using an open-source tool (e.g. ChemSpider (*8*); Virtual Computational Chemistry Laboratory (*9*); Swiss ADME (*10*)) or by estimating the data.

From this calculation, the amount of solid needed to have approximately 30–40% excess of undissolved solid in 5 mL (or the selected working volume) of buffer solutions at pH 1.2, 4.5 and 6.8 can be determined. This amount of solid should be weighed in a glass or non-leaching vial of suitable material and of appropriate volume, for instance a 10 mL tube, if 5 mL of the buffer will be used (corresponding to the expected minimum solubility condition).

If the solubility is greater than expected, the working volume should be reduced to 3 mL, while if the expected solubility is low and the API is available in sufficient quantity, higher volumes should be used.

Alternatively, the volume can be kept at 5 mL and the mass can be increased or reduced as appropriate.

The presence of undissolved solid should be checked; if the entire solid dissolves when adding the buffer, additional solid should be added until such time that some solid remains undissolved in the tube. To solve any potential issues related to solid wettability or agglomeration, the tubes should be put in the agitation system, such as shaker or magnetic stirrer, adding glass beads.

When the amount of solute and volume of buffer has been determined to obtain a saturated solution, a minimum of three replicate samples for each pH should be prepared to allow measurements at multiple time points for identification of the equilibration time. The pH of the solution should be measured at the time intervals. pH adjustments may be made, if necessary and scientifically justified.

Filtration is normally recommended to remove undissolved API from collected samples, although centrifugation is a valid alternative method, particularly if the medium volume is small.

Either approach is acceptable, and should be scientifically justified.

The samples should be filtered (using, for example, a filter pore size of 0.45 µm) during or immediately after withdrawal, or dissolved API separated from undissolved API by centrifugation as appropriate.

Solubility experiments are performed at 37 ± 1 °C; therefore, if samples are to be left at room temperature until analysis, they should be diluted immediately after centrifugation or filtration, in order to avoid precipitation of the solute. This should be taken into account for back calculations.

To determine equilibrium solubility, the concentration of the solution should be measured at different time points, for example 2 h, 4 h, 8 h, 24 h, 48 h and 72 h, until it does not deviate significantly (e.g. 10%) between sequential measurement. The shortest time needed for reaching the plateau of drug concentration against time could be considered a suitable equilibration time.

Samples should be collected over time, to establish a plateau for the amount of solute dissolved and also to monitor the stability of the API at each pH (see Section 6).

The pH value of the buffer solutions should be measured after establishing the time to obtain equilibrium.

6. Stability

The API's stability across the pH range should be monitored, in order to measure true solubility (*11*, *12*),

To distinguish the drug substance from its degradation products, a validated, stability-indicating analytical method should be employed for solubility determination of APIs such as those indicated in *The International Pharmacopoeia* (*13*) or other pharmacopoeias adapted as appropriate, if available, for example, high-performance liquid chromatographic (HPLC) analysis (see chapter *1.14.4 High-performance liquid chromatography* in *The International Pharmacopoeia* (*14*)) or an alternative, validated stability-indicating assay. An advantage of an HPLC method over a spectrophotometric one is that the HPLC method can also be employed to detect impurities and instability (*11*, *12*). If degradation of the drug substance is observed as a function of buffer composition and/or pH, it should be reported. If a stability-indicating analytical method is not available, separate stability experiments will be necessary to demonstrate that the API is stable in the buffer medium employed.

7. Recommendations for the analytical method

Calibration curves should be constructed, ideally with 5–6 standards for regression and estimation of intercept, slope, and correlation coefficient, and three additional control standards independently prepared for estimation of precision and accuracy.

If necessary, samples should be diluted to be on the range of the calibration curve, recording the dilution factor for back calculations.

Each sample should be run in duplicate and a calibration curve established. It is anticipated that at least 3–4 analytical runs are expected (e.g. the first for the samples of 2 h, 4 h, 8 h and then possibly another three for 24 h, 48 h and 72 h), depending on the stability of the samples. In the end, data for intra- and inter-day accuracy and precision estimation should be available. In general, the control standards are intercalated with the samples.

To check filter influence, control standards could be injected without and after filtration. Recovery should be between 98% and 102% (if less than this value, there is some adsorption happening; if more, some filter component is affecting the analysis). If necessary, a change of filter type or switch to centrifugation is recommended.

The specificity, linearity, range, accuracy, repeatability and intermediate precision should be determined (*12*), which should meet the minimum acceptance limits.

8. Pivotal experiment

Pivotal experiments should be designed considering the results of the preliminary experiments. The following steps are presented as a general example of a pivotal solubility experiment:

1. In triplicate, for each pH condition to be evaluated, weigh approximately a 10% excess amount of API (as determined during the preliminary test) and combine with an appropriate volume of the necessary buffer solutions (at least pH 1.2, 4.5 and 6.8 buffers) in a flask. Sufficient API and volume should be used to allow for collection of residual API following the experiment.
2. Mix and measure the pH value.
3. Stop and secure the flask to the orbital shaker, with controlled temperature and shaker speed.
4. Collect an aliquot of the supernatant solution at the time equilibrium was established in the preliminary experiment.

5. Immediately separate dissolved from undissolved API by filtration or centrifugation.
6. Record the pH value of the solution at the end of the experiment.
7. Dilute the sample to avoid precipitation before quantifying.
8. Determine the concentration of the API.

9. Reporting of results

Test results should be reported in the *Report template for equilibrium solubility experiments for Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver* appended to this protocol as Appendix 1. The report should include information on the API (chemical structure, molecular weight, known dissociation constants, etc.), the actual experimental conditions, including information on buffer composition and the analytical method, results (raw data plus mean values with standard deviations), and any observations such as, for example, the degradation of an API due to pH or buffer composition. The section describing the experimental conditions should include the initial and equilibrium pH of solutions and de facto buffer concentrations. If samples are filtered, the type and pore size of the filter should be recorded, along with data from filter adsorption studies. If samples are centrifuged, the conditions of centrifugation should be recorded. A graphic representation of the mean pH–solubility profile should be provided.

Any deviations from the protocol should be noted and duly justified.

The solubility should be reported in mg/mL. The relative standard deviation of the obtained solubility results should not be more than 10% between the replicates of each test condition.

The dose:solubility volume (DSV) represents the volume of liquid necessary to completely dissolve the highest single therapeutic dose of the API (as recommended by the approved label/SmPC) at the pH where the lowest solubility was observed. Based on the lowest solubility calculated in mg/mL, the DSV can be calculated by dividing the highest therapeutic dose (in milligrams) by the solubility (in milligrams per millilitre) obtained in the study. An API is considered highly soluble when the DSV is ≤ 250 mL over the entire pH range 1.2–6.8.

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14. Methods of analysis: 1. Physical and physicochemical methods: 1.14 Chromatography: 1.14.4 High-performance liquid chromatography. In: In: The International Pharmacopoeia, 8th ed. Geneva: World Health Organization; 2018 (http://apps.who.int/phint/en/p/docf/, accessed 14 February 2019).

Further reading

- Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996; https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex09.pdf?ua=1, accessed 14 February 2019).
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Appendix 1

Report template for equilibrium solubility experiments for Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver

Header:
Logo of the laboratory/company issuing the certificate (if applicable)
Identification No. of the study: *page X of Y*

Name and address of the laboratory
issuing the study report: _____

_____

Name of the active pharmaceutical ingredient (API) (international
nonproprietary name [INN], brand name, etc.): _____

_____

Certificates of analysis (CoAs) from manufactures provided:
assay within specifications <*Yes/No*> _____

_____

Batch number: _____
Date received: _____ Quantity received: _____
Date of manufacture (if available): _____
Expiry date/retest date: _____

Details of original manufacturer

Name and address: _____

_____

Telephone: _____
Email: _____

Information about the API

Chemical structure (please report here): _____

_____

Nature of the drug (i.e. acid, basic, neutral, amphoteric): _____
Dissociation constants [i.e. $pK_a(s)$]: _____
Molecular weight (g/mol): _____

Equilibrium solubility experiment

Apparatus: _____

Highest therapeutic dose: _____

Recorded temperature (target 37 ± 1 °C): _____

Volume of the buffer: _____

Sampling times: _____

Time to equilibrium: _____

Buffer composition (*please indicate if different buffers from those recommended in the* Protocol to conduct equilibrium solubility experiments for the purpose of BCS-based classification of APIs for biowaiver *were used*): _____

_____

_____

Separations of samples (*please indicate how and when samples were filtered, filter type and pore size. If samples are centrifuged, the conditions of centrifugation should be recorded. If separated through different methods, this should be justified*): _____

_____

_____

_____

Stability (*report and discuss any problems with pH-related stability of samples*): _____

_____

_____

Solubility method and conditions: _____

_____

_____

Brief summary of analytical methods, including validation: _____

_____

_____

Result of the *preliminary* solubility experiment

Theoretical pH	Individual pH measure-ment	Final pH before correction	Adjusted with (mL of 0.1 M HCL or NaOH)[a]	Final pH corrected	API equilibrium concentra-tion (mg/mL)[b]	Concen-tration mean (mg/mL)[c]	CV %	Concentration (mg/mL)						
								2 h	4 h	6 h	12 h	24 h	48 h	72 h
pH 1.2	1 2 3													
pH 4.5	1 2 3													
pH 6.8	1 2 3													
Potential additional pH	1 2 3													

CV: coefficient of variation; HCl: hydrochloric acid; NaOH: sodium hydroxide.

[a] Amount of acid or base needed to adjust the measured pH. The measurement should be conducted in triplicate and, per each measurement, the corresponding pH values should be reported.

[b] Report here the three measurements registered at each pH.

[c] Report here only the mean of the individual values reported in the previous column.

Result of the *pivotal* solubility experiment

Theoretical pH	Individual pH measure-ment	Final pH before correction	Adjusted with (ml of 0.1 M HCL or NaOH)[a]	Final pH corrected	Time to equilibrium	APIs weight	Buffer volume	API equilibrium concentra-tion (mg/mL)[b]	API equilibrium concentra-tion mean (mg/mL)[c]	CV %
pH 1.2	1 2 3									
pH 4.5	1 2 3									
pH 6.8	1 2 3									
Potential additional pH	1 2 3									

CV: coefficient of variation; HCl: hydrochloric acid; NaOH: sodium hydroxide.

[a] Amount of acid or base needed to adjust the measured pH. The measurement should be conducted in triplicates and, per each measurement, the corresponding pH values should be reported.

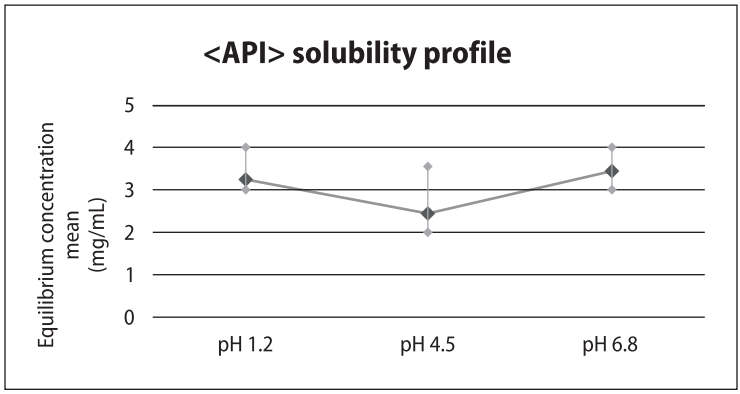
[b] Report here the three measurements registered at each pH.

[c] Report here only the mean of the individual values reported in the previous column. It is the mean solubility value for each pH.

Plot of solubility

To identify the pH of minimum solubility: plot concentration at saturation versus pH and provide a graphical representation of the results. Include error bars on the mean.

Example chart



Please report here the intermediate calculation for the dose:solubility colume (DSV) at (add additional pHs tested as appropriate):

- pH 1.2 Highest therapeutic dose (mg)/Solubility (mg/mL)] [concentration mean] =
- pH 4.5 Highest therapeutic dose(mg)/Solubility (mg/mL) [concentration mean] =
- pH 6.8 Highest therapeutic dose(mg)/Solubility (mg/mL)] [concentration mean] =

Conclusion: is the highest single therapeutic dose (according to the approved originator product labelling) soluble in 250 mL of buffer over the pH range of 1.2–6.8 at 37 ± 1 °C, i.e. in all buffers tested including buffers at pH 1.2, 4.5 and 6.8?

<Yes>/<No>

Solubility classification (*please refer to Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability*:[1]

<High>/<Low>

[1] Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; http://apps.who.int/medicinedocs/documents/s23245en/s23245en.pdf).

Name of the head of laboratory or person authorized to approve the certificate: _____

_____

Telephone: _____

Email: _____

Signature:

Date:

Annex 5

Guidelines on import procedures for medical products

Background

This document is a revision of the 1996 publication:

- Guidelines on import procedures for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, thirty-fourth report. Geneva: World Health Organization; 1996: Annex 12 (WHO Technical Report Series, No. 863; http://apps.who.int/medicinedocs/documents/s21962en/s21962en.pdf).

1. Introduction

1.1 Public health considerations demand that medical products should not be treated in the same way as ordinary commodities. Their manufacture and subsequent handling within the distribution chain, both nationally and internationally, must conform to prescribed standards and be rigorously controlled. These precautions serve to assure that patients receive quality-assured medical products, and to prevent the infiltration of substandard and suspected falsified medical products into the supply system.

1.2 The availability of medical products is sometimes limited, owing to economic constraints, difficulty in meeting norms and standards in their production, and lack of resources in their supply chain. These conditions lead to market penetration by substandard and suspected falsified medicines, which poses hazards for public health and forces the diversion of public health resources from other uses. In light of this, investments towards strengthening strategies at the customs level are deemed crucial to ensure quality-assured medical products for patients (*1*, *2*).

1.3 The global economy of scale and scope that characterizes modern trade requires continuous improvement in border control. This includes a departure from the traditional reactive control system to a risk-based and proactive approach. A country's risk-based surveillance scheme should identify risks and define the controls that will protect patients from substandard, falsified and unregulated medical products. A risk-based approach can improve the cost–benefit ratio with existing or reduced resources, through more effective and efficient controls. These guiding principles were endorsed in 1994 by the World Health Assembly in resolution WHA47.17 as having global relevance (*3*).

1.4 Within the context of its revised medicines strategy adopted in 1986 by the Thirty-ninth World Health Assembly in resolution WHA39.27 (*4*), the World Health Organization (WHO) developed *National drug regulatory legislation: guiding principles for small drug regulatory authorities* (*5*), which established a regulatory approach in line with the resources available within a small national regulatory authority (NRA), and were intended to assure not only the quality, but also the safety and efficacy of medical products distributed under its aegis.

1.5 The principles emphasize the need for the effective use of the *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce* (*6*, *7*). This constitutes a formal agreement between

participating Member States to provide information on any medical products under consideration for export, notably on its marketing authorization in the country of origin and whether or not the manufacturer complies with the *WHO good manufacturing practices for pharmaceutical products* (*8*).

1.6 To be fully effective, the WHO Certification Scheme needs to be complemented by administrative and other safeguards aimed at ensuring that imported products are in conformity with all particulars with the relevant marketing authorization, or for specific intended use, such as clinical trials, named patient programmes, emergencies or other means, as appropriate, within the importing country and that they remain secure within the distribution chain. Storage and transit facilities must provide protection against tampering and adverse conditions, and relevant controls must be applied at every stage of transportation (*9*, *10*).

1.7 Medical products containing substances controlled under international conventions have long been subjected to rigorous border control. Some of these controls, and particularly those designed to prevent the diversion and illicit interchange of products during transit, are relevant to all medical products and are therefore included in these guidelines. Only those medical products falling under the category of narcotic and psychotropic substances that are permitted by the relevant authorities shall be allowed to be imported as foreseen in the national and regional legislations and international treaties signed by the country.

2. Scope

2.1 These guidelines, which stem from the above considerations, were first developed in 1996 in consultation with NRAs, the pharmaceutical industry, the World Customs Organization and the United Nations International Drug Control Programme.[1] Following the recommendation of the 52nd Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), these guidelines were reviewed, adding critical and contemporary topics, such as: the e-commerce/internet-mediated distribution and the alert systems mechanism that should be in place between entry ports/NRAs/WHO, in case of unregistered, unlicensed, substandard and falsified medical products. Lastly, the glossary was revised and cross-references were added to other established WHO guidance documents.

[1] Since 1997, this has been part of the United Nations Office for Drug Control and Crime.

2.2 These guidelines are directed to all parties involved in the importation of medical products, including NRAs, competent trade ministries, customs authorities, port authorities and importing agents.

2.3 They are intended to promote efficiency in applying relevant regulations, to simplify the checking and handling of medical products for import and, inter alia, to provide a basis for collaboration between the various interested parties.

2.4 They are applicable to medical products destined for use within the country of import and are intended to be adopted into prevailing national procedures and legal requirements.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

falsified medical products.[2] Medical products that deliberately or fraudulently misrepresent their identity, composition or source. Any consideration related to intellectual property rights does not fall within this definition. Such deliberate or fraudulent misrepresentation refers to any substitution, adulteration or reproduction of an authorized medical product or the manufacture of a medical product that is not an authorized product.

import authority. The national agency responsible for authorizing imports (e.g. the ministry or department of trade or of imports and exports).

importation. The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

importer. An individual or company or similar legal entity importing or seeking to import a medical product. A "licensed" or "registered" importer is one who has been granted a licence for the purpose.

marketing authorization (product license, registration certificate). A legal document issued by the competent national regulatory authority that authorizes the marketing or free distribution of a medical 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 medical 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.

[2] This definition reflects the ongoing discussion in the Member State mechanism under the auspices of the World Health Assembly; see Appendix 3 in reference (*11*).

medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

national regulatory authority. The national agency responsible for the marketing authorization of, and other regulatory activities concerning, medical products.

screening technologies. The qualitative and/or semi-quantitative technologies that could rapidly acquire the analytical information or 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.

starting material. Any substance of defined quality used in the production of a medical product, but excluding packaging materials.

substandard product. An authorized product that fails to meet either its quality standards or its specifications, or both.[3]

unregistered product. A medical product that has not undergone evaluation and/or approval by the NRA for the market in which it is marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation. This medical product may or may not have obtained the relevant authorization from the national/regional regulatory authority of its geographical origin.

4. Legal responsibilities

4.1 The importation of medical products should be done in accordance with national and regional legislation and should be enforced by the NRA, customs and other relevant authorities.

4.2 National and regional guidelines providing recommendations on the implementation of legislation should be drawn up by the NRA or the ministry of health, if a NRA is not formally established, in collaboration with the customs authority and other responsible agencies and organizations.

4.3 The import of medical products should be undertaken by an importer or agency authorized by the NRA as per national and regional legislation. This normally does not include medical products in transit.

[3] These standards and specifications are normally reviewed, assessed and approved by the applicable national or regional regulatory authority before the product is authorized for marketing (*11*).

4.4 The import of all medical products should be channelled exclusively through custom posts or ports specifically authorized for this purpose. This is also applicable to medical products moving through the networking global e-commerce (such as the World Wide Web/internet).

4.5 All formalities on importation of medical products should be coordinated by the relevant authorities (customs, border control, or other as appropriate), NRA and/or ministry of health, as relevant. When justified by the workload, NRA officials may be stationed in a full-time position at such designated ports of entry. In carrying out the duties and formalities, the impact of possible delays on, for example, access to medicines and storage conditions of medical products, should be considered (for storage facilities, please see Section 9).

5. Legal basis of control

5.1 Subject to the exemptions specified in the national and regional legislation, and mentioned in paragraph 5.5 below, only medical products approved by appropriate documentation to be duly registered or authorized, as appropriate for marketing, should be cleared by relevant authorities.

5.2 The NRA should publish an updated list of authorized medical products and authorized importers permitted to import into the country for marketing. This does not include a list of exempted products and importers as per national or regional legislation. In all cases, close collaboration with the NRA is needed to verify that the product is authorized for importation and that there are no restrictions, temporary suspensions or withdrawals of marketing authorizations.

5.3 NRAs should be empowered to take legal actions and should collaborate closely with customs, police, judiciary and others to detect substandard and falsified products and to avoid the import of such products. Efficient and confidential channels for communicating information on these products and other illicit activities should be established between all responsible official bodies.

5.4 In countries where no formal system of product marketing authorization has been established, the importation of products is most effectively controlled by issuing permits in the name of the NRA to the authorized importing agency or agent. Within the framework of the WHO Certification Scheme, WHO provides a list with names and full addresses of those government organizations authorized to sign and issue a certificate of a

medical product (CPP).[4] NRAs receiving a CPP can use this list to check and verify whether the certificate they are receiving has been issued by the authorized organization (*6*, *7*). Additional measures that may be taken under these conditions include:

- provision by the NRA to the customs authorities and to the importing agency and agents of official lists of medical products permitted and/or prohibited to be imported;
- provision by the importing agent of certified information to establish that the product is authorized by licence for sale in the country of export.

5.5 The NRA should reserve discretionary powers to waive product authorization requirements in respect of consignments of medical products imported in response to emergency situations, specific intended use as in clinical trials, donation (*13*) and in response to requests from clinicians for limited supplies of an unlicensed product needed for the treatment of a specific named patient.

6. Required documentation

6.1 As a prerequisite to border and customs clearance, the importing agency or agent should be required to furnish the customs authority with the required documentation in respect of each consignment, except in cases of exemptions as per national or regional legislation (see also paragraph 5.5). For example, the following documents can be considered:

- documents issued by the NRA in the importing country, attesting that:
  - the importer is duly authorized to import the medical products;
  - the product is duly authorized to be marketed or permitted to be imported into the importing country;
- a batch-release certificate issued by the manufacturer;
- a safety data sheet, where applicable;
- a relevant invoice, bill or delivery slip for the batch, including the product name, batch number, quantity and expiry date;

[4] Information on competent authorities of countries participating in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce can be found in reference (12).

- any other documentation required by national or regional legislation for customs clearance, e.g. a certificate in accordance with the WHO Certification Scheme;
- any other document that should be issued by the competent authority of the exporting country, as applicable.

6.2 The NRA may grant exemptions to the above if the distribution is taking place through regional hubs or by international organizations.

7. Implementation of controls

7.1 Visual examination and preliminary screening technologies should be routinely undertaken by the customs authorities. Where possible, this should be done in collaboration with an inspector or enforcement officer of the NRA. The size of the consignment should be checked against invoices, bills or delivery slips, and attention should be given to the nature and conditions of the packaging and labelling. The external package should be compared with a standard when this is possible. (*Note*: spelling errors, low-quality printing and other defects may be signs of a substandard or falsified product. The external package should be intact and should not show any signs of damages or infiltrations that may change the inner content (*2*, *14–16*).)

7.2 Arrangements should be made by the NRA and other relevant authorities (i.e. national official control laboratories, ministry of health) for the sampling and subsequent physical and chemical analysis of medical products, based on established procedures following a risk-based approach.

7.3 When samples are taken for analysis to a governmental or other accredited quality control laboratory, prior to the release of the consignment as per national and regional legislation, the consignment should be placed in quarantine at approved sites. During this procedure, and throughout the time that the consignment is held legally under customs control, particular care must be taken to ensure that packages do not come into contact with potential contaminants. In addition, the package should be stored under appropriate conditions, as recommended on the label or in the safety data sheet, such as temperature, light and humidity limits (*14–16*).

7.4 A consignment suspected of being substandard, falsified or not authorized should be placed in quarantine pending the analysis of samples and forensic investigation. During this procedure, particular care must be

taken to ensure that packages do not come into contact with potential contaminants. In addition, the package should be stored under appropriate conditions as recommended on the label or in the safety data sheet, such as temperature, light, and humidity limits (*14–16*). Time is often saved if materials and reagents needed to undertake simple analytical tests and screening technologies are available at the customs border. The consignee should immediately be informed of such action; ideally, the authorized manufacturer or importer should also be promptly involved in the investigation.

7.5 National or regional regulations should define the responsibilities of the respective parties and the precise procedures to be followed by representatives from the NRA, police, border control, or ministry of health, as appropriate, for the relevant investigation and legal actions.

7.6 Falsified medical products and other products that have been imported in contravention of the law must be forfeited and destroyed, or otherwise dealt with in accordance with the procedures established by national and regional legislation, the records of which should be appropriately archived (*17*). The relevant authorities must be indemnified against any consequent legal actions and proceedings.

7.7 NRAs should notify other national or regional authorities and the WHO Global Surveillance and Monitoring System[5] of confirmed cases of imported substandard or falsified products, without delay, on the appropriate form.

7.8 The WHO Member State mechanism has prepared an overview on the different field screening devices, authentication and verification technologies, and "track and trace" models that can facilitate responses (*11*). Overt/covert technologies, forensic chemical markers, bar-coding and other forms of serializations can support the seamless tracking of products through the supply chain. The implementation of these and upcoming new technologies is considered one of the most prominent preventive measures to tackle substandard and falsified medical products.

[5] The WHO Global Surveillance and Monitoring System collects reports from focal points in the NRAs and international procurement agencies, which will forward the report via email to rapidalert@who.int where necessary. Focal points are encouraged to send any photographs, laboratory reports or other relevant documents as attachments. For further information, see reference (*18*).

8. Procedures applicable to pharmaceutical starting materials

8.1 When considering finished medical products, the responsibility for the quality assurance of starting materials (active pharmaceutical ingredients [APIs] and excipients) used in that product is vested in the manufacturer of the finished pharmaceutical product. Few NRAs have introduced authorization requirements for APIs and excipients (*10*).

8.2 Some national and regional authorities also exercise documentary and (in some cases) quality control through laboratory testing of APIs as a prerequisite to customs clearance.

8.3 Each imported pharmaceutical starting material should be accompanied by a warranty (or batch certificate) prepared by the manufacturer, for example, as recommended by the WHO pharmaceutical starting materials certification scheme (SMACS) (*19*).

8.4 Pharmaceutical starting materials purchased and imported from third-party vendors should be appropriately labelled in accordance with national regulations and accompanied by a certificate of analysis from the original manufacturer.

9. Storage facilities

9.1 Many medical products tend to degrade during storage and some need to be stored under specified conditions, such as 2–8 °C. All customs posts designated to handle consignments of medical products should be provided with secure storage facilities, with the required conditions including cold storage areas.

9.2 Customs and NRA officials should ensure that the appropriate environmental conditions are maintained for storage, and monitor that the equipment is maintained and in good working order. The facilities should be inspected periodically by the NRA.

9.3 The importer should inform the customs authorities in advance of the anticipated arrival of medical products, in order that they may be transferred from the international carrier to the designated storage facility without delay and, in appropriate cases, without breaking the cold chain.

9.4 Consignments of medical products and pharmaceutical starting materials, especially those requiring cold chain, should be accorded high priority for clearance through customs, to avoid extended storage.

10. Training requirements

10.1 When implementing these guidelines, the performance of the established procedures (including but not limited to personnel, documentation, procedures, and equipment) should be reviewed on an open-ended basis and improved in the light of on-site monitoring and evaluation. Workshops designed to facilitate efficient implementation of the guidelines and established procedures, and to foster collaborative approaches between the various responsible parties, should be organized by the NRA at intervals, in collaboration with the customs authority and other parties.

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Annex 6

Good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products

1. Background

In 2014, the 67th World Health Assembly resolution, WHA67.20, recognized that

> effective regulatory systems are an essential component of health system strengthening and contribute to better public health outcomes, that regulators are an essential part of the health workforce, and that inefficient regulatory systems themselves can be a barrier to access to safe, effective and quality medical products (*1*).

Nonetheless, regulators, globally, and in particular low- and middle-income countries, face an increasingly complex regulatory environment, with limited resources and a need to avoid duplication by communicating, collaborating, cooperating and forming coalitions to ensure product quality, safety and efficacy, as well as supply-chain security.

To this end, collaborative registration procedures (CRPs) with a view to accelerating national registrations and the regulatory life-cycle of products prequalified by the World Health Organization (WHO), or approved by reference stringent regulatory authorities (SRAs), have been developed and implemented (*2*, *3*). Based upon WHO's experience with the collaborative procedure for WHO prequalified pharmaceutical products and vaccines (*2*), and the pilot collaborative procedure of products approved by SRAs (*3*), it is possible to facilitate and accelerate national registration processes using this approach in the management of registrations and post-registration regulatory product life-cycle, based on reliance on the expertise and regulatory outcomes of recognized reference authorities.

Available assessment and inspection reports of reference SRAs or the WHO Prequalification Team (PQT), in addition to the registration dossiers, can facilitate and accelerate the adoption of national regulatory decisions by assuring national regulatory authorities (NRAs) of the positive benefit–risk of a product and its identical quality with the product already approved elsewhere, while allowing them to reflect their own judgement on the benefit–risk balance as it relates to their specific country situation and the legislation in place. This contributes substantially to savings in regulatory resources, improvements in the quality of regulatory decisions and faster availability of needed therapies for patients.

Nevertheless, it has been evident from experiences with the CRPs for products prequalified by WHO and pilot SRA collaborative registration, that it is critical to have clear NRA procedures to support acceleration of the availability of medical products, without compromising their quality, safety and efficacy, as well as providing an opportunity to harmonize dossier requirements and submission expectations.

Additionally, WHO has been facilitating regional collaborative procedures in the context of medicines regulatory harmonization in various regions. The regional mechanisms mobilize the existing regional resources to accelerate access to medical products through work-sharing and joint activities. These regional collaborative registrations have been established and supported in collaboration with their partners, in the East African Community, the Southern African Development Community, the Economic Community of West African States, the Caribbean Community and Common Market and the Association of Southeast Asian Nations. Similar initiatives are being developed for other regional economic communities and CRP can serve as an instrument to facilitate regional work-sharing.

2. Aims and objectives

This guideline is intended to serve as the NRAs' best practices model for implementing CRP and reliance and/or risk-based approaches in their overall marketing authorization system for medical products, and it should be read in conjunction with the full text of the collaborative procedures (*2*, *3*). The document also outlines the recommended approaches a NRA should take to process different types of applications, based on prior decisions and documentary evidence from the PQT, reference authorities and regional collaborative procedures.

The objectives of the document are to:

- describe the practical steps for NRAs to implement the collaborative procedure for prequalified products, SRA-approved products, or products from other reference authorities and regional harmonization;
- provide a resource for NRAs to effectively and efficiently implement collaborative reliance-based procedures for medical products, including vaccines.

This guideline is complementary to and consistent with the principles already elaborated in the draft guideline *Good regulatory practice: guidance for national regulatory authorities for medical products* (*4*). Furthermore, it supplements the guidance and best practices guidelines for marketing authorizations, which include *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for national medicines regulatory authorities* ("The Blue Book") (*5*), *Good review practices: guidelines for national and regional regulatory authorities* (*6*), and the *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 (*7*). These guidelines and best practices promote interagency communications, in order to facilitate greater regulatory convergence, thus increasing regulatory efficiency and quality of decisions, and improving patient access.

It should be remembered that WHO focal persons (as specified on the WHO website (*8*)) can be approached at any time, to provide additional explanations and assistance in the implementation of and practice of the collaborative procedure (Procedure) or other reliance approaches.

3. Scope

This guideline is focused mainly on the collaborative procedure for WHO-prequalified pharmaceutical products and vaccines and the collaborative procedure for pharmaceutical products and vaccines approved by SRAs. In addition, the principles, practical steps and tools described in this guideline may apply to a stand-alone setting outside the collaborative registration approach, for example, where the NRA specifies other authorities as reference authorities for its own reliance purposes. Although, the published Procedures apply for pharmaceutical products and vaccines, the general principles may also apply to medical devices, including in vitro diagnostics, for which the collaborative procedure guideline is under development.

This document provides recommendations to NRAs that are participating in the Procedures. Nonetheless, reliance or risk-based approaches follow the principles of good regulatory practices (GRP) and are also applicable and practised among the well-resourced and mature regulatory agencies. This enables a greater alignment and convergence with international standards for the NRAs, while they can also maximize efficient use of their own resources. Moreover, the NRAs are able to focus on value-adding activities and therefore reduce the burden of duplication of work done by trusted authorities and duplication of work for applicants/manufacturers.

In the case of national applications for registration of products assessed and prequalified by WHO or registered by reference authorities, it is possible that national applications can be submitted by other persons/legal entities that act on behalf of manufacturers with WHO-prequalified products or products approved by reference authorities. It is necessary to consider these options, and existing CRPs includes arrangements for such situations. If the applicant for national registration is not the same as the manufacturer with the WHO-prequalified or reference authority-approved product, the manufacturer with the WHO-prequalified or reference authority-approved product confirms to the NRA and WHO/reference authority by an authorization letter that the applicant is acting for, or pursuant to rights derived from, the manufacturer with the WHO-

prequalified or reference authority-approved product and that they agree with the application of the procedure in the country concerned.

Note: The CRPs cover initial registrations and variations/post approval changes.

4. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

abridged review. A limited independent assessment of specific parts of the dossier, or submission for suitability of use under local conditions and regulatory requirements, while relying on prior assessment and inspection outcomes from a reference authority or trusted institution to inform the local decision. The abridged review is based on assessment reports, and good manufacturing practices (GMP) inspection reports of reference authorities, plus specific parts of the *Common Technical Document* (CTD) (for example, stability data in Module 3 of the CTD (*9*)).

abbreviated review. See abridged review.

collaborative procedure (Procedure). The collaborative procedure to accelerate the national registration of prequalified pharmaceutical products and vaccines, or the collaborative procedure to accelerate the national registration of products approved by stringent regulatory authorities (*10*, *11*). The collaborative registration procedures cover initial registrations and post-registration variations/post-approval changes.

dossier. The regulatory submission package submitted to the national regulatory authority as an application for marketing authorization in line with the applicable country requirements and requirements specified in the respective Procedure guidelines (*2*, *3*).

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.

participating authority or participating national regulatory authority. A NRA that voluntarily agrees to implement this collaborative procedure and accept the task of processing applications for registration of WHO-prequalified pharmaceutical products and vaccines, in accordance with the terms of the Procedure. A list of participating authorities is posted on the WHO/PQT website, for pharmaceutical products (*12*) and for vaccines (*13*).

recognition. The routine acceptance of the regulatory decision of another regulator or other trusted institution. Recognition indicates that evidence of

conformity with the regulatory requirements of country A is sufficient to meet the regulatory requirements of country B.

reliance. An act whereby a regulatory authority in one jurisdiction may take into account or give significant weight to work performed by another regulator, or other trusted institution, in reaching its own decision.

reference authority. A regulatory authority that agrees to provide outcomes of its regulatory expertise (especially assessment and inspection reports) to applicants/authorization holders or inspected manufacturers; agrees to sharing of these documents with national regulatory authorities; and provides, under specified conditions in line with the principles of the Procedure, support to other parties involved in the Procedure.

stringent regulatory authority. The authority as defined by the interim definition in 2017 (*10*) and updated in 2018 (*11*).

verification. The procedure by which a regulatory authority only validates the product or submission, and ensures that the product for local marketing is equal or similar to that approved by the reference authority or trusted institution. Verification may be on the basis of assessment reports, GMP inspection reports and/or a certificate of pharmaceutical product of a reference authority.

5. Key principles

5.1 Risk-based approach

It is regulatory best practice for NRAs to implement quality risk management (*14*). In this respect, the NRAs should allocate resources and a level of effort that is proportionate to the level of risk. For example, the quality, safety and efficacy of a product prequalified by WHO, or approved by a reference authority, may be considered demonstrated compared to a product with no such prior reviews and/or approvals; therefore, the level of effort required to reach a final regulatory decision by a NRA should be differentiated accordingly.

5.2 Optimum use of available resources

Assessment activities should be aligned with resources available to the NRA. In addition, NRAs should be able to recognize their capabilities, limitations and the most efficient and effective approach to ensure that the patients are served and protected with the available resources. This includes removing duplication and identifying elements in the benefit–risk assessment that are critical in the local context. For innovative products, this may mean bridging the benefit–risk assessment done by reference SRAs to the local population, suitability of use in the local context, or stability data that suit the local climatic conditions.

5.3 Ensuring the "sameness" of products

The core principle for collaborative registrations is to ensure identical products (or that where differences exist, these are clearly stated) between the NRA and the reference NRAs, regardless of the approaches or assessment activities conducted by the NRA. The same pharmaceutical product or same vaccine is defined in the Procedures (*2*, *3*), as characterized by:

- the same qualitative and quantitative formulation;
- the same manufacturing site(s)[1] for the drug substance and finished product, including specific block(s)/unit(s), manufacturing chain, processes, control of materials and finished product, and, in the case of vaccines, also by the same batch-release scheme;
- the same specifications for the excipient(s), drug substance and finished product;
- the same essential elements of product information for pharmaceutical products, and, in the case of vaccines, by the same product information, packaging presentation and labelling.

Notwithstanding the principle and definition of the same product under the Procedures, the general principles in this guideline may be applied in other cases where the information is partly the same, but some differences between the products exist and are clearly stated and acceptable to the NRA. In those cases, the NRA should take additional precautions or steps, such as full review of corresponding data not assessed by the reference NRA, or inspecting the additional sites, as the case may be, while relying on shared information where sameness is applicable.

5.4 Compliance with nationally legislated regulatory requirements

Submissions and documentary evidence should be consistent and they should comply with applicable national legal and regulatory requirements. Collaborative registrations, or reliance approaches, do not substitute compliance with applicable national requirements; however, NRAs are encouraged to update,

[1] The sameness of the manufacturing sites for active pharmaceutical ingredients (APIs) and finished pharmaceutical product (FPPs) means that the specific site must be approved by the PQT or reference authority for the specific product under consideration, and included as part of the marketing authorization in the reference country. Any additional sites, regardless of GMP status, are not acceptable under this procedure. Any changes or variations to include additional sites should be approved by the PQT or the reference authority before inclusion in the submission to the participating NRAs.

where applicable, any legal or regulatory requirements in line with international best practices and harmonized requirements.

5.5 Flexibility to allow national regulatory authorities to adapt to their situations

No one size fits all; the best practices should permit each NRA to adapt and suit their own circumstances; for example, the practical steps and tools should be applicable across the maturity levels of NRAs, national strategies or procedures. It should be remembered that internationally harmonized practices and standards facilitate work-sharing and improve the compliance of applicants/manufacturers.

6. Essential elements of a registration system (in the context of collaborative registration procedures)

6.1 National regulatory authority agreement to participate in collaborative procedures of WHO-prequalified pharmaceutical products and vaccines or products approved by stringent regulatory authorities

To responsibly decide on participation in the CRP, the management of interested NRAs should have a good understanding of the principles of the procedure (*2*, *3*) and be aware of its benefits and feasibility, as well as commitments that are associated with participation. Proper study of the procedure is necessary. It is useful to understand to what extent current practices and policies permit the implementation of the process and how the participation corresponds with the NRA's developmental plans. The NRA management should be especially assured that there are no legal barriers preventing participation or hampering effective implementation of the procedure. This is not normally the case, as the CRP only represents the availability of additional expertise for NRA consideration in its decision-making process. Any pending issues can be clarified with the WHO focal person prior to a formal agreement on participation.

To successfully operate the procedure from the beginning, and to be able to inform local applicants about registration in this respect, it is important to prepare registration pathways for prequalified and reference SRA-approved products and to consider the following factors, especially those presented next.

The selection of focal persons who are responsible for communication with WHO and with reference national regulatory authorities

Optimally, focal persons for the registration agenda should be selected among NRA technical staff who are experienced with the registration process, from the submission of applications to adoption of decisions, with post-registration

regulatory activities. They should also be able to communicate with colleagues who are responsible for the end-to-end registration process, including staff responsible for all administrative steps, inspection, post-approval changes, pharmacovigilance and laboratory testing.

Focal persons for inspection activities should preferably be experienced GMP inspectors who are involved in inspection planning and in communication with other departments in the NRA and inspectorates in other countries.

It is important that focal persons are motivated and able to communicate in English; and that they understand the NRA application tracking process and have access to the internet. It is up to the focal persons to regularly collect and communicate to WHO, or reference SRAs, the relevant Procedure-related information, and share such information obtained from WHO or reference SRAs with responsible NRA units.

National regulatory authority application tracking systems

NRAs should adapt existing tracking systems, or implement appropriate tracking systems for applications for registration, that enable easy identification and monitoring of progress and timelines of all applications considered under CRP and other NRA pathways. All the NRA staff that are responsible for different aspects of a product throughout the life-cycle management should have access to the tracking systems.

The adoption of provisions to organize the Procedure process and meet the prescribed timelines

This may include some adaptation of the application screening process; changes in assessment practice; recording of applications in NRA databases and tracking systems; new timelines for certain registration steps; modified staff responsibilities; and/or arrangements of technical committee meetings. Adequate resources should be available to implement the Procedure, especially with regard to the capacity of involved personnel, access to a shared network, and communication with WHO and reference NRAs. In line with GRP, the changes should be reflected in relevant standard operating procedures (SOPs) and staff should be appropriately trained in the Procedure, registration pathway, and the process for reliance on outcomes from other regulatory authorities or PQT , as well as risk management science (risk-based approaches) and change management.

Regulatory fees

Regulatory fees for the Procedure applications should be decided by the NRA and this information should be publicly available to the applicants.

Information to applicants

Manufacturers should be properly informed about the existence of the new process; scope of the products for which this is applicable; possible deviations from standard national requirements; differences from current registration practices; and the benefits that come with participation. An example of information to applicants for registration is included in Appendix 1. A focal person should be identified who would respond to Procedure-specific questions and assist those submitting their first Procedure applications.

Communication

When informing WHO about participation in the Procedure(s), the NRA should mention the date it is prepared to implement the Procedure(s) and to accept the first applications for this/these registration pathway(s).

MedNet is an information platform where WHO or SRA assessment and inspection outcomes, and additional confidential information, are shared. Focal persons are invited, by WHO, to this internet-based communication platform, after it receives a duly signed agreement for participation. Each focal person must create their personal access passcode, in order to enter the shared information site. If requested, WHO can assist in MedNet learning. In the case of regional cooperation, other information platforms can be used.

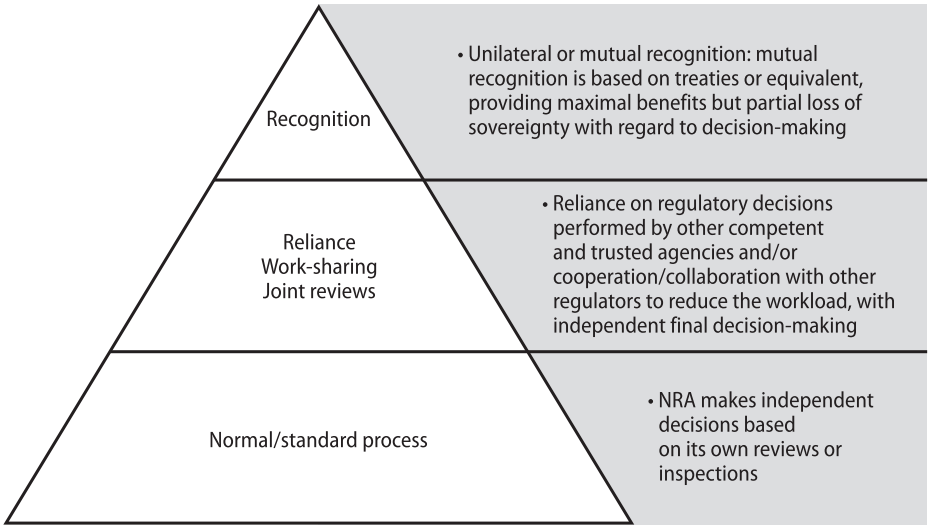
6.2 Registration pathways

NRAs should define and establish clear registration pathways, for example, for products with prior approval from reference SRAs; WHO-prequalified products; products through joint reviews or work-sharing; normal reviews; and fast-track mechanisms. This information enables manufacturers/applicants to select the most appropriate pathway and to provide the necessary documentary evidence applicable for each pathway as part of the dossier submission.

In-line with GRP, a robust registration system incorporates principles of good risk management that ensures that the level of control and resource allocation is proportionate to the level of public health risk associated with specific products. In this regard, NRAs should classify applications submitted for registration, based on the level of potential public health risk for each product. The risk class of a specific product may be determined by factors such as the route of administration; dosage form; formulation; development level (that is, new API or multisource product); competence of the companies, including compliance with regard to GMP; applicable WHO and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines, as demonstrated from past inspections; prior approval from reference authorities or WHO prequalification; and the scope of information available from the reference authorities or the PQT.

Fig. A6.1 shows an example of registration pathways for a NRA. At the base of the model is the normal registration pathway where the NRA independently performs all assessment and inspection activities in order to reach its own decision. Following this are different levels of cooperation or collaboration with other regulators, ranging from joint activities, work-sharing, reliance and, ultimately, recognition. It is important to note that the level of effort decreases as one goes up the pyramid, from independent full assessment at the base of the pyramid to complete reliance on decisions by others (recognition) at the top of the pyramid.

Fig. A6.1
Model for registration pathways for national regulatory authorities (NRAs)



NRAs may define the combination of these approaches and should clearly state the approaches applicable for collaborative registrations, that is, for products prequalified by WHO and for products approved by reference SRAs. NRAs should state the reference authorities for which recognition or reliance is applicable. It is suggested that where a list of reference authorities is stated, at the very least it should include the established reference SRAs.

6.3 Organization of assessment activities

NRAs should also consult the other applicable WHO publications that provide detailed arrangement for assessments (*5*, *6*).

A NRA has several options for organizing its assessment activities, based on its legal and regulatory framework, development plans and capabilities. The approaches described next may be adopted by the NRA.

Verification

Verification is not a scientific assessment but an administrative process to reach a regulatory decision, based on registration or authorization by a reference NRA or WHO prequalification. The NRA formalizes its decision by approving the product or submission and ensures the product for local registration and marketing conforms to the product as prequalified by WHO and approved by the reference NRA. This may require a policy, or a regulatory provision to facilitate the NRA to apply this approach. Verification should be applied where conformity with requirements of the reference authority or institution is sufficient to meet the requirements of the receiving authority or institution. This may apply to all or part of the submission.

Abridged/abbreviated review

Abridged/abbreviated review is a limited assessment of suitability of use under local conditions and regulatory requirements, while relying on prior assessment and inspection outcomes from the reference NRA or the PQT to inform the local decision. This approach focuses on value-adding activities in addition to the NRA's assessment activities and avoids duplication of the work already done by others. Desk review of inspection reports may be considered as a form of abridged/abbreviated review.

Note: These two options (verification and abridged reviews) are not mutually exclusive, as some NRAs may implement a combination of these approaches for the Procedures, where applicable. For example, some NRAs may recognize the PQT outcomes, since they address programmatic suitability for the countries for which prequalified products are mainly intended for use, while approvals from reference NRAs may require a combination of verification and abridged/abbreviated reviews to address the local context (e.g. benefit–risk in the local population; stability to allocate the storage conditions; shelf-life at the storage conditions prevailing in the country; risk management plans; and suitability of information for patients/health professionals, where applicable). Other special access mechanisms introduced by the reference SRA may address the local context in their review process, thereby enabling verification to be applicable in those cases.

The NRA should clearly identify the type of products and applications suitable for an abridged/abbreviated review or verification, as well as the abbreviated review timelines associated with those. To facilitate implementation, registration pathways, different templates and procedures, including SOPs, should

be in place to differentiate products or applications by the type of assessment to be conducted, that is, verification, abridged/abbreviated review, and /or full review. Additionally, the assessors should be trained accordingly. Sample templates for verification and abridged/abbreviated review are provided in Appendices 2 and 3, respectively.

Secondary review

NRAs may perform secondary reviews of the shared assessment and inspection outcomes from the PQT or reference NRA. Moreover, this approach may be essential where the NRA is involved or participates in the initial reviews, for example, joint reviews between the NRA and the PQT or in special access mechanisms by reference SRAs that have provisions for NRA participation. As a result, the NRA's input may be incorporated into the final decision of the PQT or the reference SRA, thereby facilitating a concurrent regulatory decision where a parallel submission has been made.

Full review

For full review, a NRA is capable, and has the resources and expertise, to carry out a full assessment of quality, preclinical and clinical data (safety and efficacy) of products with no prior approval elsewhere. This route is not recommended for the collaborative procedures, as it is considered a duplication of effort.

Verification, abridged review, and secondary reviews facilitate better resource management for the NRAs, shorten timelines compared with a full review and could improve the quality of the review. More importantly, the quality and availability of the full reports from the reference authorities are key to this process.

The NRA reserves the right to re-route any application to the normal review process if the application does not fulfil the intent of the verification or abridged/abbreviated or secondary review process, and the applicants should be made aware of this.

6.4 The effectiveness of risk-based review strategies

What metrics should be used to determine the effectiveness of risk-based review strategies in addressing the intended problems of volume, capacity and review effort, without compromising quality?

Timelines

NRAs should set timelines that take into account the level of reliance or different registration pathways, for example, recognition, reliance, work-sharing/joint reviews and full assessment. The timelines should be based on the NRA's existing

resources and benchmarking with other NRAs. Tracking mechanisms should be in place, and these should be able to track and account for the regulator's time and applicant's/manufacturer's time during the review process. Information on a predefined time for receipt of questions and provision of answers should be defined by the NRA. Typically, this is defined as 30 calendar days for the applicant/manufacturer to respond or provide additional information.

For the Procedures, the recommended timelines are specified in the Procedure, that is, the NRA should reach a decision within 90 days of the regulatory time and communicate such decision to the applicant within 30 days of reaching it. The NRAs are encouraged to streamline national processes as outlined in Sections 6.2 and 6.3.

The timelines are also affected by the quality of the submissions and the number of review cycles.

Other metrics

Other metrics that could be useful for reliance models or the Procedure include: the proportion of products approved/disapproved/withdrawn through these risk-based approaches, relative to the total approvals; the number of review cycles relative to completion of assessments; and review effort and quality of decisions.

The NRA should be able to track these metrics for each registration pathway, to assess the relative efficiencies and effectiveness of the adopted pathways; to evaluate not only accelerated decision-making, but also the impact on regulatory burden and quality of regulatory decisions; and to identify areas for improvement.

6.5 Steps of the common regulatory pathway

In principle, the CRP follows the key steps of a national registration process; however, certain steps can be simplified. According to NRA practice, the points presented next should be considered and incorporated into internal SOPs.

Procedure initiation

When the Procedure commencement date is announced by a NRA, the Procedure is applicable to new submissions to the NRA, or for products pending registration in the NRA. In situations where the applicant wishes to apply the Procedure to an application that is already pending within the NRA, the applicant should first update the dossier to ensure that the technical part of the information is the same as that approved by the PQT or reference NRA, and any deviations should be clearly stated. It is up to the NRA to decide whether or not it is more convenient to switch to the Procedure to complete the registration or to grant registration via the normal pathway, and inform the applicant accordingly (e.g. when the assessment is finished and registration is imminent).

Each applicant initiates the Procedure by submitting CRP-specific documents as part of a registration application. The correct fees should be paid and the date of receipt of the dossier/application recorded by the NRA.

Dossier format and content

Dossiers should be submitted in the appropriate format, as required by the respective NRAs, that is, hard copies, electronic format in portable document format (PDF), or electronic common technical document (eCTD), as applicable. Notwithstanding the submission format to the respective NRAs, the content of the dossier should enable verification of the sameness of the products as those of the PQT or the reference NRAs. The dossiers should be updated to include all variations approved by the PQT or reference NRA before the national submission. A current quality information summary (QIS or QIS-SRA(crp)) should be provided, where applicable, subject to exceptions in line with the PQT product-specific procedures. Additional NRA-specific documents should be included, such as application forms, product information and labelling in national format, if required. For detailed guidance on submission format and content, please refer to Section 4.2 in reference (*2*) and Section 4.1 in reference (*3*).

Screening to validate the application

The NRA should properly screen the applications, to ensure that the product is eligible for the Procedure and that all the required documentation is provided, as per the NRA procedures and CRP process. Use of a checklist is recommended (Appendix 4). The submission of the dossier should be recorded using the existing procedures for storage and management of applications. Formal deficiencies in the submitted application and the dossier should be communicated to the applicant, in line with the national practice. The screening should be performed quickly (e.g. within 2 days) and applicants should be given a defined time to respond (e.g. 30 days).

Decision on the Procedure and informing WHO

Having a complete valid CRP application, the NRA promptly decides whether or not to apply the Procedure, marks in its records that the product is being processed under the CRP, and promptly informs WHO accordingly. In the case that the NRA decides to register the product in line with the Procedure, the PQT or reference NRA shares assessment and inspection reports, typically within 30 days of receipt of the request and/or expression of interest from the applicant to participate in the CRP. This starts the 90-day regulatory period in which NRAs should decide on the registration in line with the Procedure.

Processing the application

To maximize the benefits of the PQT or reference NRA outcomes, the NRA is recommended to follow the risk-based review process, that is, to verify that the prequalified or reference NRA-approved product and national submissions are the same, and review country specific requirements, for example, prescribing and labelling information. The need for a special risk management plan follow-up should be considered. Appendix 2 is a template for verification, representing a simplified process to verify product similarity. Appendix 3 is a template for an abbreviated/abridged review, which includes verification of detailed requirements and limited scientific assessment to suit the local context, as required. Where applicable, as per country procedure, the report is tabled for consideration by a competent technical committee as soon as practicable, and within 90 calendar days of the Procedure.

Inspections

If the NRA inspectorate is involved in assessing compliance with GMP and other practices, and in data verification, the inspectors have available PQT or reference NRA inspection reports to facilitate the development of their judgement. It is advisable to organize a desk-review process instead of on-site inspections (*7*).

Laboratory testing

Preregistration laboratory testing of submitted samples is not recommended during CRPs. Instead, post-registration risk-based testing is recommended. The NRA should assess whether it is feasible to perform independent testing in its laboratories, or whether special arrangements or partnerships are necessary. WHO advice can be sought in relation to quality testing, and results from WHO-organized testing for prequalified products, including lot-release testing results for vaccines, can be shared. In other words, for vaccines, reliance on testing done by national quality control laboratories from reference authorities should serve as the basis for CRPs.

Product information

Prescribing and labelling information should be submitted in the standard national format. In the case of labelling, a mock-up presentation is normally sufficient instead of a definitive printed package of the product to be marketed, which may be difficult to produce before registration. Indications should be checked against national therapeutic guidelines, when applicable. The content of the product information should correspond to the information approved by the PQT or reference NRA. Different information content must be justified and can represent a deviation from prequalification or approval by the reference NRA.

For prequalified vaccines, the product information and labelling submitted to the NRA should be the same as that approved by the PQT.

Communication with applicants

After the NRA review process, issues to be communicated to WHO, the reference NRA, or the applicant are summarized and communicated through the normal communication procedures of the NRA. Should the applicant fail to respond in time or to provide other necessary cooperation, the NRA is entitled to terminate the procedure and to process the application in line with normal registration procedures. Such termination is communicated to the applicant and to WHO or the reference NRA.

Decision on registration and communication to WHO

The NRA may decide to refuse to register or issue a registration. Reasons for refusal and/or conditions for registration, including post-registration commitments, should be formally prepared and concurrently shared with the applicant and WHO within 30 days of the decision. The registration number, date, clock-stop days and – if applicable – deviations from the PQT or reference NRA decisions, should be notified to WHO and the reference NRA, as applicable.

Regulatory time measurement

The regulatory registration time for the purpose of the Procedure starts on the day on which the assessment and inspection reports are shared, or when a valid submission is received by the NRA (whichever is later), and ends on the date of registration. In the event of queries being raised, the clock should stop until the applicant has addressed the concern. Clock-stop time is not included in the registration time.

6.6 The focus of reviews in abridged/abbreviated assessments

The level of abridged review may vary depending on the type of product, for example, generic versus innovative product, or prescription versus non-prescription medicine, vaccines versus chemical entities, or the collaborative procedure, that is, based on WHO prequalification or reference NRA approval, or through special access mechanisms.

Quality review

Reliance is generally straightforward, as quality standards are often common across major jurisdictions, and those determined by the PQT or reference SRA are considered adequate for most NRAs. Nonetheless, applicant/manufacturer filing strategies may complicate reliance mechanisms, owing to potential

differences in indications and data and quality specifications for different markets. Notwithstanding this, the QIS or QIS-SRA(crp) is a useful document to facilitate the verification or abridged review for quality documentation, subject to exceptions as per Section 6.5, "Dossier format and content". It allows the applicant to clearly state differences, if any, for example, storage conditions and shelf-life for reference NRA approvals and easy verification of product sameness, thereby saving significant NRA resources in verification or abridged reviews. Verification or abridged reviews may focus on:

- *for APIs/drug substances*: general properties that enable identification of the potential impact of critical quality attributes on the performance of the finished product/drug product (e.g. pK_a, solubility, particle size distribution, polymorphism, where relevant); manufacturing site; manufacturing process (e.g. for APIs, purification crystallization, micronization; for drug substances, producing cell line, cell banks, purification methods, presence of viral inactivation steps); quality standards and specifications and test methods of the API/drug substance; container closure system; retest period; and storage conditions;
- *for biological substances*: the description of the molecule, including features such as glycosylation/post-translational modifications; "artificial" modifications (amino-acid substitutions, pegylation); and molecular size.
- *for FPPs/drug products*: description; unit and batch formula; production batch sizes; manufacturing site; manufacturing process; quality standards and specifications and test methods of the excipients and FPP/drug product; container closure system; shelf-life, including in-use period; and local storage conditions.

Note: In some cases, for example, approvals by reference SRAs, the NRAs may need to perform an additional independent review of stability data if the climatic conditions, or container closure system, and consequently the stability data, are not the same, but this does not preclude reliance on other quality aspects under the Procedure.

Clinical review

The NRAs should ensure the indications are consistent with national treatment guidelines, where applicable. For the collaborative procedure for reference SRA-approved innovative products, reliance tends to be more challenging, notwithstanding the same dataset that had been reviewed by the reference SRA, as the benefit–risk may not be identical in the different populations or settings. Additionally, with the adoption of various facilitated registration

mechanisms for innovative medicines, including conditional approvals or rolling submissions, the NRAs may not have similar registration pathways to facilitate approvals of such products. With this in mind, the concept of the bridging report (*15*) is recommended for the CRP for products approved by SRAs, to address differences in the target population relative to the population in the clinical trials; epidemiology and other features of the disease; concomitantly-used medicines; and, hence, the interaction potential; local therapeutic and diagnostic modalities; and other factors that can substantially lead to a different benefit–risk balance. A risk management plan should be reviewed from the point of view of local relevance.

Post-approval changes

Post WHO prequalification or reference NRA authorization, commitments should be considered and the relevant ones may be included in the local NRA registration decision. The applicants should be committed to reflect or at least notify post-approval changes. Deviations of the locally registered product from the PQT- or reference authority-approved product should be reported.

A model example of information, documentary evidence and assessment activity of a NRA applying the reliance model is provided in Appendix 5.

6.7 Managing product differences

Some differences could exist between the application dossiers, in particular for SRA-approved products. These should be clearly stated, and, in some cases, the NRA has to perform its own assessments of such data where the proposed changes were not covered in the original submission/assessment performed by reference SRA. Some common potential differences are highlighted below for illustrative purposes:

- different presentations without changing the packaging materials;
- regional labelling requirements;
- storage conditions and shelf-life.

Any change beyond the above would result in the product being considered different from the prequalified product or that approved by the reference NRA.

6.8 Managing variations/post-approval changes

Post-approval changes (variations) require significant resources for both manufacturers and the NRAs and pose a significant threat to the continued supply of quality-assured medicines and vaccines in the target countries. More

specifically, it is generally reported that it takes 2–4 years to complete approval of moderate to major change(s) in every country where a global product is registered. Consequently, these long regulatory approval timelines not only make the supply chain complex, with different versions of the product required to supply multiple countries, but also consume substantial resources for both manufacturers and NRAs.

To ensure the absence of deviations between the WHO-prequalified product, or reference NRA-approved product and the NRA-registered product, variations should only be submitted to the NRA after acceptance by the PQT or approval by reference NRAs, to ensure sameness of the products throughout the product life-cycle.

While it is expected that many NRAs have the expertise and capacity to review variations, there is significant risk associated with reviewing variations to a product approved by a different authority. Variations should be reviewed by the originating authority, to avoid the possibility/likelihood of different changes being accepted in the originating and receiving countries over time. This results in the product in the receiving country no longer being the same as that approved by the originating authority, that is, different from the product for which safety, efficacy and quality have been established.

The *WHO general guideline on variations to multisource pharmaceutical products* (*16*) provides a recommendation for expanding the capacity of individual NRAs through work-sharing and recognition of the decisions of other NRAs in the network, and convergence of regulatory requirements, thus avoiding unnecessary repetition of evaluations of the same variation by multiple NRAs.

Categorizations and management of variations

Variation terminology, fees and administrative requirements are subject to national regulations. Variations to the product that have been registered by the CRP registration pathway should first be submitted to the PQT or reference NRA for assessment. Post-approval variations differ, depending on the CRP route followed. The PQT will only categorize variations for prequalified products on a product-specific basis (*17*, *18*), while accepting SRA-approved variations and their categorization.

Once approved by the PQT or reference NRA, the applicant may implement the change and notify the NRA of such immediately (within 30 days). Variations submissions to NRAs should clearly indicate that the product has been registered by the CRP registration pathway, with same dossier, including any additional information based on PQT or reference NRA assessment, and evidence of such approval by submission of the "PQT or reference NRA approval letter" (for minor or major variations) or PQT or reference NRA acknowledgement

email (for notifications). The PQT or reference NRA will share the variation outcomes with the NRA, for variations that require prior approval.

To monitor the post-prequalification changes and to verify the compliance of manufacturers in submissions of variations, participating NRAs can benefit from visiting the PQT or reference NRA's website. WHO or reference NRA public assessment reports are continually updated with regard to the lists of approved variations.

The notifications that affect administrative information relevant to WHO or the reference NRA only are not included. Such administrative changes relevant for individual participating NRAs should be submitted in line with national legislation and guidance. As regards reference NRA-approved products, classification of variations may somewhat deviate from the PQT scheme, but similar principles of variation management should be followed, benefiting as much as possible from publicly available information.

Processing variations by the national regulatory authorities and communication to WHO

Like the assessment during the registration process, the NRA may consider performing verification based on the shared assessments of the variation by the PQT or reference NRA, instead of independent review, and issue an acknowledgement of receipt or approval within 30 days.

If a change is rejected by the NRA, this should be communicated to the applicant with an explanation for the rejection. As appropriate, there should be an opportunity for dialogue between the NRAs, WHO and the applicant, as necessary, with the aim of resolving the NRA's concerns with the application. Any significant deviations resulting in the NRA-registered product not being the same as the PQT- or reference NRA-approved product should be communicated to WHO and the reference NRA within 30 days, at which point the corresponding product is no longer considered to be in the CRP process.

Non-administrative changes submitted only to the NRA should not be approved or accepted unless justified. If the NRA decides to approve/accept a variation that is not approved or accepted by the PQT or reference NRA, the NRA should record the differences between the PQT- or reference NRA-approved and national product. The NRA informs WHO of such variations if they are major, for updates in the online list of products registered through the collaborative procedure. Depending on the nature of such variations, the product can be treated as different from the prequalified or the reference NRA product in the given parameters. As already discussed, in such cases when the NRA-registered product is no longer considered the same as the PQT- or reference NRA-approved product, the product is no longer considered to be in the CRP process.

6.9 Registration renewals: national regulatory authority and WHO actions

Renewals

The validity of registration and renewal of registration by the NRA will be based on the existing guidelines for renewal of registration of products applicable in each NRA. The renewal process represents a good opportunity to review whether all applicants' commitments were satisfied and to verify consistency (e.g. verifying all approved variations; requalification in the case of a prequalified pharmaceutical product; renewal or changes to the conditions of registration in the reference NRA are up to date for the nationally registered product) between the PQT, reference SRAs and national registration conditions.

Withdrawals, de-registrations, suspensions and de-listings

In cases where a prequalified product is withdrawn from prequalification by the manufacturer, it is suspended or de-listed by the PQT, who will then promptly, through the restricted-access website, and subject to the above-mentioned obligations of confidentiality and restrictions on use, inform the relevant participating NRA accordingly, providing the reasons for the withdrawal whenever required to do so. The same procedure applies for products registered through the collaborative procedure for SRA-approved products.

If a participating NRA de-registers or suspends the registration of a prequalified or SRA-approved product for any reason, the participating NRA informs the PQT or reference SRA thereof (together with the reason for this decision). The information should be provided without delay whenever product quality, safety or efficacy is concerned, and, in other cases, within 30 working days. A participating NRA is encouraged to consult the PQT or reference SRA before adopting a decision about de-registration or suspension of registration of a WHO-prequalified or SRA-approved product.

Other matters

In the event of a Notice of Concern (NoC) issued by the PQT or reference SRA for a site (GMP, good clinical practices [GCP] and good laboratory practices [GLP] issues) on a product registered under the procedure, the NRA should follow the position of the PQT or reference SRA, unless justified to decide otherwise. Reasons for not following the PQT or reference SRA decision should be communicated to the PQT or reference SRA.

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5. Marketing authorization of pharmaceutical products with special references to multisource (generic) products: a manual for national medicines regulatory authorities (NMRAs), 2nd ed. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf?sequence=1, accessed 15 February 2019).
6. Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 9 (WHO Technical Report Series, No. 992; http://apps.who.int/medicinedocs/documents/s21902en/s21902en.pdf, accessed 15 February 2019).
7. 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. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization 2018 (WHO Technical Report Series, No. 1010; http://apps.who.int/medicinedocs/documents/s23457en/s23457en.pdf, accessed 15 February 2019).
8. World Health Organization. Collaborative procedure for accelerated registration (https://extranet.who.int/prequal/content/collaborative-procedure-accelerated-registration, accessed 15 February 2019).
9. ICH harmonisation for better health. M4: The Common Technical Document (https://www.ich.org/products/ctd.html, accessed 15 March 2019).
10. Definition of stringent regulatory authority. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-first report. Geneva: World Health Organization; 2017:34–5 (WHO Technical Report Series, No. 1003; https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_1003_full-version.pdf?ua=1, accessed 15 February 2019).

11. Definition of "stringent regulatory authority". In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018:43–4 (WHO Technical Report Series, No. 1010; https://apps.who.int/iris/bitstream/handle/10665/272452/9789241210195-eng.pdf?ua=1, accessed 15 February 2019).
12. World Health Organization. Essential Medicines and Health Products: prequalification of medicines (http://www.who.int/prequal/, accessed 15 February 2019).
13. World Health Organization. Immunization standards. Revised procedure for expedited review of imported prequalified vaccines for use in national immunization programmes (http://www.who.int/immunization_standards/vaccine_quality/expedited_review/en/, accessed 15 February 2019).
14. ICH harmonised tripartite guideline. Quality risk management Q4. Step 4 version. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2005 (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf, accessed 15 February 2019).
15. Appendix 6: Requirements for provision of a bridging report for reference SRA-approved pharmaceutical product and vaccines for consideration of registration in participating countries. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 11 (WHO Technical Report Series, No. 1010; https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex11.pdf, accessed 16 February 2019).
16. WHO general guidance on variations to multisource pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 10 (WHO Technical Report Series, No. 996; http://apps.who.int/medicinedocs/documents/s22407en/s22407en.pdf, accessed 15 February 2019).
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18. Guidance on variations to a prequalified vaccine. Geneva: World Health Organization; 2015 (http://www.who.int/immunization_standards/vaccine_quality/PQ_VXA_Variations_V7.pdf?ua=1, accessed 15 February 2019).

Appendix 1

An example of information to applicants for registration via the WHO collaborative registration procedure

Registration of WHO-prequalified pharmaceutical products and vaccines/products approved by stringent regulatory authorities (SRAs) through the collaborative registration procedure

Since [*date*], [*name of the NRA*] participates in the World Health Organization (WHO) collaborative registration procedure (CRP) for WHO-prequalified pharmaceutical products and vaccines/collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities (SRAs), and accepts applications for registration in line with this procedure (hereinafter referred to as "the Procedure").

This Procedure serves to facilitate and accelerate the registration of products that have already been assessed and listed as prequalified by the WHO Prequalification Team (PQT)/SRAs. Detailed information about the CRP can be obtained at: https://extranet.who.int/prequal/content/collaborative-registration-faster-registration/ https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras

All applicants for national registration of WHO prequalified products/SRA-approved products are encouraged to use this registration route. With this pathway, **finalization of the valid application is expected within 90 days of regulatory time**. Subject to [*name of the NRA*]'s previous agreement, the Procedure is also applicable to pending WHO prequalified products/SRA-approved products already in national registration. Specific arrangements may be necessary.

[*Name of the NRA*] reserves the right to use the standard national registration route or to switch to it during the CRP, in case of specific products (for example, products not included in national treatment/vaccination guidelines) or lack of the applicant´s cooperation.

Applicants wishing to use this registration route should:

1. Notify WHO/the SRA of their intention to use this Procedure for registration of a particular product by sending the appropriate notification form (Appendix 2/Appendix 3 Part B) to WHO/the SRA, as outlined on the WHO website. If the applicant for national registration is different from the manufacturer with a prequalified product/SRA-approved product, the

mutual agreement between the applicant and the manufacturer is necessary and the notification to WHO/the SRA has to be sent by the manufacturer.

2. Follow the national guidance to applicants for registration, available at [*insert reference for national guideline*]. More importantly, the following should be considered:

   a. The national Application form and requirements on samples and labelling stay in place.
   b. "WHO Collaborative Procedure"/"SRA Collaborative Procedure" should be indicated as the proposed registration pathway in the national application form or in the covering letter.
   c. The Expression of Interest form (Appendix 3 Part A/Appendix 7of the Procedure), as outlined on the WHO website, has to be submitted.
   d. The technical content of the dossier has to correspond exactly to that submitted and currently approved by the PQT/SRA and as specified in the corresponding Procedure guidelines. The dossier has to be updated to reflect all post-prequalification variations approved by the PQT/SRA and accompanied by the appropriate current quality information summary (QIS)/QIS-SRA(crp). All variations still pending at the PQT/SRA have to be notified, and deviations from the prequalified product have to be clearly declared in the expression of interest form (Appendix 3 Part A/Appendix 7 of the Procedure).
   e. Additional, country specific requirements are: _____

3. A fee of _____ per product is charged for new applications considered under this procedure.

In situations where the applicant wishes to apply the Procedure to an application that is already pending with [*name of the NRA*], the applicant should first update the dossier to ensure that the technical part of the information is the same as that currently approved by the PQT/SRA, as applicable.

The post-prequalification variations should be submitted to [*name of the NRA*] within 30 days from the PQT/SRA approval. The PQT/SRA approval letter should be attached.

In case of questions/requests related to the CRP, the [name of the NRA] focal person's contact information is as follows: [*name of the NRA focal person for the CRP and their contact information*].

Appendix 2

Verification for product submitted under the WHO collaborative procedure

Note [***instructions on using the template***]**:** This template is provided for verification of products to be registered nationally through the WHO collaborative procedure for prequalified products, or products approved by reference stringent regulatory authorities (SRAs). National regulatory authorities (NRAs) are free to modify the template as they deem fit, to suit their specific requirements.

1. Product details

Dossier aspects to verify	
Proprietary product name	
International Nonproprietary Name (INN) of the active pharmaceutical ingredient (API)/ drug substance, strength, pharmaceutical form	
Applicant	
Date of application	
Application number (assigned by NRA)	
Type of product/registration	
Reference authority	
Declaration from the applicant	

2. Product quality

Dossier aspects to verify	Comments (including confirmatory statements of sameness)
Marketing status in reference SRA or WHO prequalification status	
Name and complete address of the applicant	

Table *continued*

Dossier aspects to verify	Comments (including confirmatory statements of sameness)			
Name and complete address (including specific unit/blocks) of the API/drug substance manufacturer(s)				
Name(s) and complete address(es) (including specific unit/blocks) of the manufacturer(s) of the finished pharmaceutical product(s) [FPP(s)] or biological drug products(s) (DP(s)), including the final product release if different from the manufacturer				
Description (visual appearance)				
Composition	**Component and quality standard**	**Function**	**Quantity per unit (mg)**	**%**
	Total			
Specifications for the finished product				
Container closure system (including pack sizes, container size or volume)				
Stability summary and conclusions (including the storage statement and shelf-life)				
Lot/batch-release documents				
Assessor's comments on the product quality				

3. Product information

Dossier aspects to verify	Comments
Is the information for the health-care professional provided as approved by the reference SRA or WHO Prequalification Team (PQT)?	
Is the information for the patient/user (patient information leaflet) provided as approved by the reference SRA or PQT?	
The information does not contradict national therapeutic guidelines	
Assessor's comments on the product information	

4. Labelling

The following minimum information appears on the label:

Dossier aspects to verify	Comments
Is the labelling of outer packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on outer packaging as per national requirements	
Is the labelling of internal packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on internal packaging as per national requirements	
Assessor's comments on the product labelling	

5. Applicant commitments to the WHO Prequalification Team or reference stringent regulatory authority

State any commitments by the applicant to WHO or to the reference SRA that may require follow up.

Examples:

- The applicant undertook to continue long-term testing of [*INN of API*] for a period of time sufficient to cover the whole provisional retest period [*period ending month/year*].

- The applicant undertook to continue long-term testing of [*FPP reference number, trade name [INN of API], strength, pharmaceutical form*] for a period of time sufficient to cover the whole provisional shelf-life [*period ending month/year*].
- The applicant committed that three consecutive production batches would be prospectively validated and a validation report – in accordance with the details of the validation protocol provided in the dossier – would be made available as soon as possible, for evaluation by assessors or for verification by the WHO inspection team.

6. General national regulatory authority review comments

7. Assessment of responses to [*list of questions/list of outstanding issues/request for supplementary information*]

For each question:

Question:

Response from the applicant:

Assessment of response:

Appendix 3

Abridged/abbreviated review for product submitted under the WHO collaborative procedure

Note [*instructions on using the template*]**:** This template is provided as a recommended approach including a combination of the verification and abridged review of products to be registered nationally through the WHO collaborative procedure for prequalified products, or products approved by reference stringent regulatory authorities (SRAs). National regulatory authorities (NRAs) are free to modify the template as they deem fit, to suit their specific requirements. The assumption is that the NRA has access to the final assessment outcomes from WHO or the reference SRA in the form of assessment and inspection reports, including the quality information summary (QIS), to facilitate the abridged review. This template does not cover situations where the NRAs have no access to this confidential information in order to enable the verification of the specific product quality-related outcomes from WHO or the reference SRA. The different sections, for example, quality, clinical, product information and labelling, as well as risk management plans (RMPs), may be separated into different templates, especially where different teams/disciplines are involved in the review process.

1. Product details

Dossier aspects to verify	
Proprietary product name	
International Nonproprietary Name (INN) of the active pharmaceutical ingredient (API) or drug substance, strength, pharmaceutical form	
Applicant	
Date of application	
Application number (assigned by NRA)	
Type of product/registration	
Reference authority	
Declaration from the applicant	

2. Product quality

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Name and complete address of the applicant			
Name(s) and complete address (including specific blocks/units) of the manufacturer(s) of the finished pharmaceutical product(s) [FPP(s)] or biological drug products(s) (DP(s)), including the final product release if different from the manufacturer			
Drug substance or active pharmaceutical ingredient (name, manufacturer)			
Name of API/drug substance			
General properties that may affect the performance of the finished product (for example, polymorphism, solubility in physiological media)			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Name and address(es) (including specific blocks/units) of the manufacturer(s) of the API(s)/drug substance			
Control of the API/drug substance (including the specification reference number, version and date – the copy of the specification may be included as an attachment to the report)			
Analytical procedures (including the analytical procedure reference number, version and date – the copy of the analytical procedure may be included as an attachment to the report)			
Container closure system			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission				NRA submission				Comments
Stability summary and conclusions (including storage statement and re-test period)									
Finished pharmaceutical product (FPP)/drug product (DP)									
Description									
Composition	**Component and quality standard**	**Function**	**Quantity per unit (mg)**	**%**	**Component and quality standard**	**Function**	**Quantity per unit (mg)**	**%**	
	Total				**Total**				

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission		NRA submission		Comments
Manufacturer (name, address (including specific block/unit) and responsibility)					
Commercial batch size and batch formula	**Proposed commercial batch size(s) (for example, number of dosage units)**		**Proposed commercial batch size(s) (for example, number of dosage units)**		
	Component and quality standard (and grade, if applicable)	**Quantity per batch (kg/ batch)**	**Component and quality standard (and grade, if applicable)**	**Quantity per batch (kg/ batch)**	
	Total		**Total**		

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Narrative description of the manufacturing process (no need to compare the whole manufacturing process – one can just look at the blank master production document reference number, version and date, together with information on the site)			
Control of FPP/DP (state the specification reference number, version and date – a copy of the specification may be included as an attachment to the report)			
Analytical procedures (including the analytical procedure reference number, version and date-- a copy of the analytical procedure may be included as an attachment to the report)			

Table *continued*

Dossier aspects to verify	WHO Prequalification Team (PQT) or reference SRA submission	NRA submission	Comments
Container closure system (including pack sizes, container size or volume)			
Stability summary and conclusions (including the storage statement and shelf-life)			
Lot/batch-release documents			
Assessor's comments on the product quality			

3. Clinical safety and efficacy

Pharmacokinetic/safety/efficacy-related information used for PQT or reference SRA approval		
Type of study	"X" in appropriate box	Comparator product, where applicable
Bioequivalence/comparative pharmacokinetics		
Biowaiver based on Biopharmaceutics Classification System (BCS) biowaiver		
Additional strength biowaiver		
Clinical data		
Comparative pharmacodynamic and potential immunogenicity (for biologicals)		
Other (please specify)		
Assessor's comments on pharmacokinetic/safety/efficacy-related information		

Bioequivalence/comparative pharmacokinetics			
Dossier aspects to verify	**PQT or reference SRA submission**	**NRA submission**	**Comments**
Study #			
Study title			
Clinical facility (or the contract research organization)			

Table *continued*

Bioequivalence/comparative pharmacokinetics			
Dossier aspects to verify	**PQT or reference SRA submission**	**NRA submission**	**Comments**
Bioanalytical laboratories			
Number of patients/volunteers			
Test product (name, manufacturer, batch number, batch size, location of multipoint dissolution data in physiological media and release media, if different)			
Reference product (name, manufacturer, source, batch number, expiry date)			
Results (geometric ratio and the 90% confidence intervals for the PK parameters)			
Assessor's comments on bioequivalence/comparative pharmacokinetics			

Relevant clinical studies			
Dossier aspects to verify	**PQT or reference SRA submission**	**NRA submission**	**Comments**
Study ID			
Number of study centres/ locations			
Design			
Study posology			
Study objective			
Subjects by arm entered/ completed			
Duration			
Population included in the study (age, sex, ethnicity, severity of disease)			
Diagnosis including criteria			
Primary endpoint			
Assessor's comments on relevant clinical studies			

4. Clinical data

Note: The benefit–risk profile of SRA-approved products in other markets could differ, as their use in other markets is not always considered in the SRA review process. In this respect, the SRA assessment does not always confirm the availability of data and questions that are relevant for use in other environments. For this reason, the SRA assessment reports can be considered incomplete. Therefore, the NRA has to address this local context or suitability in a local environment as part of the review process under the WHO collaborative registration procedure (CRP).

Product information	Comments
Proprietary product name	
International Nonproprietary Name (INN) of the API/drug substance, strength, pharmaceutical form	
Chemical class (new molecular entity [NME]/ therapeutic biological product, existing APIs/drug substance, new salt or ester, new dosage form, new combination product, amongst others)	
Pharmacological class	
Proposed indications, dosing regimens, age groups (confirm whether these are the same as approved by the reference SRA, WHO guidelines or national treatment guidelines)	
Existing alternatives to the proposed product for the same indication(s)	
Clinical pharmacology	
Justification for the dose/dose regimen (in the target population)	
Absorption, distribution, metabolism and excretion (ADME) (applicability in the target population, e.g. the pharmacokinetic effects of drug-demographic and drug-disease interactions, such as, renal impairment, hepatic impairment, should be described)	
Interaction studies (food and drug/drug interactions relevant for target countries that are not discussed in the SRA assessment report)	

Table *continued*

Product information	Comments
Pharmacodynamics	
Statistical methods for additional analysis, such as subgroup analyses and adjusted analyses	
Benefit–risk analysis	
Relevance of studied population for the target population (ethnicity, gender representation, age groups, etc.) as regards demonstration of safety and efficacy	
Relevance of SRA-approved conditions of use (proposed indications, dose and directions of use) as regards epidemiology and disease pattern in the target countries, as well as other implications for efficacy and safety, for example, feasibility of monitoring and precautionary measures (such as, microbial resistance testing or therapeutic drug monitoring) (applicants should have evaluated the effects of major demographic factors [e.g. age, sex, and race] and other predefined or relevant intrinsic and extrinsic factors on efficacy [such as, disease severity, prior treatment, concomitant illness, concomitant drugs, body weight, genetic variants, renal or hepatic impairment, microbial resistance]; regional differences may need to be considered with respect to multinational clinical trials)	
The adequacy of the directions for use	
The 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	
Assessor's comments on clinical data	

5. Risk management plans

***Note*:** The benefit–risk profile of SRA-approved products in other markets could differ, as their use in other markets is not always considered in the SRA review process. In this respect, the SRA assessment does not always confirm the availability of data and questions that are relevant for use in other environments. For this reason, the SRA assessment reports can be considered incomplete. Therefore, the NRA has to address this local context or suitability in a local environment as part of the review process under the WHO collaborative registration procedure (CRP).

Product overview	Comments
Proprietary product name	
International Nonproprietary Name (INN) of the API/drug substance, strength, pharmaceutical form	
Chemical class (new molecular entity (NME)/ therapeutic biological pro duct, existing API (generic) or similar biotherapeutic product, new salt or ester, new dosage form, new combination product, amongst others)	
Pharmacological class	
Proposed indications, dosing regimens, age groups (confirm whether these are the same as approved by the reference SRA, WHO guideline or national treatment guidelines)	
Risk management plan (RMP) was provided with the submission	
Epidemiology of the indications and target population (relevance of the clinical trial population to the intended target population [inclusions, exclusions, limited numbers, trial setting, use in special populations])	
Assessment of identified and potential risks (inclusion of all important risks related to the active substance, formulation, route of administration, target population, specific subpopulations and the potential for interaction from the safety specifications)	

Table *continued*

Product overview	Comments
Summary of planned pharmacovigilance activities (including post-authorization safety studies) (ongoing and planned studies in the post-authorization pharmacovigilance development plan in the target population)	
Plans for post-authorization efficacy studies (if applicable)	
Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)	
To what extent does the RMP approved by the reference SRA and applicant's commitments reflect the local situation or needs?	
Summary of the RMP	
Assessor's comments on the RMP	

6. Product information

6.1 Information for health-care professionals and corresponding sections of the patient information leaflet

***Note*:** The patient information leaflet (PIL) should fully mirror the information for health-care professionals in a user-friendly language and style. The review of the product information should take into account the local context, especially in cases where this was not accounted for in the reviews by the reference SRA. Moreover, WHO prequalification product information is specific to the expressions of interest (EOIs), that is, only taking into account the specific therapeutic indication in the EOI, while the NRA may consider broader therapeutic indications and national treatment guidelines.

Dossier aspects to verify	Comments
Is the information for the health-care professionals provided as approved by the reference SRA or PQT?	
Is the information for the patient/user (PIL) provided as approved by reference the SRA or PQT?	

Table *continued*

Dossier aspects to verify	Comments
Does the information contradict national therapeutic guidelines?	
Assessor's comments on the product information	

6.2 Labelling

The following minimum information appears on the label:

Dossier aspects to verify	Comments
Is the labelling of outer packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on outer packaging as per national requirements	
Is the labelling of internal packaging (as final packaging or mock-up presentation) provided as approved by the reference SRA or PQT?	
Additional information on internal packaging as per national requirements	
Assessor's comments on the product labelling	

7. Applicant commitments to the WHO Prequalification team or reference stringent regulatory authority

State any commitments by the applicant to WHO or to the reference SRA that may require follow up.

Examples:

- The applicant undertook to continue long-term testing of [*INN of API*] for a period of time sufficient to cover the whole provisional retest period [period ending month/year].
- The applicant undertook to continue long-term testing of [*FPP reference number, trade name [INN of API], strength, pharmaceutical form*] for a period of time sufficient to cover the whole provisional shelf-life [*period ending month/year*].

- The applicant committed that three consecutive production batches would be prospectively validated and a validation report – in accordance with the details of the validation protocol provided in the dossier – would be made available as soon as possible for evaluation by assessors or for verification by the WHO inspection team.

8. General national regulatory authority review comments

9. Assessment of responses to [*list of questions/list of outstanding issues/request for supplementary information*]

For each question:

Question:

Response from the applicant:

Assessment of response:

Appendix 4

Additional information to be included in the screening checklist

Note **[*instructions on using the template*]:** This template only provides additional considerations during screening which is specific to the WHO collaborative procedure (hereinafter referred to as "the Procedure"). The assumption is that the national regulatory authority (NRA) has a standard dossier screening checklist to ensure a valid submission is provided by the applicants. This template provides additional considerations to assist the NRA in determining the suitable registration pathway and assessment level/type.

Dossier/product information
Dossier application/screening number
Applicant
Submission date
International Nonproprietary Name, strength, dosage form

Screening details

Description	Yes/no	Comments
Has the applicant submitted the applicable expression of interest (that is, cover letter and/or applicable appendices) for the Procedure?		
Has the applicant submitted a valid marketing authorization/registration data/prequalification letter from (*cross out where not applicable*): • WHO prequalification? • Reference stringent regulatory authority (SRA; specify)[1]? • Any other country?		

[1] The reference SRA is the one whose registration the applicant would like to be considered as acceptable for reliance; for example, a product could be manufactured in country A but registered in country B. Country B NRA therefore becomes the reference SRA. In some regulatory cases, the reference SRA could be the NRA in the country of manufacture.

Table *continued*

Description	Yes/no	Comments
Has the Applicant submitted the quality information summary (QIS), as approved/endorsed by the reference authority or WHO (*cross out where not applicable*): • the QIS (for prequalified products)? • the QIS-SRA(crp)?		
Has the applicant submitted the full assessment reports from the reference authority or institution[2]?		
Has the applicant submitted the full inspection reports from the reference authority or institution1?		
Has the applicant submitted the product information (information for health-care professionals and information for the patient/user), as approved by the reference authority or institution?		
Has the applicant submitted a bridging report, or justification for exemption, as applicable?		
Has the applicant submitted the risk management plan, if applicable/required?		
Has the applicant submitted the public assessment and inspection reports from the reference authority or institution, if applicable?		

[2] This information is required for information but not for a decision on the validity of the submission. Absence of the assessment or inspection reports in the submission from the applicant/manufacturer should not constitute a failed screening or invalid submission. For example, in the WHO Prequalification Team Collaborative Procedure, the assessment and inspection reports (unredacted) are shared directly between WHO and the NRA. This may apply for other reference authorities. Thus, in these cases, the applicant/manufacturer are not in possession of the reports for submission to the NRA.

Appendix 5

Example of a national regulatory authority reliance model approach: information, documentary evidence and assessment activity

Pathway	Assessment approach	Documentary evidence (supporting documentation)	Example of products	Comments
Recognition	No scientific assessment	• Certificate of pharmaceutical product (CPP) from reference stringent regulatory authority (SRA) • Public assessment and inspection reports • Assessment and inspection reports	• Products prequalified by the World Health Organization (WHO) • National regulatory authority (NRA) may specify the NRA(s) or institutions whose decision it recognizes	CPP is not applicable for prequalified products Similarity between the local context important for this pathway/ approach
Reliance				
a. WHO prequalification	Verification, or abridged reviews, secondary review, or a combination	• Signed agreements/ consent • Quality information summary (QIS) • Assessment and inspections reports from the WHO Prequalification Team (PQT) • WHO public assessment reports and WHO public inspection reports (publicly available from the PQT website)	Products prequalified by WHO	NRAs to review the product information for consistency with local treatment guidelines and policies; information shared directly from WHO

Table *continued*

Pathway	Assessment approach	Documentary evidence (supporting documentation)	Example of products	Comments
b. Reference SRA (special access mechanisms)	Verification, or abridged reviews, or combination of both	• Signed agreements/consent • QIS-SRA(crp) – endorsed by SRA • SRA assessment reports inspection reports • Public assessment and inspection reports (publicly available)	Products with scientific opinion or similar decisions to facilitate access in low- and middle-income countries	Scientific opinions, or similar SRA decisions consider the use in target settings (outside the SRA market)
c. Reference SRA	Combination of verification and abridged review	• Signed agreements/consent • QIS-SRA(crp) – endorsed by SRA • Bridging report, if applicable • SRA assessment reports, inspection reports • Public assessment and inspection reports (publicly available)	Products approved by SRA and marketed in SRA market	Information may be shared by the applicant/ manufacturer; SRA approvals do not necessarily consider use in other settings
d. Other reference NRAs	Abridged reviews	NRA assessment and inspection reports QIS-SRA(crp) (potential use if all stakeholders agree)	Products approved by NRAs recognized as reference by the NRA	Direct interaction between the NRAs; no WHO facilitation
Work-sharing/ joint reviews	Full assessment as primary reviewer or rapporteur, and secondary reviewer for other products	Primary assessment reports from rapporteur	All types of products, depending on the scope of the regulatory network	
Information-sharing	Full assessment and inspections	Memorandum of understanding (MoU) between NRAs for information sharing (non-binding)	All products in the scope of the MoU or agreements between the NRAs	

Appendix 6

Model acknowledgement or approval letter for variations of products registered through the WHO collaborative procedure

Application number _____

The Managing Director

[*Name of applicant*]

[*Address*]

[*Date*]

Attention: Regulatory Affairs Manager

Dear Sir/Madam,

I refer to the application dated [*date of application*] for variation of:

Proprietary name (trade name) _____

_____

Approved generic name(s) _____

_____

Strength(s) per dosage unit _____

Dosage form _____

Name of authorization holder* _____

[*Must be a person or legal entity in the country in which marketing is being authorized; this letter should normally be addressed to the marketing authorization holder]

Evaluation of the application has been completed following the WHO collaborative procedure (hereinafter referred to as the Procedure). Approval of the variation under [*name of legislation*] is granted, subject to the conditions in this letter and its attachments. This letter and its attachments constitute the approval. The date of approval is the date of this letter. In part, this approval relies upon your assurance that: **no variations have been made other than (i) those notified in this application; (ii) changes that are permitted without notification or prior approval according to the guidelines of** [***name of the reference authority or institution***]**; and (iii) the variation is as approved by** [***name of the reference authority or institution***].

The conditions that apply are as follows:

General conditions applying to all products

- The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence.
- The product(s) must conform to all the details as approved by [*name of reference authority or institution*] in line with the Procedure requirements.
- No further changes may be made to the product without prior approval, except for changes of the type listed in [*name of reference authority or institution*]'s policy on "Changes to pharmaceutical aspects of registered products that may be made without prior approval". The conditions in that policy apply.

[*OPTION 1: There is no objection to the concurrent supply of changed and unchanged product.*]

[*OPTION 2: The concurrent supply of the changed and unchanged product is considered unacceptable. You should use up all existing pre-variation stock before supplying the changed product.*]

Additional specific conditions applying to this product:

[*For example, "All batches of the finished product must comply with a limit of 0.5% for Impurity A"*]

[_____]

[_____]

If you have any doubt as to the meaning of this letter and its attachments, you should contact the undersigned prior to marketing the product.

Yours faithfully

[*Name*]

[*Signature*]

authorized person under [*name of legislation*]

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, eighth edition.
2018 (CD-ROM, USB keys and online)

Quality Assurance of Pharmaceuticals. WHO guidelines, good practices, related regulatory guidance and GXP-training materials
Updated, comprehensive edition, 2018 (CD-ROM, USB keys and online)

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Fifty-second report.
WHO Technical Report Series, No. 1010, 2018 (xi + 406 pages)

International Nonproprietary Names (INN) for pharmaceutical substances
Cumulative List No. 18
2018 (available on CD-ROM only)

The selection and use of essential medicines
Report of the WHO Expert Committee, 2017 (including the 20th WHO Model List of Essential Medicines and the 6th WHO Model List for Children)
WHO Technical Report Series, No. 1006, 2017 (xxiv + 577 pages)

WHO Expert Committee on Biological Standardization
Sixty-eighth report
WHO Technical Report Series, No. 1011, 2018 (xvi + 380 pages)

Further information on these and other WHO publications can be obtained from
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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: Procedure for development of the WHO medicines quality assurance guidelines; Guidelines on Good Manufacturing Practices (GMP) for heating, ventilation and air-conditioning systems (HVAC) – illustrative part; Guidance on GMP for Validation, including the general main text, analytical procedure validation, validation of computerized systems and qualification; in the area of interchangeability of multisource medicines: the Protocol to conduct equilibrium solubility experiments for the purpose of biopharmaceutics classification system-based classification of active pharmaceutical ingredients for biowaiver; Guidelines on Import Procedures for pharmaceutical products; and the Good Practice Guidance document on implementing the collaborative procedures. All of the above are included in this report and recommended for implementation.

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