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1025

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-fourth 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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WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report

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Contents

Abbreviations

AMR	antimicrobial resistance
AMRH	African Medicines Regulatory Harmonization
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
APIMF	active pharmaceutical ingredient master file
ASEAN	Association of South-East Asian Nations
AUDA-NEPAD	African Union Development Agency-New Partnership for Africa's Development
AWaRe	access, watch and reserve
BCS	Biopharmaceutics Classification System
CRP Lite	collaborative registration procedure-Lite
EAP	WHO Expert Advisory Panel on *The International Pharmacopoeia* and Pharmaceutical Preparations
ECBS	Expert Committee on Biological Standardization
EC-EML	Expert Committee on the Selection and Use of Essential Medicines
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EDQM	European Directorate for the Quality of Medicines and HealthCare
EQAAS	WHO External Quality Assurance Assessment Scheme
EMA	European Medicines Agency
EML	*WHO Model List of Essential Medicines*
EMLc	*WHO Model List of Essential Medicines for Children*
EV71	enterovirus 71
EOI	expression of interest
EU	European Union
FPP	finished pharmaceutical product
GBT	*WHO Global Benchmarking Tool*

GC	gas chromatography
GMP	good manufacturing practices
GReIP	good reliance practices
GRP	good regulatory practices
GXP	good practices
HBEL	health-based exposure limit
HPLC	high-performance liquid chromatography
IAEA	International Atomic Energy Agency
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substances
IEC	International Electrotechnical Commission
IMWP	International Meeting of World Pharmacopoeias
INN	International Nonproprietary Name
ISO	International Organization for Standardization
LC	liquid chromatography
MDR-TB	multidrug-resistant tuberculosis
MQA	Medicines Quality Assurance (WHO team)
MSM	Member State mechanism
NRA	national regulatory authority
PDG	Pharmacopoeial Discussion Group
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PQ	prequalification
PQT	WHO Prequalification Team
QA	quality assurance
QCL	quality control laboratory
QMS	quality management system
RSS	Regulatory System Strengthening (WHO team)
SDG	Sustainable Development Goal

TB	tuberculosis
TLC	thin-layer chromatography
TRS	Technical Report Series
UNFPA	United Nations Population Fund
UNICEF	United Nations Children's Fund
USA	United States of America
USFDA	United States Food and Drug Administration
UV	ultraviolet
WFI	water for injection
WHO	World Health Organization
WLA	WHO-listed authority

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Geneva, 14–18 October 2019

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Declarations of interest

Declarations of interest made by members of the WHO Expert Committee on Specifications for Pharmaceutical Preparations and technical advisers are listed below:

Professor E. Adams, Professor M. Bermejo Sanz, Dr M. Brits, Dr T. Chanprapaph, Dr V. Dias Sousa, Dr P. Dörr, Professor R. Fernandopulle, Mr G.M. Francis, Dr A. García-Arieta, Dr B. Hasselbalch, Professor E. Kaale, Dr K. Ssanyu Kikule, Mr S. Kisoma, Dr A. Krauss, Ms G. Nolwandle Mahlangu, Dr J. Molzon, Professor J. Miller, Dr J. Norwig, Mrs L. Paleshnuik, Professor G. Pauletti, Mr R.T. Rukwata, Dr J. Sabartova, Dr B. Santoso, Dr D. Sato, Professor G. Scriba, Dr G.N. Singh, Dr L. Stoppa, Dr J. Sun and Dr M. Xu reported no conflict of interest.

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

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

PRIVATE SESSION

This private session was attended by ECSPP members, technical advisers, international organizations and state actors.

Opening

The Fifty-fourth meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) was held in Geneva, Switzerland, from 14 to 18 October 2019.

Participants of the meeting were welcomed by Dr Mariângela Simão, Assistant Director-General, Access to Medicines and Health Products, on behalf of the WHO Director-General, Dr Tedros Adhanom Ghebreyesus.

Dr Simão drew attention to the triple billion target of WHO's current General Programme of Work, which is designed to advance universal health coverage, address health emergencies and promote healthier populations by 2023 (*1*). To enable WHO to deliver on the triple billion target, the Organization is undergoing a transformation that aims to bring the full impact of WHO's work to country level and align strategies across WHO headquarters and country and regional offices. As part of the transformation, WHO is being restructured and activities related to the ECSPP will now fall under the Quality, Safety and Efficacy of Pharmaceuticals Group.

The transformation has also impacted the ways that WHO initiates, develops, implements and evaluates normative and standard-setting products. A new division has been created under the Chief Scientist's Office, to further analyse WHO's normative and standard-setting products and to define related quality assurance (QA) pathways for the future. Moreover, WHO is setting up a methodology for a more systematic monitoring of how norms and standards on the quality, safety and efficacy of medicines are implemented. This will initially focus on key guidelines such as those on bioequivalence and good manufacturing practices (GMP), and is expected to reduce the timeframe for developing guidelines and to highlight the added value of such documents, increase their use, and ultimately deepen their impact on access to health products. Teams across the Medicines and Health Products Division will contribute to this monitoring work, which will also align with other global organizations such as the Asia-Pacific Economic Cooperation (APEC), the African Medicines Regulatory Harmonization (AMRH) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Dr Simão emphasized the importance of the ECSPP in delivering the triple billion target, saying that the Director-General has identified WHO's standard-setting activities as a core function of WHO and the expert committees as the backbone of WHO's standard-setting process.

Election of chairpersons and rapporteurs

The ECSPP appointed Dr Petra Dörr as Chair of the meeting, Dr Gyanendra Nath Singh as Co-Chair and Professor Eliangiringa Kaale and Dr Justina Molzon as Rapporteurs.

1. General policy

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

Dr Sabine Kopp, Secretary of the ECSPP, ran through the rules governing participation in ECSPP meetings, which Expert Committee members and technical advisers are invited to in their personal capacities. In all cases, participation is by invitation only.

The meeting adheres to WHO procedures for expert committee meetings and includes three broad types of sessions:

a. open sessions for sharing information and updates; these are for ECSPP members, technical advisers, international organizations, state actors, Member States' mission representatives and non-state actors;

b. private sessions during which specific monographs, guidelines and other proposed documents are discussed; these are for ECSPP members, technical advisers, international organizations and state actors; and

c. closed sessions for writing and accepting the report; these are for ECSPP members only.

All decisions by the ECSPP are taken by its Expert Committee members during a closed session.

The WHO Secretariat followed up on the recommendation of the Fifty-third ECSPP meeting, to 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 good practices (GXP) or QA matters), whether they are state actors or non-state actors, to the private sessions of the ECSPP. The outcome was that the proposal would not be in line with the WHO *Framework of engagement with non-State actors* (*2*).

The Expert Committee noted the rules governing participation in ECSPP meetings.

This concluded the private session.

OPEN SESSION

This open session was attended by ECSPP members, technical advisers, international organizations, state actors, Member States' mission representatives and non-state actors.

Introduction and welcome

Dr Clive Ondari, Acting Director of WHO's Essential Medicines and Health Products Department, welcomed all participants – including non-state actors – to this part of the meeting, emphasizing the ECSPP's aim to provide information in a transparent way and highlighting the value of in-person interactions that are achieved through open sessions.

Dr Ondari introduced the ECSPP's standard-setting work, which he said makes a critical contribution towards more equitable access to needed medicines of assured quality. The ECSPP was first convened in 1947 and its recommendations are linked to many other parts of WHO, from country and regional offices to other expert committees and partnerships. Its decisions impact the quality of medicines that are very widely used and, as such, the Expert Committee serves not only WHO Member States but also a range of programmes within WHO, as well as other international organizations.

The ECSPP provides a wide spectrum of written and physical standards to help test the quality of medicines during their full life-cycle, from development to distribution to patients. It also recommends regulatory guidelines of importance with respect to multisource medicines designed to be used globally; the aim is to protect patients and facilitate access to quality medicines. Much of the Expert Committee's work is aimed at harmonizing quality assurance and regulatory guidance across countries and contexts, to boost efficiency among and within regulatory authorities and pharmacopoeias, and to reduce duplication of efforts and therefore costs.

Dr Ondari praised the work, efficiency and trend-setting of the ECSPP, highlighting some of its achievements to date, which include:

- more than 100 guidelines and GXP recommended by the ECSPP;
- more than 500 specifications and numerous test requirements in *The International Pharmacopoeia*; and
- more than 200 physical standards, International Chemical Reference Substances (ICRS), established for use with *The International Pharmacopoeia*.

Ms Emer Cooke, Director of WHO's Regulation of Medicines and other Health Technologies Unit, added her welcome to all participants and thanked the

ECSPP for all the work that it does. Ms Cooke highlighted the importance of the ECSPP's work in supporting WHO and Member States' regulatory activities and praised its collaborative nature, which is reflected in the many joint initiatives on the agenda of the Expert Committee. Ms Cooke also stressed the importance of the Expert Committee's cooperation on scientific and regulatory issues with partners within and beyond WHO.

1.2. Process for development of WHO norms and standards

Dr Sabine Kopp gave an overview of how WHO norms and standards are developed and how the ECSPP and *The International Pharmacopoeia* (*3*) fit into that process.

Developing, establishing and promoting international standards for food, biological, pharmaceutical and similar products is part of WHO's core mandate (Article 2, WHO Constitution) (*4*). It does this through expert committees that are established by the World Health Assembly or Executive Board and are governed through set rules and procedures.

The ECSPP is responsible for WHO's guidance for medicines quality assurance across the full life-cycle of medicines, from development to delivery. This includes taking responsibility for more than 100 official WHO guidance texts and guidelines. It works in close collaboration with a wide range of partners, including national and regional authorities and groupings; international organizations; professional and other associations; non-state actors; quality assurance experts; WHO Collaborating Centres; and pharmacopoeia authorities and secretariats.

Dr Kopp underscored the critical value of the ECSPP's work, particularly given the importance of access to safe and quality-assured medicines, not only for WHO but also for the broader United Nations group; for example, it features prominently in the United Nations' Sustainable Development Goals (SDGs) (*5*).

All monographs, guidance texts, GXP and guidelines adopted by the ECSPP are developed in response to recommendations and requests from WHO governing bodies and programmes, or in response to major public health needs. Before they are adopted by consensus for use, they are widely circulated for public comment (including two rounds of consultation for each document), reviewed by expert groups and discussed in annual ECSPP meetings. In all cases, the norms and standards developed by the ECSPP are intended to be tools that:

- are ready for adoption in national legalization;
- enable collaboration with other authorities;
- enable work-sharing (for example, through regional networks); and
- enable reliance on decisions from other regulatory authorities and laboratories.

All decisions taken at the ECSPP's annual meetings are recorded in publicly available meeting reports published as part of WHO's Technical Report Series (TRS) (*6*).

The Expert Committee noted the process.

2. General updates and matters for information

Meeting participants were updated on a range of WHO and partner activities related to the work of the ECSPP.

2.1. Cross-cutting pharmaceuticals quality assurance issues

2.1.1. Local manufacturing

Dr Jicui Dong, Programme Manager for WHO's Local Production Programme, provided an update on some of the programme's activities over the past year. The programme supports Member States in promoting the local production of quality-assured medical products in setting strategies and roadmaps; conducting holistic situational analyses on sustainable local production; building stakeholders' capacity towards quality assurance and sustainability; and forging strategic partnerships and collaborations, among others.

Recent achievements include those listed below.

- **An interagency statement on promoting local production of medicines and other health technologies**. This statement, which was signed by the top leadership of six international organizations, underscores the need for a holistic approach towards promoting local production that considers policy coherence; regulatory systems-strengthening; access to finance; careful assessment of the business case; access to technology for production; development of skilled human resources; and other factors, to enable manufacturers to comply with international quality standards, be competitive and engage in sustainable production.
- **A training workshop on key enabling factors for local production and supply of quality-assured medicines**. Organized in collaboration with the African Union Development Agency – New Partnership for Africa's Development (AUDA-NEPAD) and the Promoting the Quality of Medicines Program of the United States Pharmacopeia, this workshop was held in Addis Ababa, Ethiopia, in December 2018. It was attended by approximately 70 African manufacturers, regulators and partners. Technical experts from United Nations agencies and international partners delivered a holistic range of topics – such as technology transfer requirements; risk-based product selection; GMP and quality; regulatory affairs; and procurement – to build capacity in leveraging on policy, business and regulatory enablers towards quality and sustainability.
- **A WHO thematic session at the high-level Africa Pharma Conference**. This conference was organized by AUDA-NEPAD

in collaboration with the Development Finance Summit Africa in Johannesburg, South Africa, in June 2019. A key recommendation to emerge from the conference was for the African Union Commission, AUDA-NEPAD and WHO to work with relevant stakeholders to support countries to develop and implement national sector-specific strategies for local production.

- **Situational analyses on local production**. Meetings were held on sustainable local production in Lebanon in November 2018, and on the development of the Kilinto Pharmaceutical Industrial Park in Ethiopia in September 2019.

The Local Production Programme also has a range of other ongoing activities, such as piloting a risk-based assessment tool for production; developing a checklist for appropriate product selection; and organizing a second workshop on key enabling factors for successful local production and supply of quality-assured medical products (in Thailand) for the WHO South-East Asia Region.

More information is available at: https://www.who.int/phi/implementation/tech_transfer/en/ (*7*).

The Expert Committee noted the update.

2.1.2. Member State mechanism

Mr Michael Deats, Acting Coordinator for WHO's Safety and Vigilance Unit, summarized the Member State mechanism (MSM), which is the political response to substandard and falsified medical products. Given the emphasis on access to safe and affordable medicines in the SDGs (*5*), the need to tackle substandard and falsified medical products is critical.

Working in tandem with WHO's operational response (the WHO Global Surveillance and Monitoring System for substandard and falsified medical products), the MSM focuses on a range of high-level activities aimed at preventing, detecting and responding to substandard and falsified medical products (*8*). These include building the capacities of regulatory authorities and quality control laboratories; raising awareness among prescribers and the public; supporting cooperation, collaboration and knowledge exchange at national, regional and global levels; strengthening supply chains and surveillance; and contributing to other relevant areas of WHO's work.

The MSM uses a range of practical tools and tactics to support its activities, including providing specific technical assistance to Member States; carrying out medicine quality surveys; issuing relevant alerts; developing apps to enable smartphone reporting; leveraging the *WHO Global Benchmarking Tool* (GBT) (*9*); and supporting legislation to implement regulatory and criminal responses as and where appropriate.

There are eight subgroups within the MSM, which are responsible for different elements of the mechanism's work. These comprise training material; a global regulatory focal point network; technology; access to medical products; education and awareness; advocacy; medicines in transit; and medicines on the internet. The MSM is governed by a steering committee of Member States and supported by a WHO-provided secretariat.

In 2019, 10 global medical product alerts across 17 countries were published.

More information is available at www.who.int/medicines/regulation/ssffc/mechanism (*8*).

The Expert Committee noted the update.

2.1.3. Expert Committee on Biological Standardization

Dr Ivana Knezevic, Team Leader of WHO Norms, Standards and Biologicals, spoke about the latest work of the Expert Committee on Biological Standardization (ECBS). The ECBS is responsible for establishing evidence-based international norms and standards for biological products. It is responsible for a total of 97 recommendations and guidelines, including 10 general documents that apply to vaccines and biotherapeutics; 12 general documents that apply to all vaccines; 66 vaccine-specific documents; and 9 biotherapeutic-specific ones.

The ECBS also runs workshops on implementing its guidelines and recommendations. In 2019, two workshops on post-approval changes were held: one in Hanoi, Viet Nam (August) and one in Seoul, Republic of Korea (June).

It was announced that the next ECBS meeting will be held on 21–25 October 2019, when it will consider a selection of new and revised written and measurement standards. New written standards up for review include guidelines on respiratory syncytial virus vaccines and enterovirus 71 (EV71) vaccines. New measurement standards that will be reviewed include several that, once adopted, will provide the first international standard available worldwide. These include new standards on human papillomavirus and EV71 vaccines, as well as biotherapeutics such as adalimumab, insulin and darbepoetin. The upcoming meeting will also see the ECSB review a range of cross-cutting issues, including product development of vaccines and immunization policy, among other things. In addition, it will receive an update on ECSPP activities and decisions.

More information is available at www.who.int/biologicals/WHO_ECBS (*10*).

The Expert Committee noted the update.

2.1.4. Expert Committee on the Selection and Use of Essential Medicines

Ms Bernadette Cappello, Technical Officer in WHO's Innovation, Access and Use Team, briefed participants on the activities of the Expert Committee on the Selection and Use of Essential Medicines (EC-EML), which meets every two

years to update the *WHO Model List of Essential Medicines* (EML), including the *WHO Model List of Essential Medicines for Children* (EMLc) (*11–13*). There are three broad criteria for including a medicine on the list: evidence of efficacy and safety; public health relevance; and a consideration of comparative cost and cost effectiveness.

The EC-EML reviewed 65 applications for the 2019 update of the EML; 28 new medicines (and 16 new formulations) were added to the EML (*12*) and 23 were added to the EMLc (*13*). At the same time, 9 medicines and 4 formulations were deleted, and 21 applications (involving 31 medicines) were rejected.

The EC-EML also recommended an updated classification of antibiotics into three categories: access, watch and reserve (AWaRe), with recommendations on when each category should be used. The AWaRe framework aims to ensure that antibiotics are available when needed and that the right antibiotics are prescribed for the right infections (*14*). To that end, the AWaRe classification has also been applied to a further 143 commonly used antibiotics that are not included in the EML; the full classification has been published as an online database that countries can use as a stewardship tool.

Another major area of change in the 2019 EML lies in its inclusion of cancer medicines. Many new medicines added to the 2019 EML and EMLc were for cancer treatment. Following recommendations from an expert working group, new cancer medicines included in the EML meet a threshold for clinical benefit of at least 4–6 months' survival gain.

Other additions have been made for noncommunicable diseases; reproductive health and perinatal care; HIV; tuberculosis (TB); malaria; hepatitis C; and mental health and behavioural disorders.

In making its recommendations, the EC-EML acknowledged that some existing and newly added essential medicines – including insulin, immunomodulators, cancer medicines and novel oral anticoagulants – are highly priced and can have a significant budgetary impact on health systems. The EC-EML identified potential actions that could contribute to improving access to and the affordability of high-priced essential medicines; a wider adoption of biosimilars; expansion of the remit of the Medicines Patent Pool; pooled procurement and tendering; and more use of the flexibilities under the World Trade Organization's *Agreement on Trade-Related Aspects of Intellectual Property Rights* (15).

The ECSPP Secretariat noted the critical links between the ECSPP and the EML, as the annual workplan for *The International Pharmacopoeia* (*3*) is driven in large part by those medicines in the EML that lack a public standard on quality.

The ECSPP discussed the recent recalls of the "sartans" and ranitidine by regulatory authorities and manufacturers, and their possible implications in the EML.

More information is available at: www.who.int/medicines/publications/essentialmedicines (*11*).

The Expert Committee noted the update.

2.1.5. Regulatory System Strengthening Team

Mr Hiiti Sillo, Group Lead, Country Regulatory Strengthening, summarized the work of the Regulatory System Strengthening Team (RSS), which supports Member States to strengthen their regulatory systems by assessing regulatory systems; providing technical assistance; assessing regulatory functions; and supporting information and knowledge exchange through regional and global networks.

Highlights from the past year include those listed below.

- **Publication of the *WHO Global Benchmarking Tool* (GBT), Revision VI** (*9*) in December 2018. The GBT is the primary means by which WHO objectively evaluates regulatory systems. It replaces all previous tools and can be used by WHO and national regulatory authorities(NRAs) in order to identify areas for improvement, support the development of an institutional development plan and monitor progress. The tool has been used to benchmark medicines and vaccines regulatory systems in more than 70 countries to date, with more than half in the WHO African Region.
- **Technical support to regional regulatory harmonization initiatives and networks**. This includes supporting the African Medicines Regulatory Harmonization (AMRH) initiative, to expand its scope from medicines to medical products, and advancing the activities of the Association of South-East Asian Nations (ASEAN) Joint Assessment Coordination Group.
- **Progress in developing a global competency framework and global curricula** to support training and professional development of regulatory staff.
- **Development of a draft framework for WHO-listed authorities (WLAs)**, which is anticipated to have significant impact in promoting reliance, guiding procurement decisions and helping ensure the production and supply of safe, effective and quality medical products (see Section 13.5).
- Progress in developing the good regulatory practices (GRP) guidance document (see Section 13.4).
- **A meeting to discuss the structure and elements of a new guideline on good reliance practices (GRelP)** held in September 2019. Participants agreed to use a Pan American Health Organization/

WHO Regional Office for the Americas concept note as the basis for the new guideline, which will include sections on purpose, scope, definitions and considerations. This high-level guideline should be complemented by a repository of examples, case-studies and practice guides to support NRAs in adopting GRelP. WHO will develop a working draft of the high-level document by March 2020, and it will then be circulated to stakeholders and the public for comment.

- **Progress in developing a guideline for implementing quality management systems (QMSs) for NRAs** (see Section 13.3).
- **Establishment of the WHO National Control Laboratory Network for Biologicals**, which promotes GXP and the exchange of quality and technical information among control laboratories involved in testing WHO-prequalified vaccines. The network, which continues to expand its membership, was announced to be holding its third meeting in Johannesburg, South Africa, in November 2019.

More information is available at: www.who.int/medicines/regulation/rss (*16*).

The Expert Committee noted the update.

2.1.6. International Conference of Drug Regulatory Authorities

Mr Hiiti Sillo presented the latest news from the International Conference of Drug Regulatory Authorities (ICDRA) on behalf of Dr Samvel Azatyan, Group Lead of the WHO Regulatory Networks and Harmonization Group. The ICDRA has held biennial conferences since 1980, for regulatory authorities to share information and strengthen collaboration. The ICDRA is an important tool for WHO and regulatory authorities to harmonize regulation and develop international consensus on regulatory matters.

Each conference lasts three days (preceded by a two-day preconference) and covers topics such as quality; herbal medicines; homeopathy; regulatory reform; medicines safety; access to substandard and falsified medical products; regulation of clinical trials; harmonization; new technologies; and e-commerce. Every conference aims to:

- promote collaboration between national medicines regulatory authorities;
- reach a consensus on the matters of common interest;
- facilitate timely and adequate exchange of information; and
- discuss issues of international relevance.

The Eighteenth ICDRA was held in Dublin, Ireland, in September 2018, and focused on smart safety surveillance – a life-cycle approach to promoting

the safety of medical products. It was attended by more than 400 people from all over the world and covered a broad range of topics, including regulatory collaboration; certification of pharmaceutical products; regulation of medical devices; the GBT; partnership to enhance regulatory outcomes; regulatory preparedness for public health emergencies; and regulation of clinical trials.

The next ICDRA will be hosted by the Central Drugs Standard Control Organization in India, during the second half of 2020.

More information is available at: www.who.int/medicines/areas/quality_safety/regulation_legislation/icdra (*17*).

The Expert Committee noted the update.

2.2. International collaboration

2.2.1. International Atomic Energy Agency

Dr Aruna Korde summarized relevant work by the International Atomic Energy Agency (IAEA), which is the world's central intergovernmental forum for scientific and technical cooperation in the nuclear field. The IAEA works for the safe, secure and peaceful use of nuclear science and technology; this includes supporting the production of high-quality, safe and effective radiopharmaceuticals and radioisotopes.

In 2018, in recognition of the long-standing request by Member States (and recommendations emerging from three technical meetings) to strengthen GMP for radiopharmaceuticals, the IAEA began collaborating with WHO to update its *Guidelines on good manufacturing practices for radiopharmaceutical products* (*18*). It consulted with experts from Canada, Europe and the United States of America (USA) in November 2018, after which a working group developed a revised draft of the guidelines in early 2019.

The draft was presented at a consultation meeting at the IAEA in July 2019 and refined in response to comments received. The latest version of the guidelines on GMP, as presented to the ECSPP, provides an overview of GXP and covers quality management; qualification and validation; product complaints and recall; outsourced activities; personnel and training; premises; equipment; starting materials; documentation; GXP in production and quality control; and labelling.

In addition to the guidelines on GMP for radiopharmaceuticals, the IAEA has collaborated with WHO to identify and develop a set of specific monographs for priority radiopharmaceuticals to be included in *The International Pharmacopoeia* (*3*), as well as a general monograph. The list of priority radiopharmaceuticals has now been agreed on and work to develop monographs can begin (starting with establishing a radiopharmaceutical technical expert group and identifying collaborating laboratories).

Other plans for the IAEA/WHO collaboration on radiopharmaceuticals include:

- the development of IAEA/WHO guidelines on GMP for producing cold kits used in the production of radiopharmaceuticals;
- the development of IAEA/WHO guidelines on GMP for radiopharmaceutical products for investigational use; and
- a consultants' meeting on 22–25 June 2020 to draw up the first drafts of the above guidelines.

More information is available at: www.iaea.org/nuclear-science/isotopes/radiopharmaceutical-production (*19*).

The Expert Committee noted the update.

2.2.2. Pharmacopoeial Discussion Group

Dr Tsuyoshi Ando of the Japanese Pharmacopoeia summarized the latest work of the Pharmacopoeial Discussion Group (PDG), which works to harmonize pharmacopoeial standards in three regions of the world (Europe, Japan and the USA). The PDG generally meets twice a year – either face-to-face or by videoconference – and holds monthly status teleconferences and technical teleconferences in order to advance harmonization work.

In October 2019, the PDG met in Tokyo, Japan; WHO was invited as an observer. At its meeting, the PDG agreed to a number of revisions to existing work programmes, after which 28 of 31 general chapters and 46 of 60 excipient monographs listed in the PDG's current work programme have now been addressed.

The PDG meeting included in-depth discussions on several topics to resolve outstanding issues and advance areas of work. These included finding a mechanism for sharing PDG outcomes (including evaluations, drafts and final texts) with other pharmacopoeias outside the PDG and agreeing to a way forward for maintaining the ICH Q4B annexes; these topic-specific annexes report on the evaluation of specific pharmacopoeial texts and are intended to avoid redundant testing by industry (*20*).

A symposium was also held in October 2019 to celebrate the 30th anniversary of the PDG, with invited perspectives focusing on both the history and future of the PDG.

The next PDG meeting will be held in September 2020 in Rockville, USA.

More information is available at http://www.pmda.go.jp/files/000231993.pdf (*21*).

The Expert Committee noted the update.

2.2.3. United Nations Children's Fund

Dr Peter Svarrer Jakobsen gave an overview of the United Nations Children's Fund (UNICEF) quality assurance system for procurement of finished pharmaceutical products (FPPs). Last year, the agency procured supplies and services worth a total of US$ 3.48 billion for 146 countries. This includes US$ 1.45 billion spent on vaccines and US$ 124.9 million spent on medicines.

UNICEF applies its own quality assurance system but follows WHO's guidance in the *Model quality assurance system for procurement agencies* (*22*) for the procurement of medicines. All procurement activities are centralized in the UNICEF Supply Division in Copenhagen, Denmark, which coordinates approximately 900 logistics staff in around 100 countries.

UNICEF carries out a full technical evaluation of all medicines that have not been accepted or approved by WHO prequalification (PQ), the United States Food and Drug Administration (USFDA), the Global Fund Expert Review Panel, the European Medicines Agency (EMA) Article 58, or stringent regulatory authorities (excluding "for export only").

UNICEF performed around 220 inspections between 2014 and 2018; 28 manufacturers were found to be GMP non-compliant. Inspection reports are shared with international partners upon request, and GMP reports from partners are used to prioritize the agency's own GMP inspections.

More information is available at: www.unicef.org/supply (*23*).

The Expert Committee noted the update.

3. Quality assurance – collaboration initiatives

3.1. International meetings of world pharmacopoeias

Dr Sabine Kopp briefed meeting participants on the Tenth International Meeting of World Pharmacopoeias (IMWP). Each pharmacopoeia covers a different country or region but all of them work to protect public health by creating and making available public standards to help ensure the quality of medicines. Every year, they meet to share experience and expertise and find ways of working together to synchronize their efforts.

In March 2019, the Tenth IMWP was hosted by WHO in Geneva, Switzerland. At the meeting, more than 50 national and regional pharmacopoeial authorities committed to strengthen their cooperation and WHO also launched a new website offering an *Index of World Pharmacopoeias*, along with links to good pharmacopoeial practices (*24*) and reference standards.

IMWP participants discussed a white paper on the added value of pharmacopoeia standards for public health, agreeing on a structure for the document and a plan of action for carrying it forward. Other highlights from the meeting include:

- finalizing a project on models of collaboration for IMWP projects;
- exchanging information on recent challenges, including, for example, contamination following the detection of *N*-nitrosodimethylamine in "sartans"; and
- agreeing on the next IWMP meeting, planned to take place in February 2020 in Strasbourg, France.

More information is available at: www.who.int/medicines/areas/quality_safety/quality_assurance/resources/qas_worldpharmmeetings (*25*).

The Expert Committee noted the update.

4. Nomenclature, terminology and databases

4.1. International Nonproprietary Names for pharmaceutical substances

International Nonproprietary Names (INN) Technical Officers, Dr Sophie Lasseur and Dr Antonio Romeo, described WHO's work to support the development of INNs which serve to help identify pharmaceutical substances or active pharmaceutical ingredients (APIs). WHO collaborates closely with INN experts and national nomenclature committees, to choose a single name of worldwide acceptability for each API that is to be marketed as a pharmaceutical.

Every year, WHO facilitates a global INN consultation to discuss proposals for new INNs and any objections to existing ones. The number and complexity of new biological and chemical requests is increasing each year. Over the past 65 years, nearly 10 000 names have been published; 1000 of those were published in the past five years, across 110 stems. During the last INN consultation in April 2019, a total of 182 INN requests were discussed, with 163 names selected for publication in List 122 of Proposed INNs.

Another major activity of the INN Programme is the School of INNs, a virtual school that promotes INNs as a central teaching and learning theme for all health professionals. The school offers a selection of online courses in the science of nomenclature and naming of pharmaceutical substances, as well as a range of publications to raise awareness of the INN Programme in the scientific and educational community. Plans are under way to develop courses in Chinese, French and Spanish.

In 2019, the INN Secretariat collected information from Member States through an informal questionnaire to assess the impact of the INN Programme, including the extent to which INNs are implemented and used. A total of 52 Member States and one special administrative region answered the questionnaire, reflecting approximately 57% of the world's population. Key findings from the survey show that the INN system is well implemented for prescribing, dispensing and reporting adverse events of pharmaceutical products.

The results also show that, in most Member States, the use of INNs alone is not sufficient for prescribing and dispensing biological therapeutic products, or for surveilling related adverse events. The use of INNs is linked to substitution by the pharmacist and can facilitate pro-generic reimbursement and supply policies; however, the survey shows that INNs are still underused in this regard. Full results from the survey are expected to be published as an article in the coming months.

More information is available at: www.who.int/medicines/services/inn (*26*).

The Expert Committee noted the update.

4.2. Quality assurance terminology

Dr Sabine Kopp reminded participants that all terms and definitions used in ECSPP guidelines are published in the Quality Assurance of Medicines Terminology Database (*25*). Dr Kopp informed the meeting participants that the database has recently been updated.

More information is available at: www.who.int/medicines/areas/quality_safety/quality_assurance/MQA_Terminology_Oct2019.pdf?ua=1 (*27*).

The Expert Committee noted the update.

4.3. Guidelines and guidance texts adopted by the ECSPP

Dr Sabine Kopp provided information on where quality assurance guidelines adopted by the ECSPP can be accessed. After going through a robust global consultative process, all draft guidelines are evaluated by the ECSPP during its annual meeting and, if found suitable, are adopted as international standards.

All adopted guidelines are published on the WHO website (*28*) plus in e-version on memory sticks, and categorized into six broad topic areas: development; production; distribution; inspection; quality control; and other regulatory guidelines.

They can also be found through an alphabetical listing and each can also be found as an annex in the relevant annual ECSPP report.

More information is available at www.who.int/medicines/areas/quality_safety/quality_assurance (*28*).

The Expert Committee noted the update.

5. Prequalification of priority essential medicines and active pharmaceutical ingredients

5.1. Update on the prequalification of medicines

Mr Deus Mubangizi, Coordinator of the WHO Prequalification Team (PQT), updated meeting participants on the latest work of the Team, which works closely with NRAs and partner organizations in order to make quality priority medicines available for those who urgently need them. It maintains a list of prequalified medicines that serves to assure procurement agencies and other users that the medicines they supply meet the acceptable standards of quality, safety and efficacy. To get on the list, a medicine goes through a rigorous evaluation process, to ensure it meets a range of standards, including those adopted by the ECSPP. The application of ECSPP guidelines by the PQT can identify areas that require further guidance or elaboration and, hence, lead to continuous guideline development.

More than 520 medicines have been prequalified to date. In addition to evaluating products for prequalification, the PQT supports access to prequalified medicines through a range of capacity-building activities, and by supporting mechanisms like the collaborative procedure to facilitate approval by NRAs. A recent study shows that before the collaborative procedure existed, it took countries up to 10 years to register a medicine; now the median time for registration is less than three months. An approach to abridged assessment called CRP Lite (collaborative registration procedure-Lite) is being piloted as a way of further facilitating approval by NRAs.

Next steps for the PQT include continuing to assess and facilitate access to medicines; gradually expanding the scope of prequalification to cover more products in the EML; gradually expanding the mechanisms for prequalification through abridged assessment and reliance; expanding the mechanisms available for evaluating new products, with a focus on low- and middle-income countries and emergencies; and expanding the use of risk-based approaches like the Expert Review Panel.

The ECSPP discussed ongoing harmonization of prequalification procedures for different product types.

More information is available at: https://extranet.who.int/prequal (*29*).

The Expert Committee noted the update.

5.2. Update on the prequalification of active pharmaceutical ingredients

Dr Antony Fake, Technical Officer, PQT, noted that in addition to prequalifying medicines, WHO also assesses APIs, either in support of a FPP seeking prequalification or prequalifying the API in its own right. This involves a

similar process of assessment (of quality data) and inspection (of relevant manufacturing sites).

There are 143 prequalified APIs on the current WHO L*ist of Prequalified Active Pharmaceutical Ingredients* (*30*); a further 70 have been accepted in support of a FPP, as part of the API master file (APIMF) procedure. In addition, there are 30 APIs under consideration for prequalification and 18 currently being assessed for the APIMF procedure. The API pipeline remains healthy, boosted in particular by new APIs within therapies for HIV and hepatitis C.

On average, it takes more than a year for an API to achieve prequalification. In an effort to reduce this timeframe, WHO introduced deadlines for manufacturer responses in late 2018. Manufacturers now have six months to respond to the first round of questions, and up to three months for subsequent rounds. WHO also aims to review new submissions and their responses within 90 days; meeting this deadline remains a challenge but assessment times are showing a steady decline.

In May 2018, WHO also introduced the voluntary ICH Q3D guideline for APIMF and API prequalification (*31*, *32*). This guideline represents a process for evaluating and controlling elemental impurities in drug products. Manufacturers can choose whether or not to submit a risk management summary for elemental impurities that may be present in the final API. Although voluntary, the submission of risk assessments is now common.

Work is ongoing to respond to nitrosamine alerts; an initial review of APIMFs has not revealed any conditions of concern.

More information is available at: https://extranet.who.int/prequal/content/active-pharmaceutical-ingredients (*30*).

The Expert Committee noted the update.

6. Quality control – prequalification and WHO monitoring projects

6.1. Update on the prequalification of quality control laboratories

Mr Rutendo Kuwana, Technical Officer, RSS, updated meeting participants on WHO's work to prequalify quality control laboratories (QCLs). A WHO-prequalified QCL can be used to test and verify that pharmaceutical products meet international quality and safety standards and can alert regulators, procurers and manufacturers of the need for corrective action, as and where necessary.

The PQ process comprises five steps: expression of interest; submission of laboratory information; evaluation of submitted information; site inspection; and prequalification. Today, there are 50 prequalified QCLs (public and private) around the world, including 10 in the WHO African Region; 7 in the Region of the Americas; 2 in the Eastern Mediterranean Region; 19 in the European Region; 7 in the South-East Asia Region; and 5 in the Western Pacific Region.

Mr Kuwana also updated the ECSPP on some of WHO's field-sampling and testing projects to monitor the quality of medicines (both those that are WHO prequalified and those that are not); support national quality control efforts; and help NRAs contribute to health systems strengthening.

For example, WHO has carried out regular peer audits of QCLs since 2015. Based on WHO norms and standards, these peer audits serve to build capacity for QCLs. So far, 18 peer audits have been carried out across different regions of the world.

Mr Kuwana also described several other related activities, including:

- **the *GBT*** (*9*), which is a well-recognized process for benchmarking and strengthening regulatory systems and includes a specific indicator on human resources to perform laboratory testing activities;
- **a global competency framework and curriculum**, which is being developed by WHO and partners to support capacity-building and professional development of regulatory staff. These define and develop the knowledge, attitudes and practices required by regulatory staff through education, training, and experience;
- **global and regional networks of official medicines control laboratories** to support shared repositories of data, capacity-building activities, mutual auditing, and harmonization of regulatory norms and standards (including engaging in ECSPP guideline development processes); and
- **partnerships in capacity-building**, which include working with partners in France, Germany and the USA to strengthen quality assurance in specific countries and contexts.

The ECSPP asked for an update on the ongoing monitoring study in six African countries. Mr Kuwana reported that sampling of selected antimalarial medicines, reproductive health medicines and antibiotics had been completed in six African countries (Benin, Ghana, Nigeria, Sierra Leone, Togo and Uganda) and samples were being submitted to WHO-contracted laboratories for full compendial testing. Results were awaited and any non-compliances were to be reported immediately to the participating countries. In addition to the compendial testing, the study also included the use of near-infrared hand-held screening devices near points of sample collection, followed by repeat screening plus the compendial testing by the WHO-contracted laboratories, thus concurrently developing a reference library and database of near-infrared scans of the study products.

The Expert Committee noted the update.

7. Quality control – national laboratories

7.1. External Quality Assurance Assessment Scheme

Dr Herbert Schmidt, Technical Officer, Medicines Quality Assurance (MQA), presented ongoing activities in the External Quality Assurance Assessment Scheme (EQAAS), which offers a platform for pharmaceutical QCLs to measure their performance through a confidential system of blind testing.

Organized by WHO, with the assistance of the European Directorate for the Quality of Medicines and HealthCare (EDQM), the EQAAS has been evaluating the technical performance of QCLs since 2000. This proficiency testing scheme serves to demonstrate the reliability of laboratory analytical results by objective means; provide independent verification of a laboratory's competence; establish mutual confidence with collaborating networks; and support continuous improvement in performance.

The EQAAS is run according to the International Organization for Standardization and International Electrotechnical Commission (ISO/IEC) standards for proficiency testing. In all cases, the results of the testing are followed up. Laboratories that fail the test are subject to a root cause investigation, the results of which they are invited to share and use as the basis for corrective and preventive action plans and targeted training, as and where necessary. Laboratories that do not fail the test are encouraged to use the EQAAS as a stimulus for continuous improvement.

7.1.1. Update on Phase 9 (assay, immediate-release and dissolution) and Phase 10 of the EQAAS

There were 43 participants in Phase 9 of the EQAAS. These had to complete three procedures, using mebendazole chewable tablets as the common test sample:

- Test 1: determine in triplicate the percentage content of mebendazole using the liquid chromatography method:
  - three laboratories reported unacceptable results;
- Test 2: confirm the polymorphic form of mebendazole through infrared absorption spectrophotometry:
  - five laboratories reported the wrong result and nine laboratories did not report any result; and
- Test 3: carry out the dissolution test and determine the percentage of mebendazole released at 60 minutes:
  - seven laboratories reported unacceptable results and five laboratories did not report any result.

In summary, most of the laboratories passed the tests. The tests were well designed and the results obtained were subjected to sound statistical evaluation. The full report of Phase 9 results is under review and expected to be available within the coming weeks.

The Expert Committee noted the update.

7.1.2. Update on Phase 10

Four tests were proposed for the next phase (Phase 10) of the EQAAS, which are yet to be confirmed. Details of the tests will be widely communicated as soon as they have been confirmed.

The protocols for carrying out these procedures will be based on the corresponding provisions of *The International Pharmacopoeia* (*3*).

The Expert Committee noted the update and agreed to submit any comments on Phase 10 to the WHO Secretariat.

This concluded the open session.

PRIVATE SESSION

This private session was for ECSPP members, technical advisers, international organizations and state actors.

8. Quality control – specifications and tests

8.1. *The International Pharmacopoeia*

8.1.1. Update on *The International Pharmacopoeia*

Dr Herbert Schmidt updated participants on *The International Pharmacopoeia* (*3*), which is a collection of quality specifications for pharmaceutical substances and dosage forms, together with supporting general methods of analysis. This collection, which is free to use, serves as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements.

It is primarily based on medicines that are included in the EML; are the subject of invitations to submit an expression of interest (EOI) for prequalification; or are recommended by WHO/United Nations specific disease programmes. It is aligned with other major pharmacopoeias as far as possible. Before being included in the collection, every monograph must be formally adopted by the ECSPP.

First published in the 1950s, *The International Pharmacopoeia* is now in its 9th edition (2019), which is available as a digital library published on the WHO website (*3*), and on USB memory sticks. Based on decisions taken at the Fifty-third meeting of the ECSPP in 2018, the 9th edition includes new and revised texts for seven monographs on pharmaceutical substances, three monographs on dosage forms and two methods of analysis. A total of 13 texts were removed from the 9th edition. The 9th edition was made possible by the strong support of ECSPP experts; the EDQM; WHO Collaborating Centres; collaborating laboratories and organizations; the ICRS Board; and many WHO colleagues.

In total, the current *International Pharmacopoeia* covers 371 monographs on pharmaceutical substances, 142 monographs on specific dosage forms, eight monographs on general dosage forms and 72 methods of analysis.

The Expert Committee noted the update.

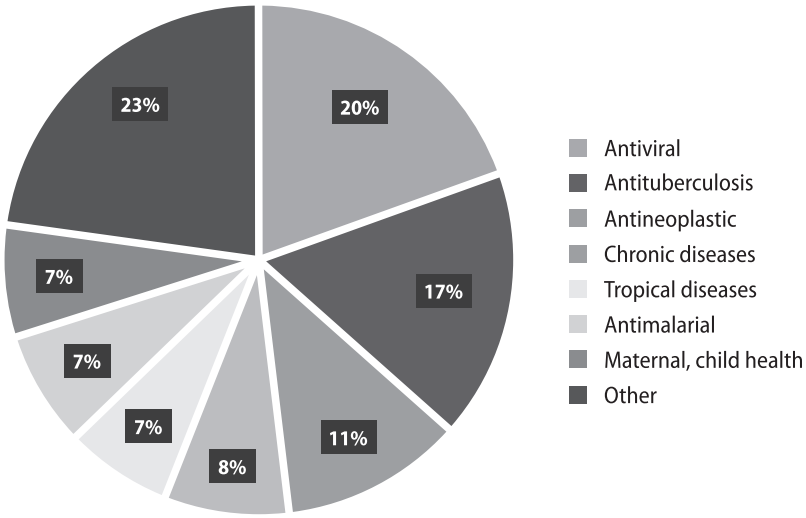
8.1.2. Workplan 2020–2021

The WHO Secretariat shared a proposed workplan for 2020–2021. This includes a listing of medicines proposed for priority development for *The International Pharmacopoeia*. These priority monographs were selected based on a survey to identify medicines that are listed in the EML or that have been invited to submit an EOI for prequalification but are not yet subject to a monograph in the current

British Pharmacopoeia, *European Pharmacopeia*, *United States Pharmacopeia*, *Japanese Pharmacopoeia* or *The International Pharmacopoeia*.

One fifth of the proposed high-priority medicines are antiviral medicines; 17% are antituberculosis medicines and 11% are antineoplastic medicines (see Fig. 1).

Fig. 1
Different types of medicines proposed for priority development



In practice, the monographs from the priority list that actually get developed will depend largely on the resources available and the extent of manufacturers' support.

The 2020–2021 workplan also lists three monographs that are proposed for omission from *The International Pharmacopoeia* because they are no longer listed in the EML or are not invited to submit an EOI for prequalification. In particular, the monographs proposed for omission are:

- chlorpheniramine hydrogen maleate (no longer mentioned in the EML or PQ EOI);
- chlorpheniramine hydrogen maleate tablets (no longer mentioned in the EML or PQ EOI); and
- capreomycin for injection (no longer listed in the EML or PQ EOI).

The ECSPP discussed details of the workplan and suggested that it would be useful, in future, to include in the workplan a list of monographs that are already under development.

The Expert Committee adopted the workplan 2020–2021 as presented, deferring the decision on whether to omit capreomycin for injection to later in the meeting proceedings (see Section 8.3.1).

8.2. Procedure for the development of monographs and other texts for inclusion in *The International Pharmacopoeia*

Dr Herbert Schmidt presented a proposal to revise the procedure for developing, revising and withdrawing monographs and other texts for *The International Pharmacopoeia*. The procedure was first drafted in March 2018. It was discussed at the 2018 ECSPP meeting and has since been further discussed at an informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines in May 2019. It was sent out for public consultation from June to August 2019.

The procedure articulates the steps involved in the full life-cycle of compendial texts: how they are developed or revised and adopted; and how they are, where appropriate, withdrawn from the compendium and archived in a publicly accessible website for posterity. The proposed revisions to this document introduce a reference to the *Good pharmacopoeial practices* document (*24*) that was developed at the IMWP. They also introduce a commitment to foster, harmonize and converge quality standards; make the link between the development of monographs and the workplan more explicit; and underscore the importance of public consultation in the procedure.

The revised procedure also covers more detail on the steps related to establishing ICRS referred to in analytical tests, with a view to speeding up the development and release of ICRS, so that newly published monographs can be used without delay.

The ECSPP discussed the latest version of the document and key aspects of the procedure, including the schedule for posting draft monographs for public comment; the communication channels available for distributing draft monographs among key stakeholders; the transparency of omissions; the challenges in acquiring candidate materials; and the need to synchronize the publication of a new monograph with the release of all appropriate reference standards.

The Expert Committee adopted the *Procedure for the elaboration, revision and omission of monographs and other texts for* The International Pharmacopoeia (Annex 1). It instructed the WHO Secretariat to maintain a flexible schedule for posting monographs for public comment, so as not to introduce unnecessary delays to the procedure. It further suggested that the Secretariat publish an excerpt of the workplan that includes proposed omissions, as a means to improve transparency on upcoming omissions.

8.3. General policy

8.3.1. Update on transition from microbiological to chromatographic assays for antibiotics

Dr Herbert Schmidt updated the ECSPP on the development of guidance on transitioning from microbiological to chromatographic assays for antibiotics. While microbiological methods have historically been used to quantify the total activity of antibiotics (by measuring the total in vitro activity against a reference microorganism), chromatographic methods have come to be considered more discriminative, more precise, and easier and faster to perform.

The transition from microbiological to chromatographic methods has been largely completed for small-molecule, single-component antibiotics. But the use of chromatographic assays for multicomponent antibiotics – including capreomycin sulfate and capreomycin for injection – remains challenging.

At its last meeting in 2018, the ECSPP encouraged continued investigations into how best to transition from microbiological to chromatographic methods for these two capreomycin-related monographs, given the medicines' importance as a second-line antibiotic for treating multidrug-resistant TB (MDR-TB). However, over the past year, new evidence has emerged about the risk of using capreomycin-containing medicines to treat MDR-TB. Following a re-evaluation by WHO of the risks and benefits of capreomycin, these medicines are no longer listed in the EML, nor are they listed in the invitation to manufacturers of antituberculosis medicines to submit an EOI for prequalification.

So far, a correlation between the mass concentration and the microbiological activity of capreomycin has not been established. This poses a problem because capreomycin for injection products are labelled in activity, and the strength of a medicine developed to meet the requirements of an ECSPP monograph would not necessarily correspond to the strength of products already on the market.

The establishment of the two corresponding ICRS for capreomycin sulfate and capreomycin sulfate for injection has also been technically challenging and demanding of resources.

In light of the latest information on capreomycin-containing medicines, the ECSPP was asked to consider a proposal to omit the monographs on capreomycin sulfate and capreomycin for injection from *The International Pharmacopoeia* in 2020.

The ECSPP held a discussion on the proposal, noting that it will take time for the EML decision to be implemented in national essential medicine lists and in practice. For example, even though capreomycin has been removed from the EOI for prequalification, there are still five capreomycin-containing medicines that are prequalified and will remain in circulation for some time.

A proposal to add a sentence or footnote stating that microbiological assays are necessary to assure acceptable potency in both the API and product monographs was discussed.

The Expert Committee discussed various options for proceeding and decided to keep both monographs in *The International Pharmacopoeia* as they are. It further instructed the Secretariat to investigate the possibility of introducing additional language to the monographs for clarification, in collaboration with interested ECSPP members.

8.4. General chapters

8.4.1. 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 ECSPP for consideration. The proposed chapter aims 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*.

Originally drafted in March 2017, the proposed chapter had been through discussion and revision, including two informal consultations, two public consultations and one ECSPP meeting, before being presented to the ECSPP in 2018. Given the large number of comments received during the 2018 public consultation, the ECSPP asked for the last revision to go through another public consultation. This was held from December 2018 to February 2019, after which the draft was also discussed during an informal consultation in May 2019 on Screening Technologies, and Pharmacopoeial Specifications for Medicines.
The ECSPP discussed some of the comments received, including the request to develop a general chapter on X-ray powder diffractometry. It noted that the PDG already has text on X-ray powder diffractometry, which is currently under revision.

The Expert Committee adopted the chapter on polymorphism. It further decided to consider whether to develop a general chapter on X-ray powder diffractometry after the revised PDG text is published.

8.4.2. Residual solvents

The ECSPP was asked to consider including a new note for guidance on residual solvents in *The International Pharmacopoeia*. Drafted in July 2019, the document covers requirements for controlling residual solvents in APIs, excipients and FPPs.

The new document is scheduled to be discussed at the informal consultation in 2020, after which it will be revised accordingly and sent out for public consultation.

The ECSPP discussed the text, proposing a selection of minor edits and holding a discussion on whether or not the document should include a list of solvents and their corresponding limits. It was noted that the source of the list – the most recent ICH document – is likely to change in the coming months, with the scheduled addition of three solvents under development.

The Expert Committee noted the progress made and recommended that the document proceed for public consultation, which will include collecting further feedback on the need for and usefulness of including a list of solvents and limits.

8.4.3. Capillary electrophoresis

The ECSPP was asked to consider revisions to the general chapter on capillary electrophoresis in *The International Pharmacopoeia* (Chapter 1.17), to align with a recent correction of the internationally harmonized texts on capillary electrophoresis developed by the PDG.

The proposed changes have already been discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines.

The Expert Committee discussed the latest version, including comments received during the latest rounds of consultation, and adopted the revised chapter.

8.4.4. Undue toxicity

The ECSPP considered a proposal to remove the test for undue toxicity (Chapter 3.7) from *The International Pharmacopoeia*, including all references to the test in the monographs on kanamycin acid sulfate and kanamycin monosulfate.

This proposal follows a 2018 recommendation from the ECBS, which suggested that GMP and comprehensive quality control measures are more appropriate than tests for undue toxicity, in assuring the quality and safety of vaccines and other biological products. The ECBS concluded that omitting innocuity tests (for undue toxicity) would not compromise the quality and safety of these products, and so recommended omitting them from all published WHO (TRS) documents and excluding them from all future ones.

The proposed revisions to *The International Pharmacopoeia* have already been discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines, and were sent out for public consultation from August to October 2019.

The Expert Committee agreed to omit the test for undue toxicity (Chapter 3.7) from *The International Pharmacopoeia* and the reference to this test in the monographs on kanamycin acid sulfate and kanamycin monosulfate.

8.5. General monographs for dosage forms and associated method texts

8.5.1. Water for injections

The ECSPP was asked to consider a small revision to the current monograph on water for injections. The revision introduces a cross-reference to the working document on *Production of water for injection by means other than distillation* (see Section 11.3 and Annex 3). The addition of specific techniques to the monograph has not been attempted at this stage, but it will go through the standard revision procedure at a later date, once the working document on production has been finalized and adopted.

The ECSPP noted the many interdependencies that exist between these two documents and with other broader WHO documents, and emphasized the need for these to be aligned before publication.

The Expert Committee agreed to align the "Manufacture" section of the monograph with the working document on *Production of water for injection by means other than distillation* (see Section 11.3 and Annex 3). It further recommended opening a new revision process to incorporate the additional tests that were raised in the consultation process.

8.5.2. Correction of ethanol/water mixtures in the reagent section

Following information submitted by a user, procedures for the production of ethanol/water mixtures in the reagents section of *The International Pharmacopoeia* were corrected. The correction was discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines, and published in the 9th edition of *The International Pharmacopoeia*.

The Expert Committee noted the correction.

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

8.6.1. Medicines for maternal, newborn, child and adolescent health

Norethisterone enantate

Norethisterone enantate injection

Based on a submission from a manufacturer and on laboratory investigations, the ECSPP was asked to consider revising the existing monograph on norethisterone enantate, and to adopt a new monograph on norethisterone enantate injection.

The draft revision and the new text were first proposed in June 2017 by a collaborating laboratory. Since then, they have been sent for public consultation (July to September 2017), presented at an ECSPP meeting (October 2017), and revised and discussed at the informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines (May 2019). A third draft of revisions, as presented to the ECSPP meeting in October 2019, is still waiting for the results of ongoing laboratory investigations and will go for public consultation from October to November 2019 before any further action is taken.

The Expert Committee noted the progress made.

Estradiol valerate and norethisterone injection

A draft monograph on estradiol valerate and norethisterone injection was proposed for inclusion in *The International Pharmacopoeia*. The methods and specifications articulated in the monograph are based on a submission from a manufacturer and on laboratory investigations.

The proposed draft was received in September 2018 and presented to the 2018 ECSPP meeting. Since then, it has been discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines. Laboratory investigations are ongoing, and the monograph is scheduled to be sent for public consultation from October to November 2019 (together with the monograph on norethisterone enantate and norethisterone enantate injection).

The Expert Committee noted the progress made.

8.6.2. Antimalarial medicines

Doxycycline hyclate

Doxycycline capsules

Doxycycline tablets

Following information received from a user of *The International Pharmacopoeia*, the ECSPP was asked to consider revising the doxycycline monographs (including doxycycline hyclate capsules and tablets). In particular, the proposed revisions include correcting the description of the buffer used in the mobile phase of the test for related substances and assay; revising the test for ethanol; deleting the test for absorption in the ultraviolet (UV) region; and adopting a range of other minor editorial changes.

The proposed revisions are in line with information found in other pharmacopoeias and in the scientific literature. They were drafted in July 2019, sent to the WHO Expert Advisory Panel on *The International Pharmacopoeia* and Pharmaceutical Preparations (EAP) in August–September 2019, and revised accordingly before being presented to the ECSPP.

The Expert Committee adopted the proposed revisions to the monograph.

Pyrimethamine

Pyrimethamine tablets

Based on a manufacturer's submission in 2017, and on subsequent laboratory investigations, a proposal has been developed to revise the existing monograph on pyrimethamine and to adopt a new monograph on pyrimethamine tablets.

The revisions and new text were first drafted in September 2017, following discussion at the 2017 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines. They were discussed at the ECSPP meeting in 2017 and again in 2018; then, after further laboratory investigations, there were further discussions at the informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines, a public consultation and subsequent revisions. In 2019, the discussion and consultation process was repeated and the documents revised for the fourth time, in response to comments received and the publication of a new draft pyrimethamine monograph in *Pharmeuropa*.

The ECSPP discussed this latest draft of proposed revisions and new text (revision 4), including comments received. It was agreed that there was no need to include an alternative assay method using UV absorbance, but the addition of an alternative option for the identity test using a diode array detector was requested.

The Expert Committee adopted the monographs, subject to the changes discussed.

8.6.3. Antibacterial medicines, including antituberculosis medicines for second-line treatment

Levofloxacin hemihydrate

Levofloxacin tablets

In 2017, the ECSPP was asked to consider revising the monographs on levofloxacin hemihydrate and levofloxacin tablets, to reflect information found in other pharmacopoeias and the scientific literature. A series of laboratory investigations were carried out by a collaborating laboratory from March 2017 to October 2018, to verify that the methods and specifications articulated in the revised and new texts were suitable. The ECSPP reviewed the results of these at its 2018 meeting, suggesting that public consultation was required on the proposed changes.

This informal consultation took place from February to March 2019. The proposed changes were also discussed during the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines. After revisions to reflect comments received at both meetings,

the draft was again sent for public consultation (June–August 2019), and again revised to reflect the comments received. An overview of specifications for related substances in major pharmacopeias was presented.

The ECSPP discussed both monographs, noting that the issues raised for ciprofloxacin with regard to the identity test also apply to levofloxacin. It advised following the same next steps.

The Expert Committee adopted both monographs, subject to finalization by a small group of experts in line with the proposed next steps. It further released "levofloxacin for system suitability" chemical reference substance, established for the *European Pharmacopoeia*, for use according to the provisions of *The International Pharmacopoeia*.

8.6.4. Antiviral medicines including antiretrovirals

Atazanavir sulfate

Based on information received from a collaborating organization, a revision to the monograph on atazanavir sulfate was proposed. In particular, the proposal suggests changing the recrystallization solvent used in identity test A, from acetone to methanol.

The proposed revision was discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines and, on the advice of experts at that meeting, was published in the 9th edition of *The International Pharmacopoeia*.

The Expert Committee noted the revision to the monograph.

Dolutegravir sodium

Dolutegravir tablets

Dolutegravir, lamivudine and tenofovir disoproxil tablets

In 2018, the ECSPP was asked to consider including three new monographs, on dolutegravir sodium, dolutegravir tablets, and dolutegravir, lamivudine and tenofovir disoproxil tablets, in *The International Pharmacopoeia*. The proposed monographs would be the first public standards on dolutegravir, and, as such, are expected to play an important role in ensuring access to safe, effective and quality-assured antiretrovirals.

This year, the proposed text for all three monographs, which were initially drafted by a collaborating laboratory, were discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines and then sent out for public consultation from September to October 2019. The texts remain in development, with further laboratory tests required for both product monographs. All three are scheduled to go to the 2020 informal consultation and be posted for public comment before being brought back to the ECSPP next year.

The ECSPP discussed all three monographs and suggested some minor editorial changes. In addition, the monograph on dolutegravir tablets uses high-performance liquid chromatography (HPLC) for assay but a UV absorbance is suggested as a potential alternative.

The Expert Committee noted the progress made and agreed with the next steps.

Lamivudine

Lamivudine oral solution

The ECSPP was asked to consider revising the existing monograph on lamivudine and to adopt a new monograph on lamivudine oral solution. In particular, the proposals suggest revising the test for related substances (to introduce more specific limits for the impurities) and the assay by HPLC, as well as the addition of a test for lamivudine enantiomer (impurity D) in the monograph on lamivudine.

The proposed revisions and new text were discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines. The texts remain in development, with further laboratory tests pending. Both are scheduled to go to the 2020 informal consultation and be posted for public comment before being brought back to the ECSPP next year. An overview of specifications and limits used in other pharmacopeias was presented.

The ECSPP discussed the current drafts of the monographs, emphasizing the need for limits to be aligned with other pharmacopoeias as far as possible.

The Expert Committee noted the progress made and agreed with the next steps.

Oseltamivir phosphate

Oseltamivir capsules

Oseltamivir powder for oral suspension

The ECSPP considered a proposal to revise the existing monographs on oseltamivir phosphate and oseltamivir capsules and to adopt a new monograph on oseltamivir powder for oral suspension.

Based on information submitted by a manufacturer, a first draft of the revisions to the oseltamivir phosphate monograph was presented to the ECSPP for discussion. The monographs on oseltamivir capsules and powder still need to be drafted. All specifications and provisions in the monographs will then need to be verified and validated through laboratory investigation, and then sent out for public consultation before submitting the monographs to the ECSPP for potential adoption in 2020.

The Expert Committee noted the progress made and agreed with the next steps.

Tenofovir disoproxil fumarate

A proposal was made to revise the existing monograph on tenofovir disoproxil fumarate, to add a test for tenofovir disoproxil enantiomer (impurity G) and make some other minor editorial changes.

These changes are proposed to align *The International Pharmacopoeia* with the latest information found in other pharmacopoeias and the scientific literature and to reflect the results of laboratory investigations performed by a collaborating laboratory.

A first draft of the revisions was prepared in July 2019 and sent for initial comments. It remains in development. All proposed revisions still need to be verified and validated through laboratory investigation, and then sent out for public consultation before submitting the monographs to the ECSPP for potential adoption in 2020.

The Expert Committee noted the progress made and agreed with the next steps.

Ritonavir

Ritonavir tablets

The ECSPP first discussed revising existing monographs on ritonavir and ritonavir tablets in 2017. Since then, drafts of these monographs have been discussed at two informal consultations on Quality Control Laboratory Tools and Specifications for Medicines (in 2017 and 2018) and at the ECSPP meeting in October 2018. Laboratory reports for both monographs have been received and are due for internal discussions.

Development of the revised monographs is ongoing. It is being carried out in collaboration with the *British Pharmacopoeia*, in an effort to share the workload of laboratory investigations, base specifications on more samples from more regions of the world, and ensure alignment with other pharmacopoeias as far as possible.

The ECSPP discussed the monographs, suggesting some amendments and harmonization of the test for related substances with other pharmacopoeias. It noted that a new monograph on ritonavir oral solution has not yet been developed, as samples have not yet been made available.

The Expert Committee noted the progress made.

Sofosbuvir

Sofosbuvir tablets

The draft text for two new monographs on sofosbuvir and sofosbuvir tablets was proposed. Based on information submitted by two manufacturers, the proposed monographs were drafted by a collaborating laboratory in April 2019 and then

discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines.

Both monographs are scheduled to be sent for public consultation from December 2019 to January 2020.

The ECSPP discussed various aspects of the monographs, including the test for related substances and the nomenclature of impurities. It noted the increasing role of sofosbuvir in addressing public health needs in low- and middle-income countries and suggested that development of both monographs should be expedited.

The Expert Committee adopted both monographs, subject to finalization by a small group of experts.

8.6.5. Other medicines for infectious diseases

Ciprofloxacin hydrochloride

Ciprofloxacin tablets

A proposal was made to revise the existing monograph on ciprofloxacin hydrochloride in *The International Pharmacopoeia* and to adopt a new monograph on ciprofloxacin tablets.

These changes are proposed to reflect the results of laboratory investigations performed by a collaborating laboratory.

The revisions and new text were first drafted in April 2019. They were discussed at the May 2019 informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines and sent for public consultation from July to September 2019. A revised version of both texts was drafted in September 2019, in response to comments received.

The ECSPP discussed various aspects of the draft monographs, including the proposed identity tests and the impurity limits. It highlighted the need for harmonization with other pharmacopoeias as far as possible. In response to the discussion, the WHO Secretariat proposed a series of next steps that comprise incorporating a third option for the identity test using a liquid chromatography (LC) and UV method (while keeping the option based on HPLC and thin-layer chromatography [TLC]); completing additional investigations to confirm the new option; sending the revised monographs for public consultation; reviewing them at the next informal consultation; and, subject to expert endorsement, publishing them in the 10th edition of *The International Pharmacopoeia*.

The Expert Committee adopted the monographs, subject to finalization by a small group of experts in line with the proposed next steps. It further released "ciprofloxacin for peak identification" chemical reference substance, established for the *European Pharmacopoeia*, for use according to the provisions of The International Pharmacopoeia.

8.6.6. Medicines for tropical diseases

Albendazole

Albendazole chewable tablets

Albendazole tablets

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 still includes the test for related substances by TLC. Consequently, a revision of the monograph on albendazole was proposed, in order to replace the TLC test for related substances with an HPLC test. At the same time, new text will be added to inform users that the substance shows polymorphism, to introduce a test on "clarity and colour of solution", to update the style of the monograph, and to make several other minor edits. A new monograph on albendazole tablets was also proposed.

The revised and new drafts were completed in February 2018 and discussed at the informal consultation on Screening Technologies and Pharmacopoeial Specifications for Medicines in May 2018. In October 2018, the ECSPP adopted the monographs, subject to their finalization by a group of experts.

Some issues remain, particularly with the dissolution test, and a concern over the polymorphic form. For this reason, experts at the 2019 informal consultation recognized a need for further tests and verification and advised carrying out more investigations before re-submitting the draft monographs to the ECSPP. These are ongoing.

The Expert Committee noted the progress made and requested that these monographs be further discussed at the next informal consultation. They should then be further developed or directly sent for public consultation, before being submitted to the ECSPP for possible adoption in 2020.

9. Quality control – international reference materials

9.1. Update on International Chemical Reference Substances

Dr Andrea Lodi, Council of Europe, and Dr Herbert Schmidt, gave a report from the custodian centre of the dedicated ECSPP subgroup on ICRS.

The EDQM has been responsible for establishing, storing and distributing ICRS since 2010. Since the last meeting of the ECSPP in October 2018, the ICRS Board has released standards on the following:

- metacycline ICRS 1
- artemether ICRS 3
- albendazole ICRS 1
- ethinylestradiol ICRS 4.

It also released the following chemical reference substances, established by the EDQM for use according to the provisions of *The International Pharmacopoeia*:

- ciprofloxacin hydrochloride for peak identification
- levofloxacin for system suitability.

Dr Lodi summarized some of the key achievements of the EDQM in relation to ICRS in 2018. In particular, the EDQM established nine reference substances for WHO, including four new ones; brought all the leaflets that come with the ICRS up to the same level; and monitored 18 standards (with no significant findings on quality to report). Most recently, the EDQM has introduced the concept of "procurability" of candidate materials, in an effort to address the problem of ensuring that all reference standards are available for any given monograph.

The WHO Secretariat expressed its gratitude to:

- the EDQM for its work in establishing, storing and distributing ICRS and for providing guidance and support to primary standards;
- the ICRS Board for reviewing the establishment reports and releasing the ICRS; and
- 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 informed the ECSPP that there has been no substantial progress in developing new guidance text for the graphic representation of pharmaceutical substances. New text is required to replace the existing guidance, which was last updated in 1996. However, this will not be easy to achieve because many of the molecules are different now and new technologies necessitate major changes compared to the previous version.

The WHO Secretariat is working to progress on this document and will report back at next year's meeting.

The Expert Committee noted the update.

11. Quality assurance – good manufacturing practices and inspection

11.1. Inspection guidelines and good practices with partner organizations

11.1.1. Revision of *WHO good manufacturing practices for sterile pharmaceutical products*

Dr Roberto Conocchia, EMA, Dr Mustapha Chafai, Technical Officer, PQT, Dr Joey Gouws, Group Lead for Inspection, and Dr Sabine Kopp, presented the progress in revising the *WHO good manufacturing practices for sterile pharmaceutical products* (*33*), which has been ongoing since 2017. This work represents a collaborative effort between the European Union (EU), the EMA, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and WHO, to try and align standards across the world. Establishing a common language is expected to benefit authorities and manufacturers, would save resources and would ultimately improve patients' access to quality medicines.

The revised guidance includes new sections on scope, utilities and environmental and process-monitoring and introduces the principles of quality risk management to allow for the inclusion of new technologies and innovative processes. First drafted at the end of 2017, the guidance was refined internally and sent out for public consultation from December 2017 to March 2018.

Compared to the original, the main changes are as follows:

- introduction of new technologies;
- text on quality risk management principles;
- structure for a more logical flow; and
- details to clarify multiple sections.

The public consultation raised 6200 comments from more than 140 companies and organizations. Over the past year, a working group of experts has worked through these comments, discussing key issues raised by industry, such as the concern that enforcing the new expectations may create shortages for medicines and cost increases for some important lifesaving antibiotics. Other key topics of discussion included sterilization of lyophilizers; multi-use of product filters; ISO classification; and pre-use and post-use integrity testing.

The group continued to refine the document through several rounds of revisions and sent it to the EU and PIC/S inspectorates for comment in September 2019. A consolidated document is expected from the working group by October 2019 and the approval of this document is expected at the November 2019 meeting of the Inspection Working Group at the EMA.

The EU plans to hold a targeted stakeholders' consultation at the beginning of 2020 and, after reviewing the feedback received, to publish the document in June 2020. During the consultation, stakeholders will be invited to comment on specific elements of the text, through a targeted questionnaire.

The ECSPP commended the effort to harmonize this guidance and suggested that a similar effort could be extended to other products. However, given that the document has tripled in length and changed substantially since it was last put out for public comment in 2017, the ECSPP emphasized the need for a second public consultation before the document can be considered for adoption by WHO.

It further agreed that the EU-led targeted consultation would not be sufficient for this purpose because the opportunity for commenting will be restricted. Some WHO Member States are not members of either the EU or PIC/S and so have not been involved in refining the document since 2017; they may have feedback on parts of the document that are not open for comment in the questionnaire. The ECSPP was clear that there must be full transparency in commenting on the text before it can consider adopting it.

The Expert Committee recommended a second round of public consultation on the current version of the guidance, to be held in parallel to the targeted EU consultation. It asked for an update on progress at its next meeting in 2020, with the possible adoption of a revised guideline.

11.1.2. *International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products*

Dr Aruna Korde and Dr Sabine Kopp summarized the progress by the IAEA and WHO in updating *Guidelines on good manufacturing practices for radiopharmaceutical products* (*18*), as recommended by IAEA experts in early 2018. They noted that the previous version covered compounding and dispensing radiopharmaceuticals; investigational radiopharmaceuticals; and industrially manufactured radiopharmaceuticals. The guidelines under discussion relate to the first of these.

The first draft of the new guideline was developed following an IAEA consultation on harmonization of health regulations related to the production of radiopharmaceuticals, held in November 2018. The draft was refined by WHO and IAEA in turn, before being widely circulated for public consultation from January to March 2019. All comments received were collated and considered by the IAEA and WHO through a consultative process, and the draft was revised accordingly. A second round of public consultation was held in September 2019. There were approximately 30 comments received, mostly requesting minor editorial changes, which were reviewed by the IAEA experts.

The ECSPP noted that this guideline is not intended to be a standalone document but rather a companion document to other relevant WHO guidance. It also goes hand in hand with IAEA guidelines on radioactivity and so focuses on health-related guidance only. It is envisaged that the document will also be complemented by two further guidelines yet to be developed: one for the cold kits used in the production of radiopharmaceuticals and one for radiopharmaceuticals for investigational use.

Key discussion points of the ECSPP included issues related to stability; mechanisms for informing users of quality issues; qualification requirements for personnel; and consistency in language and style. Suggestions for amendments in each of these areas were made and it was suggested that these should be taken back to the working group for incorporation into the document.

The Expert Committee adopted the *International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products* (Annex 2), subject to finalization by a small group of experts.

11.2. Update on the cleaning validation

Mr Vimal Sachdeva, Technical Officer, PQT, and Dr Valeria Gigante, Technical Officer, Medicines Quality Assurance, reported on the progress in updating the WHO *Cleaning validation* guidance (Appendix 3 to the WHO *Good manufacturing practices: guidelines on validation* (*34*)), as recommended by the ECSPP at its meeting in 2018. The work to update the WHO *Supplementary guidelines on good manufacturing practices: validation* (*35*) and its seven appendices commenced in 2013; the main text and three appendices (on *Analytical method validation*, *Validation of computerized systems* and *Qualification of systems and equipment*) have already been revised and adopted by the ECSPP (*36*–*38*).

In July 2019, the update to the cleaning validation appendix was discussed during the informal consultation on Good Practices for Health Products Manufacture and Inspection. A lot of discussion focused on safe cleaning limits for carry-over, which are important to prevent cross-contamination of pharmaceutical products manufactured in shared facilities. In particular, participants at the consultation discussed whether or not to adopt an approach for establishing cleaning limits based on health-based exposure limits (HBELs), integrating toxicological and pharmacological data and relevant corrective factors. The primary concept of HBELs is for the pharmaceutical manufacturers to perform risk assessment to identify whether or not a dedicated facility is required for highly potent and/or highly sensitizing molecules; if not, they can use a shared facility. In addition, the HBEL concept can be applied for calculating maximum allowable carry-over during cleaning validation.

The ECSPP discussed recommendations emerging from the July 2019 informal GMP consultation on how to develop or revise guidance on cleaning validation.

The Expert Committee noted that the HBEL approach is rooted in pre-clinical and clinical studies and, as such, is considered to be a more scientific and evidence-based approach than the current three criteria (visual examination, 10 ppm and 1/1000 of maximum daily dose) used for establishing cleaning limits. However, it also noted that adopting an HBEL approach could have far-reaching impacts on manufacturers. Small manufacturers may struggle to meet an HBEL-based requirement because they would need to either hire an in-house toxicologist or outsource the work. Manufacturers with legacy products may find it similarly costly to apply the requirement retrospectively.

The ECSPP also noted that HBEL setting has already been adopted by the EMA and that it is already being implemented. This places PQ inspectorates in a difficult situation as they cannot inspect against the HBEL requirement because it is not in the WHO guidelines that set their mandate.

The ECSPP recognized the value of developing a harmonized approach across guidelines – for both inspectorates and manufacturers – but also acknowledged the mammoth task involved in integrating an HBEL approach into WHO procedures. It proposed that, in the first instance, a separate *Points to consider* document be developed to introduce the topic, and to highlight the complexities involved, and to look into establishing a common understanding. Following this, an appropriate set of guidelines can then be developed for all stakeholders.

The Expert Committee endorsed the development of a *Points to consider* document in line with the discussion.

11.3. Update on water for injection

Dr Adriaan J. Van Zyl and Dr Sabine Kopp gave an update on the development of a working document on water for injection (WFI) by means other than distillation. In recent years, following extensive consultation with stakeholders, several pharmacopoeias have adopted revised monographs on WFI that allow production by non-distillation technologies, such as reverse osmosis. In 2017, the ECSPP recommended that the WHO Secretariat should collect feedback on whether or not to revise the WHO specifications and GMP on WFI, and how to do so.

A working document for public inquiry was circulated in March 2018 and comments received were consolidated one month later. The issue was discussed at a consultation on Screening Technologies, Sampling and Specifications for Medicines in May 2018 and then again during an informal consultation on

Good Practices for Health Products Manufacture and Inspection in July 2018. Comments and feedback were consolidated and presented, along with the document, to the ECSPP in October 2018.

Following discussion, the ECSPP agreed that the monograph in *The International Pharmacopoeia* (*Water for injections*) and WHO *Good manufacturing practices: water for pharmaceutical use* (*39*) should be revised to allow technologies other than distillation for production of WFI.

In early 2019, the WHO Secretariat prepared a draft guidance text for the production of WFI by means other than distillation. It was sent to stakeholders, including the EAP, and put out for public consultation from February to March 2019. The text and comments were discussed at two informal consultations (Screening Technologies and Pharmacopoeial Specifications for Medicines; and Regulatory Guidance for Multisource Products) in May 2019, and again, with all new comments, at the informal consultation on Good Practices for Health Products Manufacture and Inspection in July 2019. The text was then revised and sent out again for feedback, including to the EAP and the public. The main requests raised by the comments received include expanding quality risk management, including alert and action limits; removing pH as a quality parameter in testing for WFI; and implementing several editorial changes. The text was revised accordingly, for presentation to the ECSPP.

The ECSPP discussed the latest changes and proposed various revisions to the document for clarification.

The Expert Committee also considered the options for publishing the new WFI text, emphasizing the value of having an integrated set of guidelines across WHO, but recognizing that this could cause delays in making the document available.

The Expert Committee adopted *Production of water for injection by means other than distillation* (Annex 3) and noted that it should be integrated into WHO's existing guideline on *Water for pharmaceutical use* (*39*).

11.4. Guidance on good data and record management practices

Dr Adriaan J. Van Zyl and Dr Sabine Kopp presented a proposal for updating the WHO *Guidance on good data and record management practices* (*40*) to reflect on experience gained from implementation.

The proposal is based on dividing the existing guideline into two parts: main requirements and examples (in a way similar to the new heating, ventilation and air-conditioning systems series (*41*)). This proposal was presented at two informal consultations in 2019 – one with regulators and one with inspectors. Both consultations recommended further developing the proposal and reporting to the ECSPP.

The proposed main text covers 10 main areas: basic principles; quality risk management; management review; outsourcing; training; data; data integrity; good documentation practices; computerized systems; and corrective and preventive actions.

The other proposed text includes 10 specific examples in management of data integrity, ranging from quality risk management to data entry, changes and controls, among other things.

The next steps include sending out the draft texts for public consultation and further revision and refinement based on comments received.

The Expert Committee noted the progress made and agreed with the next steps.

11.5. Update on the development of good chromatography practices

Dr Adriaan J. Van Zyl and Dr Sabine Kopp summarized the progress in developing new guidance on good chromatography practices, as recommended by the ECSPP in its last meeting in October 2018. The new guidance acknowledges the increasing use of methods such as HPLC and gas chromatography (GC) and the need to ensure that the results of these are attributable, legible, contemporaneous, original and accurate. To that end, it aims to provide information on good practices in the analysis of samples where HPLC and GC are used.

A first draft of the guidance was developed in early 2019 and sent to stakeholders, including the EAP, and put out for public consultation from February to May 2019. The text and comments received were discussed at the informal consultation on Good Practices for Health Products Manufacture and Inspection in July 2019 and the guidance was revised to address feedback at that meeting. The revised guidance was again sent to the EAP and put out for public consultation from July to September 2019. All comments were again consolidated and the text was revised accordingly.

The ECSPP reviewed the document in its current form and suggested several further edits for clarification and accuracy. It also discussed several unresolved issues raised by the feedback, most notably concerns about the definitions – for example, their alignment with other pharmacopoeias, their level of detail and whether they are required at all.

Other topics of discussion included integration; column management; chromatographic methods (acquisition and processing); and permitted changes to chromatographic conditions.

The Expert Committee adopted the *Good chromatography practices* (Annex 4).

11.6. Quality management system requirements for national good manufacturing practice inspectorates

Dr Dimitrios Catsoulacos, Technical Officer, PQT, and Dr Valeria Gigante described the progress in revising guidance documents related to inspectorates and inspections, as recommended by the ECSPP at its Fifty-first meeting in October 2016. This includes two documents: *Guidance for inspection of drug distribution channels* (*42*) and *Quality system requirements for national good manufacturing practice inspectorates* (*43*). The former was published in 1999 and defined the minimum standards at the time for establishing a quality system for inspectorates to supervise distribution operations; and gave general guidance on conducting and documenting inspections and collecting product samples. The latter was published in 2002 and included the basic requirements for establishing a quality system for a GMP inspectorate.

In 2018, the ECSPP endorsed a recommendation to merge the guidelines on inspection of drug distribution channels and quality system requirements for GMP inspectorates, while broadening the scope to include all good practice-related inspections carried out by NRAs and to align the content with current ISO-related norms.

The first draft of a combined guideline was developed early in 2019. It has undergone two public consultations and was discussed at the informal consultation on Good Practices for Health Products Manufacture and Inspection in July 2019. It has since been revised in response to the comments received.

The ECSPP reviewed the latest draft and discussed some outstanding requests for restructuring the document. Specific topics of discussion included documentation (both general and related to inspection processes), workplan development and the use of subcontracted personnel.

The Expert Committee noted the efforts made to align the guideline, not only with ISO-related norms but also with the *WHO guideline on the implementation of quality management systems for national regulatory authorities* (Annex 13).

The Expert Committee adopted the *Quality management system requirements for national inspectorates* (Annex 5).

11.7. Environmental aspects of manufacturing for the prevention of antimicrobial resistance

Ms Stephanie Croft, Technical Officer, PQT, and Dr Valeria Gigante spoke about antimicrobial resistance (AMR) in relation to manufacturing and inspection. Against a backdrop of rising global concern about AMR, the ECSPP, at its last meeting in October 2018, asked the WHO Secretariat to develop a document outlining points for manufacturers and inspectors to consider in preventing AMR.

Such a *Points to consider* document was drafted in early 2019, building on the November 2018 decision of the WHO Executive Board to provide technical input to GMP guidance on waste and wastewater management from the production of critically important antimicrobials. The drafted document aims to, among other things:

- raise awareness among manufacturers, GMP inspectors and inspectorates of the existing GMP guidance that applies to the production of antimicrobials;
- encourage Member States to establish and enforce appropriate requirements on their local pharmaceutical production facilities; and
- consider options for reducing and mitigating the uncontrolled disposal of waste and wastewater containing antimicrobials, with a focus on the role of GMP and inspectors in this.

Comments on the *Points to consider* document were collected from WHO colleagues working on AMR; the PQT; the EAP; the Joint Meeting on Regulatory Guidance for Multisource Products; the EMA GMP Inspection Working Group; and the public, from May to June 2019.

The draft, and feedback on it, was then discussed at the July 2019 informal consultation on Good Practices for Health Products Manufacture and Inspection and revised accordingly. In particular, the scope was narrowed and amended to be a policy document for use by manufacturers when they carry out self-audits, and also for inspectors during GMP inspections. In the meantime, it was also discussed at the International API teleconference groups in August 2019 and was mentioned in the July 2019 draft of the Organisation for Economic Co-operation and Development (OECD) document entitled *Pharmaceutical residues in freshwater* (*44*).

The informal consultation also considered proposals on the potential role of GMP inspectors to tackle AMR, and on the need to revise the WHO GMP main text to address this issue. It was decided against revising the main text but to propose a more gradual approach instead. Two recommendations for next steps emerged from the discussion:

- raise awareness by circulating the revised *Points to consider* document to manufacturers and others; and
- sensitize manufacturers to the new expectations, by collecting information on current waste and wastewater management practices at pharmaceutical manufacturing facilities, through a survey designed to verify the *Points to consider* recommendations. Outcomes of the survey could also be used to establish further recommendations on appropriate action.

The ECSPP reviewed the latest version of the document, noting that while the document has been restructured, the majority of the content has not changed. It further noted that the document focuses purely on contamination of the environment through production and does not attempt to address the many other drivers of AMR.

Topics of discussion included the value of using examples to illustrate the extent of the problem and the potential challenges to implementing the points to consider in practice. The ECSPP also acknowledged the importance of ensuring collaboration between product and environment inspections, and of not mandating the new expectations, to allow for regulatory authorities that may have no jurisdiction over waste and wastewater.

The Expert Committee also discussed both recommendations that emerged from the July 2019 informal discussion.

The Expert Committee acknowledged the importance of tackling AMR and adopted the *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance* (Annex 6). It further recommended the WHO PQT to conduct a survey of manufacturers as proposed, to raise awareness of AMR.

11.8. Update and recommendations from the meeting on Good Practices for Health Products Manufacture and Inspection

Dr Sabine Kopp informed the ECSPP that a copy of the report from the meeting on Good Practices for Health Products Manufacture and Inspection (held in July 2019) has been made available.

The Expert Committee noted the report.

12. Quality assurance – distribution and supply chain

12.1. Update of the *Good storage and distribution practices* guideline

When it last met in October 2018, the ECSPP recommended consolidating guidance on good storage practices and good distribution practices with elements from the guidelines on inspecting drug distribution channels; and to harmonize it with EU and PIC/S standards. Dr Adriaan J. Van Zyl and Dr Sabine Kopp updated the ECSPP on the progress to date.

A draft consolidated document was prepared in early 2019, then sent to the EAP and sent out for public consultation from April to June 2019. It was then discussed, alongside comments received, at the informal consultation on Good Practices for Health Products Manufacture and Inspection in July 2019. A revised version was prepared to address feedback from the consultation and re-sent to the EAP and put out for a second public consultation from August to September 2019.

As it stands, the document sets out the steps required by different stakeholders in the supply chain to fulfil their responsibilities in avoiding the introduction of substandard and falsified products into the market. In particular, it offers guidelines for storing and distributing medical products; it is intended to supplement, rather than replace, national or regional guidelines to meet specific needs or contexts.

The ECSPP reviewed the latest draft, along with comments received, and considered the various requests for revision, including on issues such as personnel; labelling and storage conditions; stock control and retesting; appropriate transportation; and qualified suppliers. The Expert Committee emphasized the need to ensure consistency and accuracy in how the document uses specific terms and to align with WHO terminology.

The Expert Committee adopted the *Good storage and distribution practices for medical products* (Annex 7), subject to the changes discussed.

12.2. Shelf-life for supply and procurement of medical products

Dr Adriaan J. Van Zyl and Dr Sabine Kopp summarized the progress in developing a document on remaining shelf-life for procurement and supply of medical products. The need for such a document was clearly articulated at the last ECSPP meeting in October 2018, where the ECSPP acknowledged considerable differences in existing guidelines on the acceptable shelf-life of products bought and supplied by procurement agencies.

The proposed text was drafted in early 2019, based on information collected from several different agencies and interested parties and an informal discussion with stakeholders. A draft was sent to members of the Interagency

Pharmaceutical Coordination group and others during a public consultation, and the comments received were reviewed at the informal consultation on Good Practices for Health Products Manufacture and Inspection in July 2019. The draft was updated and sent to the EAP and put out for public consultation from July to September 2019; feedback was consolidated for the ECSPP.

The document aims to facilitate national authorization of imports; support efficient processing; ensure sufficient stocks; address barriers to access and supply; prevent dumping and stock-outs; and prevent donations of near out-of-date medical products.

The ECSPP acknowledged the value of this document in guiding procurement agencies, regulators and other stakeholders; in harmonizing policies in this area; and in addressing the problem of short remaining shelf-life of donated medicines during emergencies. It reviewed the latest draft of the policy, including the proposed changes suggested by the consultation. Key topics of discussion included whether or not to remove the annex and how to refine the title, objectives and scope of the document. The Expert Committee emphasized the value of providing an illustrative example (rather than strict recommendations) within the appendix; and the need to ensure the document is a *Points to consider* document rather than a policy, and that it is targeted at Member States and regulatory authorities as well as donors, manufacturers and suppliers.

The Expert Committee adopted the *Points to consider for setting the remaining shelf-life of medical products upon delivery* (Annex 8), subject to the changes discussed.

12.3. Update and new WHO guidance, procedures and operational documents for pharmaceutical procurement

12.3.1. WHO/United Nations Population Fund prequalification guidance on contraceptive devices and condoms

Ms Seloi Mogatle, United Nations Population Fund (UNFPA), Dr Mario Festin, Medical Officer, WHO Reproductive Health and Research, and Dr Sabine Kopp summarized the WHO/UNFPA collaboration to update the existing prequalification guidance for contraceptive devices and condoms, which was originally published in 2008 (*45*, *46*) and no longer reflects the understanding and evidence in the field.

As agreed at the ECSPP meeting in October 2018, UNFPA and WHO have separated out different aspects of the current procedure for contraceptive devices and condoms and are developing seven different documents:

- prequalification programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices;

- technical specifications for male latex condoms;
- specifications for plain lubricants;
- condom quality assurance;
- guidance on testing of male latex condoms;
- recommendations for condom storage and shipping temperatures; and
- guidance on conducting post-market surveillance of condoms.

All seven documents were restructured and revised in the first half of 2019, then sent to the EAP and put out for public consultation in July 2019. The comments received were reviewed by a group of specialists in October 2019, prior to being presented to the ECSPP.

At UNFPA's request, the ECSPP focused on the first three documents (on UNFPA's Prequalification Programme guidance, condom quality assurance and specifications for plain lubricants), noting that all comments have been addressed. It suggested some further minor revisions, including recommending changes to clarify that, while the specifications for plain lubricants are principally targeted at procurement agencies, they may also be used by regulators for public procurement.

The next steps for the remaining four documents include incorporating comments from the latest consultations and then bringing them back to the ECSPP for possible adoption at its next meeting in 2020.

The Expert Committee adopted the following guidelines: *World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices* (Annex 9); *World Health Organization/United Nations Population Fund technical specifications for male latex condoms* (Annex 10); and *World Health Organization/United Nations Population Fund specifications for plain lubricants* (Annex 11), subject to the changes discussed. It further recommended proceeding with the next steps as discussed.

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*

Professor Giovanni Pauletti, Professor Marival Bermejo Sanz and Dr Valeria Gigante gave an overview of the WHO Biowaiver Project and presented the Project's work over the past year. As part of its 2006 guidance on waiving bioequivalence requirements for immediate-release oral solid dosage forms in the EML, WHO provided a list of APIs that are eligible for biowaiver. In 2017, at its Fifty-second meeting, the ECSPP recommended that the WHO Secretariat revise this biowaiver list, based on laboratory data.

The first phase of the Biowaiver Project started in 2018, using a sound methodology as detailed in the WHO protocol for performing equilibrium solubility experiments (*47*) to classify APIs for biowaiver according to the Biopharmaceutics Classification System (BCS) framework . The first set of three APIs prioritized for the revised WHO Biowaiver List using this method was based on four criteria:

- the API must be contained in medicines listed in the EML;
- the API must be intended to be formulated as immediate-release, solid oral dosage forms;
- the API must belong to therapeutic areas of major public interest; and
- specific physical-chemical properties for the API must be known.

The first set of APIs was agreed, after consultation, at the 2018 ECSPP meeting and then classified (Cycle I). A second set of 14 APIs was also prioritized and these were classified in 2019 as part of Cycle II. The results of the APIs studied during both cycles are summarized in Table 1.

Table 1
WHO solubility classification of active pharmaceutical ingredients prioritized from the *WHO Model List of Essential Medicines* (*12*)

Medicine	Therapeutic area	Indication [a]	Highest therapeutic dose (mg) [b]	API PQ EOI / PQ	2019 WHO classification
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	No	II/IV

Table 1 *continued*

Medicine	Therapeutic area	Indication[a]	Highest therapeutic dose (mg)[b]	API PQ EOI / PQ	2019 WHO classification
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	No	II/IV
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
codeine (sulfate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of *P. vivax* and *P. ovale* infections)	15	No	I/III
pyrimethamine	Antiprotozoal medicines	Antimalarial medicines	75	Yes	II/IV

Table 1 *continued*

Medicine	Therapeutic area	Indication [a]	Highest therapeutic dose (mg) [b]	API PQ EOI / PQ	2019 WHO classification
raltegravir (potassium)	Antiviral medicines	Antiretrovirals (HIV in pregnant women and in second-line)	400	Yes	II/IV
rifampicin	Antibacterials	Antituberculosis/ antileprosy medicines	750	Yes	II/IV
tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III

API: active pharmaceutical ingredient; PQ: prequalification; PQ EOI: expression of Interest for prequalification (*30*); WHO: World Health Organization.

[a] *21st WHO Model List of Essential Medicines* (2019) (*12*).

[b] According to the WHO guidelines, *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*48*), APIs belonging to Classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (i.e. either Class I or Class III). The present solubility characterization is already sufficient to provide an indication on whether or not an API is eligible for biowaiver.

Note. For exemption from an in vivo bioequivalence study, an immediate-release, multisource (generic) product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to those of the reference product. A risk-based evaluation should also account for the excipients used in the formulation of the finished pharmaceutical product.

Compared with the 2006 classification, this latest classification means that three compounds (aciclovir, amoxicillin, ethionamide) have moved from high- to low-solubility groups.

Professor Pauletti pointed out some of the technical challenges encountered during Cycle II, which include issues around the amount of API used for the solubility studies; the analytical documentation; the physical properties of the API; and API stability.

Dr Gigante presented a third set of 10 APIs that have been prioritized as the potential focus of Cycle III, through collaboration with PQT-Assessment and a public consultation:

1. chloroquine (malaria)
2. cycloserine (MDR-TB)

3. delamanid (MDR-TB)
4. emtricitabine (HIV)
5. entecavir (hepatitis B)
6. mefloquine (malaria)
7. miltefosine (leishmaniasis)
8. oseltamivir (influenza)
9. paracetamol (analgesic)
10. sofosbuvir (hepatitis C).

The ECSPP congratulated the project team on their valuable work and agreed that the project generates robust experimental data to support a revised WHO BCS-based classification system. The Expert Committee discussed various aspects of the project and made some suggestions for improvement. Topics of discussion included, among other things, the criteria for decision-making; plans for permeability studies; and the potential impact of excipients and polymorphs on solubility.

In discussing plans for Cycle III, the low solubility of delamanid was highlighted, with a suggestion that it be removed from the list of compounds to be classified.

The ECSPP agreed to proceed with the publication of the outcome of Cycles I and II to replace the old listing that was based on literature. This will be a living document, published in the report of the ECSPP and updated as data become available (Annex 12).

The Expert Committee took note of the results and recommended continuing the BCS-based classification of APIs contained in medicines listed in the EML and prioritized according to Member States' and WHO partners' needs. It further recommended publishing the results of Cycle II, and proceeding with Cycle III, subject to the removal of delamanid.

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

Dr Sabine Kopp gave a brief update on the revision process of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce ("the scheme"), as twice recommended by the ECSPP.

The scheme is an international voluntary agreement designed to assure participating countries of the quality of pharmaceutical products they import and export. In operation since 1969, the scheme works by issuing three different types of certificates for quality assurance: a certificate of a pharmaceutical product; a statement of the marketing authorization status of a pharmaceutical product; and a batch certificate.

A number of problems operating the scheme have been raised since 2007, and the ECSPP recommended at its Forty-third meeting in 2008 that the scheme be revised. An interim solution – a Q&A document on the scheme's function – was developed in 2010 (and revised in 2015 (*49*)) but the scheme itself remains unchanged.

In 2017, the ECSPP once again called for the scheme to be revised and a series of revisions were then proposed by the WHO Secretariat and sent out for public consultation in 2018. These revisions were discussed at last year's ECSPP meeting in October 2018.

Since then, a second round of consultation has raised a large number of comments. The WHO Secretariat is developing a list of regulatory authorities that are interested in collaborating with WHO in consolidating and addressing these comments and funding is being sought to bring these stakeholders together in a meeting.

The Expert Committee noted the update and endorsed the next steps as proposed.

13.3. Guideline on the implementation of quality management systems for national regulatory authorities

Mr Hiiti Sillo and Ms Mariana Roldao Santos, Scientist, RSS, summarized the progress on developing guidance on establishing, implementing and maintaining QMSs for NRAs. The working document, which has been in development since late 2017, has been prepared by a drafting group of regulatory experts. It has been designed to support NRAs to develop, implement and improve QMSs based on good standards and principles (*50*). The document offers recommendations on what NRAs should implement and maintain under their QMSs to effectively and efficiently fulfil their functions; it is hoped that the new guideline will promote consistency in regulatory practices within and across NRAs and so boost mutual reliance and recognition among Member States.

Since the last ECSPP meeting, the draft guideline was sent for public consultation from January to March 2019. In June 2019, the RSS Team hosted an informal consultation with international stakeholders, to discuss comments received. Some of the main concerns raised by participants included the length of the draft guideline; its ability to be of practical use to NRAs; and its dependency on ISO 9001 (*50*). Recommendations made during the informal consultation guided further revision of the document, which then went for a second round of public consultation from July to September 2019. It has been revised again in light of comments received.

The main changes in the document since the ECSPP last saw it include the following:

- a structural and content change to align the guideline with key GBT indicators and to avoid dependency on ISO 9001;
- a reduction in length (it is now nearly half the original length);
- removal of duplications of and dependency on ISO 9001;
- the development of a more accessible and easier to read version; and
- the addition of new practical tools to better enable NRAs to implement QMSs (for example, a situational analysis, gap analysis, roadmap and activity plan).

The ECSPP reviewed the latest draft and discussed the comments and proposed revisions. It emphasized the need for a harmonized approach and noted the significant collaborative work done over the past year to align the document with the guideline on *Quality management system requirements for national inspectorates* (Annex 5) and with the GBT (*9*). The value of having both general and specific QMS guidelines was debated, with the need for coherence, consistency and cross-referencing underscored.

Other topics of discussion included the scope of the document; training requirements of personnel conducting internal audits; and the need for a stepwise approach to implementing the guideline. The Expert Committee also suggested further revisions for clarification.

The Expert Committee adopted the *WHO guideline on the implementation of quality management systems for national regulatory authorities* (Annex 13), subject to the changes discussed.

13.4. Update on good regulatory practices

Mr Michael Ward, Coordinator, RSS, updated the ECSPP on the ongoing development of *Good regulatory practices: guidelines for national regulatory authorities for medical products*. Originally drafted in 2016 (*51*), this guideline was a response to requests from Member States for guidance on how to develop legal frameworks, and aimed to outline internationally accepted principles of GRP and show how they can be applied to the regulation of medical products for human use.

The draft document was first revised in 2016 after an initial stakeholder consultation, and again in late 2017 following comments received from a public consultation (late 2016), an internal consultation (July 2017) and presentation to the ECSPP (October 2017). Since then, little progress has been made until last month (September 2019), when a consultative meeting with experts from around the world discussed the guideline again.

After discussion of the revised guideline, participants agreed to move forward with a short and concise document that focuses on scope; intended use; purpose; principles; and elaborated examples for policy-makers and regulators.

The concise guidance on principles will be complemented by a series of guidance documents that provide practical tools and tactics for implementing GRP, such as case-studies and practice guides or manuals based on the needs of regulators from low- and middle-income countries.

Plans for progressing the guideline include revising it based on comments received at the September 2019 consultative meeting and then sending it for public consultation in early 2020. Further revisions will follow, as well as an internal consultation before the guideline is presented to the ECSPP for endorsement in October 2020.

The Expert Committee noted the update.

13.5. Update on new regulatory concepts and tools

Mr Michael Ward presented a proposed framework for evaluating and publicly designating regulatory authorities as "WHO-listed authorities" (WLAs). The proposal includes a definition of a WLA, as well as a set of procedures on how to go about designating one.

A concept note on the proposed framework was published in May 2019 for public comment and a total of 493 comments were received, emphasizing the need for a strong definition of what a WLA is, as well as robust criteria for regional regulatory systems and a clear scope of products to be included, among other things.

Following the public consultation, a draft policy and operational guidance was developed and shared at a consultative meeting in September 2019. The draft policy includes proposed definitions for:

- **WHO-listed authority (WLA)**: a NRA or a regional regulatory system which has been documented to comply with all the indicators and requirements specified by WHO for listing, based on an established benchmarking and performance evaluation process. A regulatory authority can be listed for one or more product categories, or for one or more regulatory functions; and
- **regional regulatory system**: a system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory or legal framework. The common framework must ensure equivalence between the members in terms of regulatory requirements, practices and quality assurance policies. The regional body, where it exists, may have enforcement powers to ensure compliance with the common regulatory framework. A regional regulatory system so described may be considered a single entity and therefore eligible for listing as a WLA.

It is also proposed to present the topic to the ECBS in October 2019 and the draft policy and guidance documents are expected to be released in 2020. They will be tested over six months, with the expectation of them becoming fully operational in 2021.

It is hoped that the new framework will promote trust between regulatory authorities; increase the pool of authorities contributing to the WHO Prequalification Programme; and boost investment in and improvement of regulatory systems.

Once the new definition is accepted, it will need to be integrated across all relevant documents that currently refer to stringent regulatory authorities. This could be a significant amount of work, which should start now in a parallel process, in order to identify all the potentially affected documents.

The Expert Committee noted the update.

14. Closing remarks

The Chair thanked the ECSPP for its standard-setting work, which has an impact for many people in all of WHO's Member States, by enabling access to quality-assured medical products. She thanked the WHO Secretariat for its work in supporting the Expert Committee, and she thanked everyone for their active participation and contributions. Dr Sabine Kopp thanked all members of the ECSPP for their contributions and for the high-quality discussions held during the meeting. Dr Kopp thanked the Chair, the Co-Chair and the Rapporteurs for contributing to an efficient meeting. The Chair closed the meeting and wished the participants a safe journey home.

15. Summary and recommendations

The WHO ECSPP advises the Director-General of WHO in the area of medicines quality assurance. It oversees the maintenance of *The International Pharmacopoeia* (*3*) 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 ECSPP's guidance documents are developed through a broad consensus-building process, including iterative public consultation. Representatives from international organizations, state actors, non-state actors, pharmacopoeias and relevant WHO departments are invited to the ECSPP's annual meetings, to provide updates and input to the Expert Committee's discussions.

At its Fifty-fourth meeting, held from 14 to 18 October 2019 in Geneva, Switzerland, the ECSPP heard updates on cross-cutting issues from other WHO bodies, including the ECBS, the Expert Committee on the Selection and Use of Essential Medicines, the Local Production Programme, the MSM on substandard and falsified medical products, the PQT, the RSS unit and the INN team. Updates were also presented by partner organizations, including the IAEA, the PDG and UNICEF.

The EDQM updated the ECSPP on its activities as the custodian centre in charge of ICRS for use with monographs of *The International Pharmacopoeia*. Results from the latest phase of the EQAAS, which is organized by WHO with the assistance of the EDQM, were also presented.

The ECSPP reviewed new and revised specifications and general texts for quality control testing of medicines for inclusion in *The International Pharmacopoeia*. The Expert Committee adopted 13 guidelines and 16 pharmacopoeial texts (two general chapters, 13 new and revised monographs and one correction), omitted three pharmacopoeial texts, and confirmed the release of six new ICRS established by the custodial centre for use in connection with *The International Pharmacopoeia*.

The ECSPP also agreed to publish the outcomes of the WHO Biowaiver Project as an annex to its report; this will be a living document that will be updated as data become available.

The sections that follow summarize the specific decisions and recommendations made by the ECSPP during its Fifty-fourth meeting in 2019.

15.1. Guidelines and decisions adopted and recommended for use

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

- *Procedure for the elaboration, revision and omission of monographs and other texts for* The International Pharmacopoeia (Annex 1);

- *International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceuticals* (Annex 2);
- *Production of water for injection by means other than distillation* (Annex 3);
- *Good chromatography practices* (Annex 4);
- *Quality management system requirements for national inspectorates* (Annex 5);
- *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance* (Annex 6);
- *Good storage and distribution practices for medical products* (Annex 7);
- *Points to consider for setting the remaining shelf-life of medical products upon delivery* (Annex 8);
- *World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices* (Annex 9);
- *World Health Organization/United Nations Population Fund technical specifications for male latex condoms* (Annex 10);
- *World Health Organization/United Nations Population Fund specifications for plain lubricants* (Annex 11);
- *WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for* WHO Model List of Essential Medicines *immediate-release, solid oral dosage forms* (Annex 12); and
- *WHO guideline on the implementation of quality management systems for national regulatory authorities* (Annex 13).

15.2. Texts adopted for inclusion in *The International Pharmacopoeia*

The ECSPP adopted a series of texts, chapters and monograph, as listed next.

15.2.1. General texts

- Workplan 2020–2021

15.2.2. General chapters

- Polymorphism (new)
- Capillary electrophoresis (revision)

15.2.3. Monographs

General monographs for dosage forms and associated method texts

- Water for injections (revision)
- Ethanol/water mixtures in the reagent section (correction)

For antimalarial medicines

- doxycycline hyclate (revision)
- doxycycline capsules (revision)
- doxycycline tablets (revision)
- pyrimethamine (revision)
- pyrimethamine tablets (new)

For antibacterials, including antituberculosis medicines

- levofloxacin hemihydrate (revision)
- levofloxacin tablets (revision)

For antiviral medicines, including antiretrovirals

- atazanavir sulfate (revision)
- sofosbuvir (new)
- sofosbuvir tablets (new)

Other medicines for infectious diseases

- ciprofloxacin hydrochloride (revision)
- ciprofloxacin tablets (new)

15.2.4. Omissions

The ECSPP agreed to omit the following texts from *The International Pharmacopoeia*:

- undue toxicity (including the whole of Chapter 3.7 and all reference to the undue toxicity test in the monographs on kanamycin acid sulfate and kanamycin monosulfate);
- chlorpheniramine hydrogen maleate (monograph); and
- chlorpheniramine hydrogen maleate tablets (monograph).

15.2.5. International Chemical Reference Substances

The ECSPP confirmed the release of the following ICRS that have been newly characterized by the custodial centre, EDQM:

- metacycline ICRS 1
- artemether ICRS 3
- albendazole ICRS 1
- ethinylestradiol ICRS 4.

The ECSPP also authorized the following chemical reference substances, established by the EDQM, for use according to the respective monographs in *The International Pharmacopoeia*:

- ciprofloxacin hydrochloride for peak identification
- levofloxacin for system suitability.

15.3. Recommendations

The ECSPP made a series of recommendations related to quality assurance. It recommended that the WHO Secretariat, in collaboration with experts, as appropriate, should take the actions listed below. Progress on the suggested actions will be reported to the ECSPP at its Fifty-fifth meeting scheduled for October 2020.

15.3.1. *The International Pharmacopoeia*

- Continue the development of monographs, general methods and texts and general supplementary information, as well as the establishment of ICRS.
- Include a list of monographs that are already under development in future workplans.
- Maintain a flexible schedule for posting draft monographs for public comment.
- Publish an excerpt of the workplan that includes proposed omissions as a means to improve transparency on upcoming omissions.
- Investigate the possibility of introducing additional language to the monographs on capreomycin sulfate and capreomycin sulfate for injection for clarification, in collaboration with interested ECSPP members.
- Reconsider the potential to develop a general chapter on X-ray powder diffractometry, after publication of the PDG chapter that is currently under development.

15.3.2. Quality control – national laboratories

- Continue offering the EQAAS for the capacity-building of QCLs.

15.3.3. Good manufacturing practices and related areas

- Carry out another round of public consultation on the current version of the GMP for sterile products, to be held in parallel to the targeted EU consultation, and provide an update on the progress at the ECSPP's next meeting in 2020, with the possible adoption of a revised guideline.
- Develop a *Points to consider* document on cleaning validation, introducing the possibility of using HBEL-based approaches to setting safe cleaning limits and establishing a common understanding on which to develop guidelines that are appropriate for all stakeholders.
- Consider how to integrate the adopted text on water for injection into WHO's existing guideline on *Water for pharmaceutical use* (*39*).
- Send out the draft WHO *Guideline on data integrity* (*52*) for public consultation and refinement, based on comments received, to replace the current WHO *Guidance on good data and record management* (*40*).
- Conduct a survey of manufacturers designed to raise awareness of AMR and to verify the recommendations made in the newly-adopted *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance* (Annex 6).
- Envisage, in collaboration with the IAEA, to complement the GMP text for radiopharmaceuticals by two further guidelines yet to be developed: one for investigational radiopharmaceuticals and one for the cold kits used in the production of radiopharmaceuticals.

15.3.4. Distribution and supply chain

- Continue the joint WHO/UNFPA development of revised prequalification guidance for contraceptive devices and condoms, including:
  - condom quality assurance;
  - guidance on testing of male latex condoms;
  - recommendations for condom storage and shipping temperatures; and
  - guidance on conducting post-market surveillance of condoms.

15.3.5. Regulatory mechanisms

- Start the next phase of the WHO Biowaiver Project, to continue the BCS-based classification of nine further APIs, including: chloroquine, cycloserine, emtricitabine, entecavir, mefloquine, miltefosine, oseltamivir, paracetamol and sofosbuvir.
- Continue with preparatory work to revise the WHO *Certification scheme on the quality of pharmaceutical products moving in international commerce*.
- Send out the draft *Good regulatory practices: guidelines for national regulatory authorities for medical products* for public consultation and refinement, based on comments received.

15.3.6. Other

- Continue to provide the database of terms and definitions covered by the ECSPP on the WHO website.
- Continue efforts to progress work in developing new guidance text for the graphic representation of pharmaceutical substances.

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Annex 1

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

1. Introduction

Monographs in *The International Pharmacopoeia* (*1*) are essential standards to ensure the quality of medicines, thus contributing to their safe and efficacious use. They are developed and maintained in an open and transparent process, in line with the principles outlined in *Good pharmacopoeial practices* (*2*), and aim to foster harmonization and convergence of compendial quality standards to ultimately increase access to affordable, quality-assured medicines.

The procedure described next outlines the life-cycle of texts in *The International Pharmacopoeia*: how they are developed, revised and, if appropriate, finally omitted from the compendium. The text also includes steps related to the establishment of the International Chemical Reference Substances (ICRS) referred to in analytical tests.

2. Elaboration of monographs

The steps of the development procedure are listed next.[1,2]

Step 1: Identify medicines for which pharmacopoeial monographs need to be developed or revised. Set up a biannual workplan prioritizing medicines that are included in the *WHO Model List of Essential Medicines* (EML) (*3*) (or are otherwise relevant for World Health Organization [WHO] health programmes), preferably not already described in pharmacopoeias. Determine whether or not monographs for the corresponding active pharmaceutical ingredients also need to be developed or revised. Confirm the workplan with all WHO parties concerned, including the Department of Essential Medicines and Health Products, specific disease programmes and the WHO Prequalification Team (PQT).

Step 2: Search for relevant information on the product in the public domain, including other pharmacopoeias.

Step 3: Share the workplan with other pharmacopoeias and identify ways of collaboration to reduce the workload of the monograph development

[1] The procedure for the elaboration, revision and omission of monographs and other texts for *The International Pharmacopoeia* was developed by the Secretariat of *The International Pharmacopoeia*, in consultation with the partners involved: ECSPP experts; the European Directorate for the Quality of Medicines and HealthCare (EDQM); WHO Collaborating Centres; collaborating laboratories and organizations; and the ICRS Board. The steps are therefore described from the perspective of all partners involved.

[2] The steps are listed in their chronological order. However, certain steps may overlap during the development of monographs and other compendial texts.

and to promote converged or harmonized quality standards that are globally applicable and recognized.

Step 4: Contact manufacturers of WHO prequalified medicines and/or of medicines authorized by WHO-listed national regulatory systems with an appropriate maturity level,[3] to request quality control specifications and samples of their products.

Step 5: Assign WHO Collaborating Centres, collaborating laboratories and/or specific experts, if appropriate, to participate in the establishment or revision of the monograph.

Step 6: Set up a first version of the monograph, based on the available information and on discussions with the partners involved. Perform laboratory investigations to develop, adapt, optimize, verify or validate the proposed analytical procedures. Verify the suitability of the proposed specifications, by analysing medicines from different regions or markets of the world. Identify which of the required reference substances would need to be newly established or are already available either as ICRS or as reference substances established by another pharmacopoeia. If reference is made to already established ICRS or reference substances established by other pharmacopoeias, include these reference substances in the laboratory investigations and advise on their suitability for the new intended use(s). Issue a laboratory report describing the tests performed and the results obtained. Based on mutual agreements, share the laboratory report with other pharmacopoeias, with a view to fostering harmonization and convergence of compendial quality standards.

Step 7: Follow the consultative process of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP). Circulate the draft text for comments and provide the document on the website of *The International Pharmacopoeia*.

Step 8: Collate the comments received during the public consultation and review them with the partners involved. If necessary, arrange with the laboratories involved for additional laboratory investigations.

Step 9: Discuss the comments received and, if applicable, the results of the additional investigations, at an informal consultation with experts. Revise the draft text based on the discussions, as appropriate.

[3] It is intended to refer in the final version of the document to the *WHO Global Benchmarking Tool* (GBT) (*4*), which is currently under discussion.

Step 10: Repeat steps 7 to 9 until the text is deemed suitable for adoption.

Step 11: Identify and contact manufacturers (or other potential donors of candidate materials) to ascertain the availability of candidate materials for the establishment of the ICRS described in the text. Discuss with the organization for the establishment, storage and distribution of ICRS – the EDQM – the strategy to establish the proposed ICRS and its impact on the analytical provisions of the monograph.

Step 12: Submit the draft monograph (together with the laboratory report and a compilation of the comments received during the public consultation) to the ECSPP, for information, discussion and/or possible adoption, depending on the maturity of the monograph. If the text is adopted, proceed with step 13. If not, repeat steps 7 to 11.

Step 13: Incorporate all changes agreed during the final discussions leading to adoption, together with any editorial changes.

Step 14: Confirm the final text with the experts and laboratories involved in the final discussions and publish the adopted monograph in a new edition or supplement of *The International Pharmacopoeia*.[4]

Step 15: Identify already established ICRS referred to in the monograph. Review the ICRS establishment report(s) to evaluate whether the intended uses and the quantity per vial are still valid and appropriate, or need to be amended or revised in view of the analytical provisions of the new standard.

Step 16: Identify newly to-be-established ICRS referred to in the monograph. Revert to potential donors of candidate material (Step 11) and initiate the shipment of the material to the organization in charge of ICRS.

Step 17: Perform laboratory investigations to characterize the candidate material and/or to ensure the suitability of the material for its new or revised intended uses. Issue an ICRS establishment or re-establishment report. If information in the ICRS leaflet of already established ICRS has to be revised, assign a new batch number to the ICRS.

Step 18: Submit the establishment report to the ICRS Board. Start the distribution of the ICRS after the reference substance is released by the ICRS Board and the corresponding new monograph is published.

[4] Subject to the availability of the necessary resources, the Secretariat aims to publish adopted texts for inclusion in *The International Pharmacopoeia* after each meeting of the ECSPP.

Step 19: Submit the ICRS report to the ECSPP to confirm the release of the reference standard and/or the change(s) in the leaflets.

3. Omission of monographs

Step 1: Identify monographs on medicines (or other pharmaceutical products) that are described in *The International Pharmacopoeia* but are no longer included in the EML or otherwise relevant for WHO health programmes.

Step 2: Submit the list of monographs (and other texts) proposed for omission to the ECSPP, for possible approval.

Step 3: Transfer omitted texts to a publicly accessible archive section on the WHO website, together with the following note: "These monographs will be neither updated nor revised, nor will the corresponding International Chemical Reference Substances be further monitored. Users will need to ensure that the product complies with current rules and regulations governing medicines and related products in their respective territories".

Step 4: Remove the ICRS referred to in omitted monographs from the ICRS catalogue one year after the monograph has been transferred to the archive page on the WHO website.

4. Elaboration, revision and omission of other pharmacopoeial texts

In principle, the steps outlined above apply to all texts. Some specific texts may, however, necessitate deviations. The steps in the development of pharmacopoeial texts, however, shall always include public consultation, consideration of comments received, if appropriate, and adoption of the texts by the ECSPP.

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Annex 2

International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products

Acknowledgements

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1. Scope

This guideline provides a general overview of the minimum good manufacturing practices (GMP) requirements for radiopharmaceutical products. The main principles of GMP are described in detail in the WHO guidelines related to pharmaceutical products (*1*, *2*), as well as in those for sterile pharmaceutical products (*3*).

The procedures necessary to manufacture, prepare and control radiopharmaceutical products are in large part determined by the nature of these products, the methods of manufacture and their intended use. The recommendations in this guideline are applicable to:

- the production, preparation or compounding of radiopharmaceuticals in hospital radiopharmacies, including diagnostic and therapeutic products;
- the production or compounding of radiopharmaceuticals in centralized radiopharmacies;
- the production or compounding of radiopharmaceuticals in nuclear centres and institutes;
- the production of radiopharmaceuticals by industrial manufacturers; and
- the production of cyclotron-based radiopharmaceuticals.

The scope of this guidance does not include:

- radiopharmaceutical dispensing (i.e. the drawing of a patient's specific unit dose from a bulk vial of a radiopharmaceutical product);
- regulatory authority-approved radiopharmaceutical preparation (i.e. the use of approved kits and approved generators in order to produce a radiopharmaceutical product as per instructions of the marketing authorization holder);
- handling of ready-to-administer radiopharmaceutical products (e.g. receipt, storage, assay, etc.);
- production or compounding of non-radioactive compounds, including cold kits; or
- production of investigational radiopharmaceutical products.

2. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

"as low as reasonably achievable". ALARA is an acronym standing for "as low as reasonably achievable", used to define the principle of underlying optimization of radiation protection. This is practised based on the principles of time, distance and shielding, as well as an emphasis on creating adequate awareness among all stakeholders.

dispensing. The generation of a patient-specific unit dose, which involves physical withdrawal of the radiopharmaceutical from the bulk single-use or multidose vial into a syringe; dilution with an appropriate diluent as necessary; measurement of the radioactivity content; and labelling of the syringe.

good manufacturing practices for radiopharmaceutical products. Good manufacturing practices (GMP) for radiopharmaceutical products are a set of practices, using a traceable process, that ensure that radiopharmaceutical products are consistently produced and controlled to the quality standards appropriate for their intended use, and designed to consistently yield the radiopharmaceutical product. GMP fall under the umbrella of the overall quality management system (QMS).

manufacturing or production. Within the scope of this guidance, these terms refer to all the operations performed leading up to the finished radiopharmaceutical product, including the purchase of starting materials, production, quality control, release and storage of radiopharmaceuticals.

preparation or kit-reconstitution. Within the scope of this guidance, preparation or kit-reconstitution refers to all the procedures carried out as per instructions from a marketing authorization holder, which involves the addition of radionuclide solution approved by regulatory authorities to an approved cold kit.

primary packaging. Any packaging material that comes into direct contact with the finished radiopharmaceutical product (i.e. an immediate container, such as a vial or a syringe).

quality control. A set of analytical tests designed to demonstrate compliance of the quality of starting materials, intermediates and final radiopharmaceutical products with predetermined specifications for quality acceptance.

quality management system. An appropriate system encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will satisfy the given requirements for quality.

radiopharmaceutical compounding. This term refers to producing radiopharmaceuticals with no marketing authorization but pursuant to the order for a specific patient or patients from a physician certified/qualified for practice of nuclear medicine. In various regions of the world, this practice may also be referred to as "in-house preparation", "in-house-manufacturing" or "hospital preparation".

radiopharmaceutical product. Any pharmaceutical product that, when ready for use, contains one or more radionuclides (radioactive isotopes) included for medicinal purposes.

secondary packaging. The shielded container housing the primary packaging.

3. Quality management system

3.1 There should be a quality management system (QMS) that covers the organizational structure, job descriptions, procedures, processes, resources and actions necessary to ensure adequate confidence that the radiopharmaceutical product or service will consistently yield a product of intended quality.

3.2 Principles of risk management should be applied in the establishment, implementation and management of the QMS and GMP.

3.3 Risk assessment should include a thorough identification and evaluation of all possible risks associated with the manufacturing process, and controls should be identified in order to minimize those risks to an acceptable level.

3.4 Risk assessment and risk controls should be commensurate with the complexity of the risk identified. Because radiopharmaceuticals are significantly different from "traditional" medicines, in both their characteristics and the production process, the GMP requirements applicable to the manufacture of "traditional" pharmaceuticals may often be different from those applied to the manufacture of radiopharmaceutical products.

3.5 Radiopharmaceutical-specific characteristics generally include the following:

- a simple distribution chain, with direct delivery of the finished product from the manufacturer to the nuclear medicine department;
- a small batch size;
- a limited shelf-life of minutes to several days; and
- a quality control (QC) sample representing the entire batch.

In addition:

- diagnostic radiopharmaceuticals often have a low potential to exert pharmacological or toxic effects, owing to the micro-dose levels administered; and
- radiopharmaceuticals are often administered prior to completion of all QC testing. Tests such as sterility and determination of endotoxin content and radionuclidic purity may need to be performed post-release. Hence, the application of GMP is essential in order to minimize possible risks to the quality that may not be identified through QC pre-release testing.

3.6 The risk assessment should cover the unique nature of these agents, with controls that are tailored to the actual production process, the nature of the radiopharmaceutical itself, the level of risk associated and the clinical indication. The preparation and control of these agents should be in compliance with applicable national radiation safety regulations and be based on the principles of ALARA (*4*, *5*) (see Glossary)

4. Qualification and validation

4.1 Qualification of instruments and equipment and validation of procedures should be done.

4.2 Validation and qualification activities should be planned,organized and documented.

4.3 Qualification of premises, utilities, equipment and instruments should demonstrate that they have been designed, installed, operated and performed (as applicable) in accordance with the requirements of GMP and that they are appropriate for their intended use.

4.4 The extent of qualification and validation activities should be in accordance with a risk-based approach considering the complexity and critical aspects of the intended radiopharmaceutical production.

4.5 A schedule of planned preventive maintenance should be established. Procedures and records should be maintained.

4.6 There should be a schedule for regular calibration and verification. Procedures and records should be maintained.

4.7 Process validation should be carried out after all other qualification and validation have been successfully completed.

4.8 Process validation should be done by including an adequate number of batch preparations, or batches of preparations, of the intended radiopharmaceutical(s), following the same procedures, covering the intended range of batch size and with the same production and quality specifications as typically intended routine batches. The number of batches and the range of batch size should be predetermined as part of a risk assessment performed prior to process validation.

4.9 Cleaning validation should be especially focused on surfaces that come into direct contact with the operators or with starting materials, intermediates and finished products.

4.10 Non-pharmacopoeia analytical procedures should be validated. Compendial analytical procedures should be verified for their suitability under actual conditions. This should be documented and records maintained.

4.11 General principles on validation of analytical procedures may be followed (*6*, *7*); however, the unique nature of radioactivity should be considered and specific adaptations should be made, where required (*7*).

4.12 Revalidation of certain processes (e.g. aseptic process simulation) should be performed on a periodic basis, in accordance with a written procedure. Requalification of equipment should be considered when appropriate, for example, in case of significant changes and/or of deviations.

4.13 Validation and qualification activities and results obtained, including the responsibilities of personnel, should all be documented. Records should be maintained.

4.14 Processes and procedures should be validated, as apropriate.

5. Product complaints

5.1 There should be a written procedure for handling and investigating product complaints.

5.2 The procedure should describe the actions to be taken in case of a complaint.

6. Product recall

6.1 There should be a written procedure to recall a radiopharmaceutical product, when required.

6.2 Since the return of radioactive products is generally not practical, the main purpose of recall procedures for radiopharmaceutical products should be to prevent their use rather than an actual return. If necessary, the return of radioactive products should be carried out in accordance with national and, where applicable, international transport regulations (*8*).

7. Outsourced activities

7.1 Contractors should be evaluated and qualified in accordance with a written procedure. Records should be maintained. The responsibilities of each party should be clearly described in a written agreement.

8. Personnel and training

8.1 The manufacturing establishment should have an adequate number of personnel to carry out the intended operations.

8.2 The responsibilities placed on any individual should not be so extensive as to present an increased risk to the quality of the product.

8.3 The manufacturing establishment and its personnel should be under the supervision of a responsible person(s) who has the appropriate qualifications and experience as required by national legislation.

8.4 Personnel should have appropriate qualifications, training and experience related to their responsibilities and job description.

8.5 Personnel should receive relevant training in GMP, procedural training and training related to the preparation and control of radiopharmaceutical products.

8.6 A written training programme should be followed. Topics should also include the handling of radioactive materials and safety. Personnel should take periodic courses and receive training to keep abreast of the latest developments in their fields.

8.7 Training and assessment following training should be documented. Records should be maintained.

8.8 All personnel handling radioactive materials should be monitored for possible contamination and radiation exposure.

8.9 Personnel working in clean areas should observe good personal hygiene. They should report any personal medical condition that may adversely affect products.

9. Premises

9.1 Facilities should be located, designed, constructed, adapted and maintained, in order to suit the operations to be carried out. The laboratories for the handling of radioactive materials should be appropriately designed. Consideration should be given to radiation protection, ALARA compliance, a high level of cleanliness and the appropriate controls to minimize possible microbial contamination.

9.2 Lighting, heating, ventilation and air-conditioning (HVAC) systems should be designed to maintain an appropriate temperature and relative humidity where required, in order to ensure the appropriate equipment performance, material storage, safety and comfort of personnel.

9.3 Facilities should be correctly maintained. Special precautions should be exercised, in order to ensure that facility repairs and maintenance operations do not compromise product quality. There should be adequate space for the operations to be carried out allowing for efficient workflow, effective communication and overall supervision. Facilities should also be designed in a manner that minimizes the risk of entry of insects, pests and vermin.

9.4 Interior surfaces (walls, floors and ceilings) should be smooth, impervious and free from cracks. They should not shed particles and should allow for easy cleaning and decontamination.

9.5 Drains should be avoided wherever possible, and should not be present in clean rooms. Where drains are required, these should be appropriately designed.

9.6 Sinks should be excluded from clean areas.

9.7 Pipes and valves should be appropriately marked, designed and located, in order to facilitate cleaning and decontamination. Vent filters should be appropriately controlled.

9.8 Technical area (e.g. rooms to access the rear of hot cells) access points should be configured in a way to minimize the entrance of maintenance and technical personnel to the production (clean) areas.

9.9 The HVAC system and pressure cascade design for the different areas should be appropriately designed and maintained, in order to minimize the risk of product contamination and to protect personnel from the risks of radiation exposure. The pressure differentials should be controlled, monitored and recorded. Appropriate controls should be put in place to promote the containment of radioactivite gases and vapours.

9.10 Radioactive gas emissions should be effectively controlled and monitored, in order to minimize the risk of unnecessary radiation exposure to personnel and the surrounding environment. Alarm systems should be in place.

9.11 Radioactive gas should be removed through separate air-handling units fitted with the appropriate filters before being exhausted. These should be regularly checked for performance. The recirculation of radioactive contaminated air should not be allowed.

9.12 All operations such as the handling, storage and distribution of materials and products, as well as waste disposal, should be performed in compliance with national regulations and guidance.

9.13 A dedicated area with the appropriate equipment should be used for the manufacture of any radiopharmaceutical product involving human blood or plasma.

9.14 QC laboratories should be separated from production areas.

10. Equipment

10.1 Equipment should be appropriately qualified for its intended use. This includes user requirement specifications, design qualification (if applicable), installation qualification, operational qualification and performance qualification. Equipment and devices, as appropriate, should be calibrated and maintained. Consideration should be given to reducing the risk of product contamination, minimizing the risk of staff radiation exposure and optimizing ergonomics, in order to facilitate the operation, maintenance and cleaning of equipment. Records should be retained (*9*).

10.2 Equipment maintenance, qualification and calibration operations should be recorded and the records maintained.

10.3 Computerized systems, such as those controlling equipment, should be included in validation.

10.4 The dose calibrator (also known as the activity meter) should be qualified using suitable reference standards. If such a reference standard recognized by a national authority is not available, dose-calibrator manufacturer recommendations or published literature may be used when deciding upon the appropriate dial setting.

11. Starting materials

11.1 Starting materials of appropriate quality should be used for radiopharmaceutical production. Written procedures for material acceptance should be established for starting materials to be subsequently used in radiopharmaceutical production.

11.2 Specifications for starting materials should be established. Specifications should include, for example, the identity, purity or certification of origin (if applicable) and any other parameters or characteristics required in order to make the material suitable for its intended use.

11.3 Starting materials should be accepted by performing in-house testing. Where this is not possible, and in lieu of testing, a review of the certificate of analysis supplied by the reliable material manufacturer to confirm compliance with the specification may be acceptable.

11.4 The status of materials should be clear. This includes: (i) accepted materials; (ii) quarantined materials; and (iii) rejected materials.

11.5 Rejected materials should be securely stored in an area that is separate from other materials.

11.6 Waste materials should be disposed of in accordance with the national requirements.

12. Documentation

12.1 Good documentation practices should be followed.

12.2 Documents should ensure the traceability of radiopharmaceutical production (including the processes and the product).

12.3 The processing records of regular production batches must provide a clear and complete account of the manufacturing history of each batch of a radiopharmaceutical product, showing that it has been manufactured,

tested, dispensed into containers and delivered in accordance with the applicable standard operating procedures (SOPs).

12.4 A controlled system of written SOPs must be created, in order to cover the requirements for major aspects of radiopharmaceutical manufacturing. The SOPs should be approved, signed and dated by the appropriate responsible person(s). No approved SOP document should be changed without an appropriate review, evaluation and approval by the responsible person(s). The SOPs should be reviewed periodically, in order to ensure applicability.

12.5 Documentation should be retained for a period appropriate to the nature of the document content.

13. Good practices in production

13.1 Access to restricted areas should be by authorized and trained personnel only.

13.2 Only the minimum number of personnel required should be present in clean areas.

13.3 Processes should be designed to minimize the risk of contamination, cross-contaminations and mix-ups. The following measures may be adopted to minimize these risks:

- processing and filling in segregated areas;
- avoiding the manufacture of different products at the same time, either in the same dedicated space or by the same personnel;
- performing decontamination and visual pre-checks of the manufacturing area; and
- using manufacturing "closed systems", whenever possible.

13.4 The critical aseptic operations, such as final product vial assembly, vial filling or sterility testing, should be carried out under aseptic conditions of a clean area of grade A in grade B background (*10*).

13.5 Both raw materials and final radiopharmaceutical products should be stored under appropriate controlled conditions.

13.6 The stability and shelf-life of the finished product should be defined in a written protocol in agreement with the competent authority.

13.7 The expiration dates and times for radiopharmaceutical products should be based upon the results of an adequate number of stability studies.

14. Good practices in quality control

14.1 A radiopharmaceutical's final product acceptance criteria, including criteria for release, should be established and documented in a written SOP.

14.2 Sampling procedures should consider the nature and characteristics of the material being sampled (e.g. a small batch size and/or its radioactive content), in order to make sure that the samples are representative of the radiopharmaceutical batch.

14.3 The QC procedures should be described in written SOPs.

14.4 QC samples should be prepared, handled and stored in a way to ensure adequate identification and segregation of the test samples, to avoid mix-ups and cross-contamination.

14.5 A final radiopharmaceutical product that fails to meet the acceptance criteria should be rejected and segregated. Such events should be investigated and the investigation outcome and proposed actions documented.

14.6 The release of a batch should be performed by a responsible person. Under certain circumstances (e.g. radiopharmaceticals with an extremely short radioactive half-life and/or shelf-life), a final radiopharmaceutical drug product may need to be released and delivered prior to completion of all final drug product characterization testing. Under these circumstances, a SOP that clearly describes the required release process should be established and documented.

14.7 Batch release by the manufacturer should be carried out by a responsible person who is independent of the person carrying out the production and QC.

15. Labelling

15.1 Finished radiopharmaceutical products should be clearly labelled.

15.2 Whenever possible, a portion of the primary packaging container should be left uncovered, in order to allow for inspection of the contents.

15.3 The content of the labels for radiopharmaceutical products should comply with national legislation and international agreements, where applicable.

15.4 In the absence of regulatory authority requirements, the following information should be listed on the primary packaging container label:

- the name of the product and batch number;
- the name of the manufacturer;
- the amount of activity in SI units;
- for liquid radiopharmaceuticals, the total activity or the radioactive concentration per millilitre at the calibration date and time, and the volume of liquid;
- for capsules, the radioactivity of each capsule at the calibration date and time, and the number of capsules in the container;
- where relevant, the international symbol for radioactivity;
- the expiration date and time; and
- cautionary statements, e.g. "Caution: radioactive material".

Note: reporting information about an activity on a primary label may not always be possible, for reasons of radiation protection. In this case, the information may be reported on the secondary packaging label.

15.5 In the absence of regulatory authority requirements, the following information may be listed on the secondary packaging container label, in addition to any information listed on the primary packaging:

- the qualitative composition;
- excipient information;
- the route of administration;
- any special storage instructions; and
- the address of the manufacturer.

References

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Additional reading

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Annex 3

Production of water for injection by means other than distillation

1. Introduction

1.1 Water is widely used in the pharmaceutical industry. It is often used as a raw material; an ingredient in formulations; to prepare reagents; in cleaning; and in the manufacture of active pharmaceutical ingredients), intermediates and finished pharmaceutical products.

1.2 Water for pharmaceutical use must meet quality requirements and specifications, as published in relevant standards and pharmacopoeias. Water of the required quality for its intended use should be produced by appropriate methods.

2. Scope

2.1 This document provides guidance for the production of water for injection (WFI) by means other than distillation. The principles described in this guideline may be applied to other grades of water, meeting other specifications.

2.2 The document is not exhaustive but aims to provide guidance on the main principles to be considered. Other guidelines and literature should also be consulted (*1*, *2*).

3. Monographs

3.1 Manufacturers should have appropriate specifications for WFI.

3.2 Monographs for WFI are published in *The International Pharmacopoeia* (*1*), as well as various national pharmacopoeias, and provide for the minimum requirements for the quality of WFI.

3.3 WFI should meet the specification as published in current monographs of the relevant pharmacopoeia recognized by the national medicines regulatory authority.

4. Life-cycle approach

4.1 Good practices during each stage of the life-cycle of WFI should be considered.

4.2 Stages include, but are not limited to, the collection and treatment of source water; treatment of drinking water; treatment of purified water; and the production, storage, distribution, use and control of WFI.

4.3 Principles of risk management (*3*) and data governance should be applied in each relevant stage of the life-cycle.

5. Risk assessment

5.1 An appropriate method for the production of WFI should be used.

5.2 Risks and controls should be identified for each stage of the life-cycle of the production, storage, distribution, use and control of WFI.

5.3 Risks identified should be analysed and evaluated to determine the scope and extent of validation and qualification of the system, including the computerized controls used for the production, control and monitoring of WFI. Risk management should be an ongoing part of the quality management process for WFI. A mechanism to review or monitor events associated with production, storage, distribution and use of WFI should be implemented.

5.4 Where production methods other than distillation are used, specific attention should be given to ensure:

- the appropriateness of user requirement specifications;
- feed-water quality;
- the sequence of purification stages required;
- the extent of pretreatment required;
- appropriately designed and located sampling points;
- controls are in place to prevent "dead legs"; and
- in-line monitoring.

6. Control strategy

6.1 The WFI system should be appropriately qualified and validated.

6.2 There should be controls to minimize the risk of contamination of WFI produced, stored or circulated.

6.3 An appropriate control strategy should be defined to ensure that all risks identified are eliminated, or reduced to an acceptable level.

6.4 All parts of the system (pretreatment, treatment, storage and distribution) should be appropriately designed and constructed. Materials for construction should not be reactive, additive, absorptive or adversely affect the quality of water and should be suitable for the sanitizing method used.

6.5 Treatment (also referred to as pretreatment) of water entering the system should ensure adequate removal of chemicals (organic and inorganic), particles, matter and microbiological impurities. The treatment should not have a detrimental effect on the materials of construction or downstream components of the water system.

6.6 Techniques such as deionization, electro-deionization, nanofiltration, ultrafiltration, water softening, descaling, prefiltration, degasification, and ultraviolet treatment, along with other techniques, may be considered in conjunction with a single- or double-pass reverse osmosis system.

6.7 These should allow for sanitization (thermal or chemical, or a combination thereof) when required. The method of sanitization should be appropriate, effective and validated. Sanitization should be done at specified intervals, in accordance with a documented procedure.

6.8 Appropriate sampling techniques should be used to sample water for analysis, at defined sampling locations, in accordance with a documented sampling procedure and a schedule.

7. Good practices in the production of water for injection

7.1 WFI should be prepared either from water that complies with World Health Organization guidelines for drinking water (*4*), national standards for drinking water as a minimum quality feedwater, or purified water.

7.2 The results of water testing should be trended. Trend data should be reviewed routinely, in order to determine the potential for deterioration in the system.

7.3 Appropriate alert and action limits, in addition to specification limits, should be specified. Trend data should be assessed routinely and used to revise limits where appropriate.

7.4 The system should be monitored for its ongoing performance within defined parameters, including but not limited to, conductivity, total organic carbon (TOC) and microbial contamination.

7.5 A combination of online and offline monitoring of WFI should be done, to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with online instruments. Use of rapid microbiological methods is encouraged for timely monitoring, and aids with rapid responses to prevent deterioration of the system.

7.6 The outlet of reverse osmosis systems should be monitored, to ensure that potential breaches are identified. This may include monitoring the conductivity of the water, and pressure.

7.7 The system should remain in a validated state throughout its life-cycle.

References

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Further reading

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Annex 4

Good chromatography practices

1. Introduction and scope

1.1 The use of chromatography methods such as high-performance liquid chromatography, also referred to as high-pressure liquid chromatography (HPLC), and gas chromatography (GC) in quality control laboratory analysis has increased significantly in recent years. Observations during inspections have shown that there was a need for a specific good practices (GXP) document.

1.2 HPLC and GC methods are used in, for example, the identification of materials and products, for determination of assay and related substances in materials and products, as well as in validation such as process validation and cleaning validation. *Note*: Although thin-layer chromatography methods are also used, this approach is not specifically addressed in detail in this document.

1.3 Owing to the criticality of the results obtained through chromatography, it must be ensured that the data acquired meet ALCOA+ principles (i.e. attributable, legible, contemporaneous, original and accurate, with additional emphases [see Glossary]).

1.5 This document provides information on GXP to be considered in the analysis of samples when chromatographic methods and systems are used. The principles should be applied in the analysis of, for example, raw materials, starting materials, intermediates, in-process materials and finished products.

1.6 The principles contained in this guideline are applicable to general chromatographic analysis used in, for example, assay determination, testing for related substances and impurities, process validation, cleaning validation, cleaning verification and stability testing.

2. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts. *Note*: For general definitions relating to chromatography, see the relevant pharmacopoeia recognized by the national medicines regulatory authority.

ALCOA. A commonly used acronym for "attributable, legible, contemporaneous, original and accurate".

ALCOA+. A commonly used acronym for "attributable, legible, contemporaneous, original and accurate" that puts additional emphasis on the attributes of being complete, consistent, enduring and available – implicit basic ALCOA principles.

audit trail. 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 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.

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

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.

data. All original records and true copies of original records, including source data and metadata and all subsequent transformations and reports of these data, that are generated or recorded at the time of the good manufacturing practices (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.

metadata. Data about data that provide the contextual information required to understand those data. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. 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.

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

sample set. The combination of samples, standards and blanks prepared for analysis, which includes the specified sequence to be injected or analysed.

source data. Original data obtained as the first-capture of information, whether recorded on paper or electronically.

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

3. Chromatographic systems

3.1 Chromatographic systems should meet regulatory and GXP requirements. This should include, for example, ensuring that data are acquired, processed and stored in accordance with ALCOA+ principles (see Glossary).

3.2 Supplier selection and vendor qualification should ensure that hardware and software are suitable for their intended application.

3.3 Valid agreements should specify the respective responsibilities between the purchaser and supplier and include arrangements for after-sales services.

3.4 Chromatographic systems selected, installed and qualified should be appropriate for their intended use.

3.5 The environment in which such systems are placed should be appropriate to support their performance. This may include, for example, control of temperature and relative humidity in the area.

4. Qualification, validation, maintenance and calibration

4.1 The scope and the extent of validation and qualification of chromatographic systems should be determined based on risk management principles. This includes hardware and software.

4.2 The approach to, and execution of, validation and qualification should be described in an authorized document such as a validation master plan.

4.3 All stages of qualification should be considered and may include, for example, user requirement specifications (URS), design qualification (DQ), factory acceptance test (FAT), site acceptance test (SAT), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

4.4 Validation and qualification should be described in protocols and recorded in reports. Reports should contain documented evidence and include, for example, screenshots, printouts or other source data and metadata of tests executed as part of validation and qualification.

4.5 The data should provide evidence of the consistency of performance of the system and reliable and accurate results.

4.6 Parameters such as, but not limited to, password control, audit trail, access and privileges should be described and verified during validation and qualification.

4.7 Maintenance, preventive maintenance and calibration of chromatographic systems should be done in accordance with written procedures. Records should be maintained.

4.8 Root cause analysis, impact assessment and risk assessment should be done when any calibration parameter is found to be out of calibration or not meeting the predefined limits. Appropriate corrective and preventive action should be taken and documented.

5. Access and privileges

5.1 There should be a standard operating procedure (SOP) for the creation and deletion of user groups and users of the chromatographic system, indicating the relevant privileges allocated to each user. Records should be maintained.

5.2 An up-to-date record of user groups and users should be maintained.

5.3 Users in each group should be appropriately qualified for the responsibility and privileges allocated.

5.4 Where required, justification should be provided for privileges granted to user groups or users, including all exceptions.

5.5 User privileges reflected in written procedures should be a true reflection of the privileges allocated electronically.

5.6 Administrator access rights should not be given to other users on the system.

6. Audit trail

6.1 Chromatographic systems should have an audit trail(s) which reflect(s), for example, users, dates, times, original data and results, changes and reasons for change.

6.2 Full audit trails should be enabled from the time of installation of software.

6.1. Audit trails should remain enabled throughout the life-cycle of a chromatographic system.

6.3 Audit trails should be reviewed in accordance with an SOP and include systems and project audit trails. There should be evidence of regular review of an audit trail (for example, each sample sequence or sample set in chromatographic analysis) and of periodic review of audit trails. (Periodic review should be done at specified intervals, based on risk management principles.)

6.4 Audit trails are part of metadata and should be stored as part of the data set for all chromatographic analyses.

7. Date and time functions

7.1 Chromatographic systems should have date and time functions enabled from the time of installation of the software.

7.2 The date and time function should be locked, and access to change the date and time should be controlled. (This includes changes to time zone setting.)

7.3 All GMP actions on chromatographic systems should be date- and time-tracked.

8. Electronic systems

Note: This includes computerized systems.

8.1 Written procedures should be followed when a new electronic system is taken into use. Procedures should also be followed for the removal of a system from use. Records should be maintained.

8.2 Software selected, installed and applied for acquisition, processing and calculation of results should be suitable for its intended use, validated, and render results meeting regulatory, GXP and ALCOA+ principles.

8.3 It is preferable that all chromatographic systems be linked to a network system where data are stored and managed on a centralized server.

8.4 Stand-alone systems should be appropriately managed. Risk assessment should be done to ensure that sufficient controls are in place to eliminate the risks associated with stand-alone systems. These include, but are not limited to, access, privileges, date and time function, audit trail, data back-up and data management.

8.1. Electronic data management systems (EDMS) should be considered for the appropriate management of data, including acquisition, processing and storage of data. EDMS should be appropriate for their intended use and ensure the accuracy and reliability of data acquired and processed.

9. Solvents, buffer solutions and mobile phases

9.1 Solvents, buffer solutions and mobile phases should be prepared, stored and used in accordance with authorized specifications and procedures and a relevant pharmacopoeia recognized by the national medicines regulatory authority. These should be used within appropriate, scientifically justifiable timelines.

9.2 Records for their preparation and use should be maintained.

9.3 Chemicals, reagents and other materials used should be of appropriate grade and quality.

9.4 Liquid mobile phases should be filtered, degassed and pressurized when required.

9.5 Carrier gases used for gas chromatography should have the appropriate purity and be suitable for their intended use.

10. Column management

10.1 Columns used in chromatography should be appropriate for their intended use.

10.2 Columns should be purchased from approved suppliers.

10.3 Columns should be verified on initial receipt and checked for their suitability as part of the chromatographic system, prior to use in analysis.

10.4 Tubing and fittings should be appropriate to ensure that the system performs as expected.

10.5 The number of theoretical plates (column efficiency) should be monitored to ensure efficiency is obtained for acceptable chromatography.

10.6 Columns should be equilibrated before the analysis. The column oven (and column) temperature should be controlled when specified in the analytical procedure.

10.7 The required flow rate should be specified in relevant test procedures. It should be appropriate for the column to be used, to ensure optimal chromatographic separation without exceeding recommended maximum backpressure.

10.8 The use of columns should be recorded in a traceable manner. This includes, for example, the unique column identification number, number of injections and washing of the column.

10.9 Columns should be washed (cleaned or flushed) according to defined procedures describing the steps and parameters, such as sequence, temperature, flow rate and time.

10.10 Columns should be stored in a manner that ensures that they are not damaged.

11. Sample management and sample set

Note: Inappropriate management of samples may result in errors during analysis. Written procedures should be followed to avoid such risks.

11.1 Sample management in the laboratory (including the receipt and preparation of samples) should be considered an important aspect in good chromatography practices.

11.2 Samples received for analysis should be entered in an appropriate record that ensures the traceability of the sample detail and analysis.

11.3 Samples should be stored under appropriate conditions.

11.4 Samples (as well as blank and standard solutions) should be prepared in accordance with the authorized specifications and standard test procedures. Records for the preparation should be maintained.

11.5 Official, secondary or working standards used should be traceable to the records maintained for their purchase, preparation and storage.

11.6 Standard and sample solutions prepared for use in chromatography should be used within defined timelines derived from analytical procedure validation and stability data, as appropriate.

11.7 The sample set should be defined. The vials with standard solution(s), sample solution(s) and blank solution(s) should be verified to ensure the correct sequence of injections in the chromatographic system before starting the sequence of injections.

11.8 Where carry-over or interference in analysis is relevant, suitable precautions should be taken, such as the inclusion of a blank in the sequence of injections.

11.9 The use of "trial injections", "system check injections", or other injections that are not specified as part of a sample set, is not recommended. In exceptional cases where this is done, authorized procedures should clearly describe this approach. (Normally, only standard solutions may be used for this purpose, unless otherwise needed and justified e.g. biologics). The electronic record of results in such cases should be saved and stored, together with the results of the sample set for analysis.

11.10 A system suitability test (SST) should be part of the sample set. The SST should be performed as described in the respective pharmacopoeia monograph or validated in-house specification and standard test procedure. The SST should meet the predefined acceptance criteria, before samples are injected and throughout the analysis.

11.11 Acceptance criteria should be set for the SST, bracketing standards, deviation from relative retention and any other aspect that may be deemed necessary for the chromatographic analysis. This includes acceptability of peak shapes.

11.12 Bracketing standards (standard solution injections) should be included in the sample set, at defined intervals, where appropriate. The number of bracketing standards included in a sample set should be defined. Compliance with the defined acceptance criteria should be verified.

11.13 Where blank interferences are detected, these should be within predefined limits.

12. Chromatographic methods (acquisition and processing)

12.1 Chromatographic methods should be suitable for their intended use. Appropriate acceptance criteria should be specified for parameters such as selectivity (resolution and/or peak-to-valley ratio), sensitivity (signal-to-noise ratio), peak symmetry, repeatability and integration conditions (if applicable).

12.2 Where non-pharmacopoeia methods are to be used, these should be developed, validated and described in detail in standard procedures. These procedures should be followed by qualified, trained, experienced personnel.

12.3 It is preferable that methods are created and saved in the chromatographic system by authorized personnel. The method selected for analysis from the saved methods should not be modified, unless approved for the intended purpose by authorized personnel.

12.4 Data acquisition and processing software should be appropriately validated or verified as being suitable for use. Methods selected for acquisition and processing should be traceable and reflected in the audit trail.

12.5 Methods should be proven to remain in a validated state throughout their life-cycle.

12.6 Chromatographic conditions (such as the composition of the mobile phase, pH, column dimensions) may be adjusted, within specified limits and in accordance with written procedures, to obtain the separation required. The adjustments made should be within the limits specified (such as defined in the design space of the analytical procedure). The SST requirements (e.g. resolution, symmetry, repeatability) should be met, and retention times and relative retention should be similar.

13. Peak integration

13.1 Peak areas in chromatograms should be accurately and consistently integrated in a scientifically sound manner.

13.2 Where possible, HPLC and GC instruments should be interfaced with computerized chromatographic data-capturing and processing systems that are capable of applying the integration parameters set, automatically and consistently.

13.3 To facilitate the accurate integration of chromatographic peaks, it is preferable that all of the peaks are fully separated. However, when quantitative data are to be obtained from unresolved peaks, the laboratory should have clear policies as to how such peaks should be integrated. This should include a description of the type of integration to be used, with a justification for its use, including, for example:

- tangential skim;
- exponential skim;
- exponential curve fitting;
- straight line skim;
- front peak skim;
- rear peak skim;
- peak-to-valley ratio; and
- valley height ratio.

13.4 Validated methods, specified chromatographic conditions and good chromatography practices should facilitate obtaining symmetrical peaks. Where atypical peak shapes are observed, these should be investigated and appropriate action taken.

13.5 Where manual integration has to be done, authorized procedures should be followed. Records should be maintained and include the authorization and justification for manual integration.

13.6 Using a procedure to integrate peak height or area by manually setting the baseline using chromatographic software should only be allowed in exceptional cases. Only trained, experienced users should be granted privileges to do so. Records and justification should be given when this procedure is followed.

13.7 Where smoothing is applied, the type of "filter" used and the extent of smoothing should be justified.

14. Data management

14.1 Chromatographic data should be managed in accordance with this guideline and other related guidelines (*1*–*3*).

14.2 Procedures should be followed for timely processing and review of data and reporting of results.

14.3 Data should be backed up according to procedures, and records maintained as proof thereof. Special care should be taken to ensure frequent back-up of data from stand-alone systems, to prevent loss of data.

14.4 Data should be safely stored in a way that includes control over access to data. Backed-up data should be stored at a separate location. Some data should be randomly selected for restoration and verification, at defined intervals, in accordance with a written procedure.

14.5 Where appropriate, paper printed records (including data and metadata) may be retained as part of the analytical report reflecting analyses performed.

14.6 Procedures should be in place to allow for recovery of chromatographic data in case of disasters such as instrument failure, viruses, hardware or software failure and power failure.

14.7 Complete data should be retained for appropriate periods of time, to allow for data verification, inspection, registration or other reasons.

Note: See other guidelines addressing computerized systems (*1*), data integrity (*2*) and good documentation practices (*3*).

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Annex 5

Quality management system requirements for national inspectorates

Background

During the Joint Meeting on Regulatory Guidance for Multisource Products (Copenhagen, July 2016), several World Health Organization (WHO) guidance documents were identified for update. In October 2016, the Fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) confirmed the need to update the selected guidelines.

Following up on the recommendation from the Fiftieth ECSPP, the WHO Secretariat conducted a detailed analysis of the cluster of guidelines proposed for revision. The outcome of this analysis was discussed during the informal consultation on Good Practices for Health Products Manufacture and Inspection (Geneva, July 2018). In particular, considering that the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (*1*) defines the basic requirements applicable to quality systems for the operation of inspection services within national regulatory authorities (NRAs) concerned with good manufacturing practices (GMP) inspections, the WHO Secretariat proposed a strategy for revision that includes aligning the guidance with the principles of ISO 9001:2015 (*2*) and with relevant Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) guidance (*3*), as well as broadening its scope to include all good practices (GXP)-related inspections conducted by an NRA.

The Fifty-second ECSPP endorsed the proposal for revision and recommended the WHO Secretariat to revise the *WHO Quality systems requirements for national good manufacturing practice inspectorates* (*1*), aligning its content to international standards and the latest quality management systems (QMS) principles, and to expanding the scope.

1. Introduction

1.1 This document describes the quality management system (QMS) requirements for the operation of inspection services within national regulatory authorities (NRA) or other state structures (for the purpose of this guidance, the term "NRA" will be used in the text to represent both NRAs and other state structures). It is intended that each inspection service uses these requirements as the basis for developing and implementing its own QMS. Where the inspectorate operates under the umbrella of the NRA QMS, consideration should be given to the *WHO guideline on the implementation of quality management systems for national regulatory authorities* (*4*).

1.2 The adoption of a common standard for QMS requirements is an essential element in achieving consistency in inspection practices and facilitating structured communication with other units of the NRA, as well as enabling mutual confidence and permitting recognition between pharmaceutical inspectorates.

2. Scope

2.1 This document outlines the QMS requirements for pharmaceutical inspectorates that are competent for the oversight of GXP operations.

3. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

corrective actions. Steps taken to eliminate the cause of existing nonconformities in order to prevent recurrence. The corrective action process tries to make sure that existing nonconformities and potentially undesirable situations do not happen again.

good practices (GXP). The group of good practice guides governing the preclinical, clinical, manufacturing, testing, storage, distribution and post-market activities for regulated pharmaceuticals, biologicals and medical devices, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacovigilance practices (GPP) and good distribution practices (GDP).

internal audit. An examination and assessment of all or part of a quality system, with the specific purpose of improving it. An internal audit should be conducted by an independent (of the function to be audited) and qualified team of experts designated by the management for this purpose.

quality indicators. Selected data intended to be monitored and used in assessing trends in performance.

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality manual. A document that includes the quality policy and objectives and describes the various elements of the QMS.

quality policy. A brief statement that describes the organization's purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

rapid alert. An urgent notification submitted by an NRA participating in the rapid alert system concerning measures taken against a product placed on the market that poses a risk to consumers' health and/or safety.

risk management. The systematic application of quality management policies, procedures and practices to the tasks of assessing, controlling, communicating and reviewing risk.

standard operating procedure (SOP). An authorized written procedure giving detailed instructions for performing a task or following a process in accordance with legislation, official guidance or internal standards.

4. Quality management system

4.1 The concept of a QMS is wide-ranging and covers all matters that are necessary to implement the inspectorate's quality policy and to meet predefined objectives.

4.2 The QMS should define the inspectorate's scope and context within the regulatory mandate, as well as covering all functions, processes and activities.

4.3 The primary aims of an inspectorate's QMS are:

1. to ensure its ability to consistently provide services that meet the organization's objectives, legal requirements and interested parties' expectations; and

2. to facilitate continual improvement and provide a sound basis for sustainable development to comply with statutory and regulatory requirements.

4.4 The QMS should at least describe and manage organizational structure, responsibilities, procedures, systems, processes and resources required, to provide value and achieve results for the inspectorate and relevant interested parties.

4.5 Typically, the legal basis for the establishment of the inspectorate, its mandate, the quality policy and the principles of the QMS should be documented in a quality manual or equivalent document.

4.6 The QMS should enable senior ("top") management to best use available resources and systems in order to achieve the inspectorate's targets and quality objectives. Senior management's commitment and active participation is essential to ensure implementation of the QMS and to support staff within the inspectorate.

5. Context of the inspectorate

5.1 The legal basis for the establishment of the inspectorate and its mandate, as well as statutory and regulatory responsibilities and functions, should be clearly defined.

5.2 The inspectorate should determine its scope and strategic direction, in order to achieve the intended objectives.

5.3 The structure and operation of the inspectorate should be such that impartiality and independence are safeguarded. Rules for deontology, confidentiality, ethics and conflicts of interest should be clearly defined and obeyed. Where relevant, the inspectorate should implement a policy that distinguishes between the process of inspection and that of providing an advisory service. This service should be of benefit to all of industry and not solely to individual organizations.

5.4 The relationship of the inspectorate with other departments within the same NRA, and other agencies and organizations outside the inspectorate, as well as any other stakeholders, should be described and documented where relevant.

6. Management and leadership

6.1 Senior management should make a formal commitment to the implementation of a documented quality policy that is compatible with statutory requirements and relevant objectives.

6.2 Senior management should ensure that the inspectorate's services and functions are aligned with regulatory requirements and the NRA's objectives, as well as meeting interested parties' expectations.

6.3 Senior management is accountable for the integration of QMS requirements into the inspectorate's processes and functions; for communicating the importance of QMS principles; and for the overall effectiveness of the QMS. In addition, senior management should promote the application of risk management principles and support the engagement and contribution of personnel in improving the QMS.

6.4 Senior management should ensure that the pharmaceutical inspectorate has sufficient and appropriate resources at all levels to enable it to meet its objectives. Responsibilities, authorities and the reporting structure for relevant roles should be clearly defined and documented in the QMS. The structure should be defined in organization charts.

6.5 An appropriately experienced and qualified person should be nominated as a QMS responsible person. This person should have direct access to senior management. If necessary, this task may be assigned to more than one person.

6.6 There shall be a system for periodic management review of the QMS effectiveness, including process improvements. Such reviews should be documented and records should be maintained for a defined period.

7. Management system planning

7.1 The inspectorate should establish appropriate objectives for the intended level of service and of its functions, which should be consistent with the quality policy and regulatory requirements. Principles of risk management and sustainable development should be considered for the establishment of these objectives.

7.2 These objectives should be communicated to personnel at all levels and be updated whenever necessary.

7.3 Appropriate resources should be available to meet these objectives. Roles and responsibilities should be defined and, where appropriate, timelines for completion should be established. Systems for monitoring and evaluating results should be established. All necessary information on quality objectives should be maintained.

7.4 A documented change management system should be established, to ensure that change requests are assessed, approved or rejected; that appropriate resources are allocated; and that roles and responsibilities are defined. Any change should be documented, communicated to the personnel and evaluated after implementation, to ensure the objectives are met. The change management system should ensure that continual improvement is undertaken in a timely and effective manner.

8. Resources

8.1 The inspectorate should have an organizational structure, required resources (financial, human, facilities and others) and documented procedures that enable it to meet its objectives; to perform inspection activities in accordance with official GXP guidelines and national legislation; and to carry out its functions and operations satisfactorily. Where necessary, measures and resources for the safety of personnel should be available.

Personnel

8.2 The inspectorate should employ the required personnel possessing the appropriate expertise to perform its functions, including inspections, and to determine whether the inspected entities comply with the principles of current GXP guidelines and with relevant legislation.

8.3 Personnel responsible for inspections should have appropriate qualifications, including education, training, experience and knowledge of the inspection process and subject, and should be periodically evaluated. They should have the ability to make professional judgements as to the conformity of the inspected party with the requirements of GXP and the relevant legislation, and be able to apply risk management principles in their decision-making process.

8.4 The inspectorate should ensure that induction and continuous training is provided to inspection personnel on administrative, regulatory and technical topics, to maintain the inspectors' competency aligned with current industry practice, technological advancements and regulatory changes. Training should be documented and its effectiveness assessed periodically.

8.5 The inspectorate should maintain documented and up-to-date information on the relevant qualifications, training and experience of each inspector.

8.6 Personnel should have clear, up-to-date and documented job descriptions specifying their duties and responsibilities.

8.7 When products are procured from a third party and/or services are subcontracted to an external body or expert, the inspectorate should ensure that the third party meets predefined documented criteria, qualifications and the relevant requirements of the quality management system. Senior management should ensure that these external bodies or experts are periodically evaluated. Third party responsibilities and liability should be clearly defined in the contract or agreement.

8.8 All personnel employed or contracted by the inspectorate should be bound by the requirements of the quality system, obey the inspectorate's code of conduct and not be subject to any commercial, financial or other pressures that might affect their judgement and freedom to act. They should not be under the control of the pharmaceutical industry and must be assessed for potential conflict of interest. Personnel and third-party declarations of conflict of interest should be maintained, reviewed periodically and updated where necessary. It should be ensured that any decision-making process remains with the inspectorate and is not influenced by any third party.

Infrastructure

8.9 Personnel should be provided with the necessary infrastructure and appropriate work environment to enable them perform their functions and meet the quality objectives. Infrastructure includes, but is not limited to:

- buildings, workspace and associated facilities;
- qualified equipment, including hardware and software;
- transportation resources; and
- information and communication technology.

9. Documentation

General

9.1 The inspectorate should establish and maintain a system for the control of all documentation, including electronic files, relating to the inspectorate's QMS and activities. This should include policies, procedures, guidelines, records and any documents of external origin, such as legislation, which

may directly or indirectly influence the activities of the inspectorate; or documents received from pharmaceutical companies and relevant organizations, as appropriate.

9.2 The inspectorate should ensure that its functions and operations are described in SOPs that clearly define the required responsibilities, processes and actions. These may include, but not be limited to, training; inspections; reporting after inspections; handling of complaints; licensing (issue, suspension, withdrawal); certification; handling of quality, safety and efficacy issues; documentation control; change and deviation management; inspection planning; risk management; and the handling of appeals.

9.3 The system and activities relating to advising on, issue, withdrawal or suspension of licences, registration or certifications; and the application of other regulatory sanctions on facilities, organizations, products or operations, should be detailed in procedures and be in accordance with relevant guidelines and national legislation.

9.4 The inspectorate should establish procedures describing communication with other NRA units and external interested parties (e.g. industry, media) considering any statutory and regulatory requirements, where appropriate. Similarly, a procedure for exchanging regulatory information with other NRAs or national quality control laboratories should be available.

9.5 Activities relating to the sampling and testing of pharmaceutical products and raw materials should be described in a procedure that should also include the process for handling nonconforming products (e.g. substandard or falsified medical products).

9.6 The inspectorate should have procedures on handling quality, safety and efficacy issues that may lead to recall or withdrawal of products from the market. Where applicable, the inspectorate should establish and maintain a system for communicating rapid alerts. Records of recalls and withdrawals should be maintained in accordance with national legislation.

9.7 The inspectorate should have documented procedures for dealing with complaints arising from its activities or those of its personnel and any contracted person or organization. A record should be maintained of all complaints received and the actions taken by the inspectorate. These records should be retained for a specified period of time.

9.8 The inspectorate should have procedures for consideration of appeals against its decisions.

9.9 The documentation control system should ensure that:

- documents are identified by title, author, reviewer, approver and unique identification. They should be dated and authorized by the appropriate persons prior to issue;
- current versions of documents are held by nominated personnel;
- a register of all relevant documents and document holders is maintained;
- superseded documents are withdrawn from use but are retained for defined periods of time;
- any changes to documents are made in a controlled manner and are properly authorized. There should be a means of identifying changes in individual documents;
- records relating to the inspectorate's activities and functions are readily available and are retained for an adequate period, in line with legal requirements or internal standards;
- records comply with the relevant obligations under national legislation;
- records are safely stored during their retention period and held under conditions that guarantee their security and confidentiality unless otherwise required by national legislation. The destruction of records after their retention period should follow a predefined procedure; and
- electronic documentation and record management systems provide at least the same level of assurance, compliance, accuracy and security as a manual system.

Inspection process and documents

9.10 An inspection should be categorized in accordance with GXP guidelines (e.g. GMP, GDP, GCP) and its scope (e.g. product, process) and type (e.g. triggered, routine, follow-up) should be appropriately defined and documented.

9.11 The inspectorate should plan inspections in advance and elaborate a written programme as part of the inspectorate's annual workplan. Risk management principles should be considered when establishing an inspection programme and prioritizing inspections, as well as when conducting an inspection. Where repeated inspections of a company or organization have to be carried out, the frequency should be determined based on risk management principles defined in a procedure.

9.12 Inspection-related documents and records, as defined in relevant inspection procedures (e.g. inspection plan, aide-mémoire, checklists, worksheets and company documents and records), should be maintained for a defined period.

9.13 When more than one inspector is involved in an inspection, a lead inspector should be appointed to coordinate inspection activities. The inspection report should be prepared by the lead inspector, with the assistance of all participating inspectors and/or experts, and should be agreed upon by all participating inspectors and/or experts.

9.14 The inspection report should follow a pre-approved format. Observations and/or data obtained in the course of inspection should be recorded in a timely manner, in order to prevent loss of relevant information.

9.15 The inspection report should be sent to the inspected company or organization within the inspectorate's established timelines. The lead inspector and all concerned inspectors and/or experts should participate in assessing the company's response, to determine the appropriateness of corrective and preventive actions as well as the GXP compliance status of the company or organization.

9.16 Completed inspections should be reviewed to ensure that all reporting and regulatory requirements are met.

10. Operational planning and performance evaluation

10.1 An annual workplan should be developed, documented and periodically reviewed by senior management, including all the inspectorate's activities, in accordance with a written procedure. Regulatory, statutory and scientific requirements should be taken into account during the planning of operations and services. Consideration should also be given to the availability of required resources and the ability to consistently provide services that meet legislative requirements and stakeholder expectations. Risk management principles should be used during planning, to determine, monitor and manage risks and to identify opportunities for process improvements. Any changes to the workplan should follow the inspectorate's change management system.

10.2 Appropriate quality indicators and methods should be established, in order to monitor and periodically evaluate the inspectorate's processes and level of improvement and service (including contracted-out services) and demonstrate that they were carried out as planned and met predefined

quality objectives. These quality indicators, methods, analyses and results should be documented.

10.3 The results of the analyses should be used to evaluate the performance and effectiveness of the QMS, the adequacy of actions taken to address risks, and the need for further improvements.

Internal audits

10.4 The inspectorate should implement a system of periodic and documented internal audits of its operations, to assess compliance with the requirements of the QMS. Internal audits should be conducted at least once a year.

10.5 Internal audit processes, criteria, scope and documents should be defined. Auditors' qualifications and selection criteria should be documented. Internal audit records, including the findings, conclusions, recommendations and follow-up actions, should be retained for a defined period.

10.6 Corrective actions corresponding to audit findings should be identified, documented and implemented in a timely manner. The effectiveness of these actions should be evaluated and the risk plan should be updated to take note of the root causes of the nonconformances.

Management review

10.7 Senior management should review the inspectorate's QMS at planned intervals, to ensure its continuing suitability, adequacy, effectiveness and alignment with the inspectorate's strategic direction and legislative requirements. Management reviews should be conducted at least once a year.

10.8 A management review should include, but not be limited to:

- the status of the actions from previous management reviews;
- any internal or external changes affecting the QMS;
- any deviations affecting the functionality of the QMS;
- the extent to which quality objectives have been met;
- process performance analyses;
- audit results and the effectiveness of corrective actions;
- complaints and appeals;
- the adequacy of resources;

- any identified risks and mitigation measures; and
- opportunities for improvements.

11. Publications

11.1 The inspectorate should issue and maintain an up-to-date list of inspected and licensed facilities and organizations, including information on the outcome of inspections. This list may become publicly available in accordance with national legislation.

11.2 The inspectorate should ensure that other relevant publications, such as technical guides, GXP guidelines and regulatory requirements, are publicly available.

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Annex 6

Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance

1. Introduction and scope

1.1 Background

According to research by UN Environment (*1*), growing antimicrobial resistance (AMR) linked to the discharge of drugs and particular chemicals into the environment is one of the most worrying health threats of today. AMR accounts for an estimated 700 000 deaths per year worldwide and, by 2030, will represent up to US$ 3.4 trillion in gross domestic product (GDP) loss (*2*). AMR has been identified as a priority at the World Health Assembly since 1998 (*3*), with rising momentum throughout the years. Since 1998, there have been a series of World Health Assembly resolutions on AMR. These paved the way to the Sixty-eighth World Health Assembly in May 2015, where the World Health Assembly endorsed a global action plan to tackle AMR, including antibiotic resistance, the most urgent drug resistance trend (*4*). More recently, the *Thirteenth General Programme of Work (2019–2023)* highlighted the need to address this emerging threat, under the section for "Tackling antimicrobial resistance" (*2*). It is only recently that the need to address waste and wastewater management from pharmaceutical production has been explicitly addressed. Namely, on 30 November 2018, the World Health Organization's (WHO's) Executive Board meeting decided that technical input will be provided to good manufacturing practices (GMP) guidance on waste and wastewater management from the production of critically important antimicrobials (*5*, *6*). The present *Points to consider* document was written further to this recent decision.

We are entering a post-antibiotic era, where simple and previously treatable bacterial infections can kill and where routine medical procedures that rely on antibiotic preventative treatment, such as joint replacements and chemotherapy, will not be possible. The 2014 O'Neill report commissioned by the Government of the United Kingdom of Great Britain and Northern Ireland estimated that antimicrobial-resistant infections may become the leading cause of death globally by 2050 (*7*).

The environment plays an important role in antimicrobial resistance. Microorganisms in soil, rivers and seawater can develop resistance through contact with resistant microbes (transfer of resistance genes), antibiotics and disinfectant agents released by human activity (*1*), as well as heavy metals (*8*, *9*) that may propagate AMR in the environment. People and livestock could then be exposed to more resistant bacteria through food, water and air (*1*).

Pharmaceuticals entering the environment from industrial manufacturing activities are not the major source of antimicrobial resistance, but in countries that contribute the most to the production of antimicrobials, this issue can be significant. The levels of pollution with antimicrobials have been measured in waters in the proximity of pharmaceutical production facilities. Antimicrobial

concentrations in some effluents are too low to be lethal to exposed bacteria but may still be sufficient to induce antimicrobial resistance (*1*, *10*), but high concentrations have been found downstream of antimicrobial manufacturing sites in several countries. Scientific literature reports a correlation between the type and number of highly resistant bacteria and the level of antimicrobial pollution (*10*). This led to manufacturing sites being identified as one of the hot spots for development of AMR, but this knowledge dates from only a few years ago (*11*).

Poor control of waste (solid[1] or liquid) and wastewater, such as that encountered in some of the countries that are major global producers of pharmaceuticals, can often lead to the entry of antimicrobials into waters that are contaminated with pathogenic bacteria from untreated sewage. This increases the risk of development of AMR. Furthermore, a vast array of contaminants in municipal and industrial wastewater increases pressure on bacteria to become resistant (*1*, *11*). Eventually, from the passage of the production cycle to the effluent pipe, antimicrobial molecules (precursors and by-products) turn from valuable medicine to hazardous waste that has an impact on the efficacy of the product as well as human health and the environment.

Concentrations in river water depend on wastewater treatment facilities, as well as antimicrobial use in the populations they serve. Treatment plants are generally designed to remove conventional pollutants such as nutrients, organic matter, suspended solids and pathogens, but not pharmaceuticals such as antimicrobial agents (*1*). The level of treatment of manufacturing effluents or pharmaceutical waste (solid or liquid) can vary significantly, resulting in the necessity for municipal wastewater treatment plants to handle the waste. However, the activated waste may up-concentrate some antimicrobial agents, as well as antimicrobial-resistant bacteria, increasing the risk for AMR in environments where the sludge is applied. Recent evidence indicates the presence of a selection pressure for AMR within environments receiving wastewater from antimicrobial manufacturing, as opposed to environments receiving wastewater from municipal sewage treatment plants (*12*) that do not receive waste from antimicrobial manufacturing.

It is therefore important to significantly reduce the concentration of antimicrobials prior to disposal into the environment. However, the recommended approach in the absence of established standards would be to apply the precautionary principle, i.e. to not emit any waste until there is proof that the discharge does not have an adverse effect on human health or the environment.

[1] Solid waste is also considered in this document because, if not properly disposed of, different types of solid waste may leach into the surrounding environment and contaminate effluents.

Several initiatives have already been put in place by the United Nations (*13*, *14*), WHO (*4*), nongovernmental institutions (*15–17*), governments (*18–24*) and the industry itself (*25–29*). Industry should be committed to caring for the environment, and responsible manufacturing is encouraged by taking steps to minimize the environmental impact of operations and products, while also balancing the need to produce high-quality, life-saving medication.

This document is to be considered as a time-limited document that addresses the current needs for guidance on how GMP should be implemented to waste and wastewater management for production of antimicrobials. It leverages on the existing GMP and makes reference to relevant literature rather than containing detailed instructions. This document may be updated in the future, as the knowledge about suitable technologies on how to remove antimicrobial residues is expected to increase within the next few years and the requirements may be modified/adapted in consequence.

1.2 Purpose

The purpose of this document is to:

- provide recommendations and expectations for manufacturing facilities for medicines regarding waste management, to mitigate/prevent potential antimicrobial resistance;
- raise awareness of medicines' manufacturers, national regulatory authorities (NRAs) and especially GMP inspectorates and inspectors in all Member States, on sections of relevant GMP guidance that are applicable to the management of waste/wastewater from the production of antimicrobials, while emphasizing the importance of all aspects of GMP implementation and considering the parts of GMP that may not have a direct impact on product quality; and
- provide clarification on the interpretation of those clauses and specific measures that should be taken to be considered compliant with the relevant sections of GMP guidance, without changing the scope of GMP.

This document is not intended to cover AMR issues that are related to the human or veterinary use of antimicrobials or to other types of environmental contamination (*1*), such as the excretion of antimicrobials during their use. It should not be considered to provide exhaustive information on methods that can be used to control and reduce contamination of the environment with antimicrobials and related chemicals, such as active precursors or by-products coming from pharmaceutical production processes. It should also not be considered to provide information on the levels of antimicrobial residues that are considered acceptable.

1.3 Target audience

This document is targeted to:

- all pharmaceutical manufacturers engaging in synthesis and/or production of antimicrobials (primarily manufacturing sites for active pharmaceutical ingredients [APIs] and, secondly, manufacturing sites for finished pharmaceutical products [FPPs]);
- GMP inspectors and inspectorates from national medicines regulatory authorities;
- regulatory bodies that are responsible for enforcing environmental protection standards and waste/wastewater management in all Member States – consistent with a multidisciplinary approach, including but not limited to ministries of health, ministries of environment or pollution control boards, and ministries of agriculture, as appropriate; and
- waste and wastewater management services that handle antimicrobial waste and/or process effluents from the pharmaceutical industry.

2. Glossary

The definitions given below apply to the terms as used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

antimicrobial resistance (AMR). Antibiotic resistance develops when bacteria adapt and grow in the presence of antibiotics. The development of resistance is linked to how often antibiotics are used. Because many antibiotics belong to the same class of medicines, resistance to one specific antibiotic agent can lead to resistance to a whole related class. Resistance that develops in one organism or location can also spread rapidly and unpredictably through, for instance, the exchange of genetic material between different bacteria, and can affect antibiotic treatment of a wide range of infections and diseases. Drug-resistant bacteria can circulate in populations of human beings and animals, through food, water and the environment, and transmission is influenced by trade, travel and both human and animal migration. Resistant bacteria can be found in food, animals

and food products destined for consumption by humans. Some of these features also apply to medicines that are used to treat viral, parasitic and fungal diseases, hence the broader term antimicrobial resistance.

finished pharmaceutical product (FPP). A finished dosage form of a pharmaceutical product that has undergone all stages of manufacture, including packaging in its final container and labelling.

3. Review of the environmental aspects of good manufacturing practices

GMP are, a priori, intended to control the manufacture of medicines, and in principle do not focus on the environmental aspects of these. However, GMP include many aspects related to the protection of the environment and workers. If fully implemented, GMP should therefore prevent many different types of waste from contaminating the environment.

Given that the lack of control in the downstream processes of manufacturing medicines will ultimately lead to their loss in efficacy, we may no longer focus only on the aspects of GMP that are directly linked to the quality of medicines. Medicines that are no longer effective lose their value and it is therefore crucial for manufacturers and all stakeholders to take action in order to protect the efficacy of those medicines. Only one major class of antibiotics has been discovered since 1987 (*30*) and too few antibacterial agents are in development to meet the challenge of multidrug resistance (*4*).

The *WHO good manufacturing practices for pharmaceutical products: main principles* (*31*) and *WHO good manufacturing principles for active pharmaceutical ingredients* (*32*) contain a limited set of clauses related to environmental issues. Waste and wastewater management are addressed only briefly. The following clauses are the only ones considered to be of relevance:

> ***WHO good manufacturing practices for pharmaceutical products: main principles. Annex 2, WHO Technical Report Series, No. 986, 2014 (31)***
>
> ***Waste materials***
>
> *14.44 Provisions should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.*
>
> *14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points*

outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

WHO good manufacturing practices for active pharmaceutical ingredients. Annex 2, WHO Technical Report Series, No. 957, 2010 (32)

4.6 Sewage and refuse

4.60 Sewage, refuse and other waste (e.g. solids, liquids or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

On the other hand, the *WHO good manufacturing practices for pharmaceutical products containing hazardous substances* (*33*) contains more detailed requirements regarding waste and wastewater management, which can be applied to the production of antimicrobials. These guidelines cover those hazardous substances traditionally belonging to reproductive health hormones and highly potent materials such as steroids or sensitizing medicines such as beta-lactam antibiotics. According to these guidelines, a hazardous substance or product is a "product or substance that may present a substantial risk of injury, to health or to the environment". As antimicrobials are deemed to present a substantial risk of injury to both health and the environment, when released into the environment through their action on microorganisms, they should be considered for inclusion in the scope of this guidance.

The following clause is considered to be of general relevance to the protection of the operators, the environment and the public:

WHO good manufacturing practices for pharmaceutical products containing hazardous substances. Annex 3, WHO Technical Report Series, No. 957, 2010 (33)

General

2.1 Facilities should be designed and operated in accordance with the main GMP principles, as follows:

- *to ensure quality of product;*
- *to protect the operators from possible harmful effects of products containing hazardous substances; and*
- *to protect the environment from contamination and thereby protect the public from possible harmful effects of products containing hazardous substances.*

The guidelines require risk assessments to determine the potential hazards to the operators and to the environment of hazardous substances contained in all types of waste, as per the following clauses:

> ***Risk assessment***
>
> *4.1 Not all products containing hazardous substances are equally potent and risk assessments should be carried out to determine the potential hazards to operators and to the environment. The risk assessment should also determine which phases of the product production and control cycles, from manufacture of the API to distribution of the finished product, would fall under the requirements of these guidelines. Risk assessments applicable to the environment should include airborne contamination as well as liquid effluent contamination.*
>
> *4.2 Assuming that the risk assessment determines that the products or materials being handled pose a risk to the operators and/or the public and/or the environment, the guidelines to be followed for the design and operation of the facility should be as detailed in this document.*

Such risk assessments should therefore be performed by manufacturers as required, in principle, for any substance deemed to be hazardous.

The guidance already has a requirement prohibiting discharge of hazardous substances into normal drainage systems:

> ***Environmental protection***
>
> *7.1 Due to the hazardous nature of the products being handled in the facility, neither the product nor its residues should be allowed to escape into the atmosphere or to be discharged directly to normal drainage systems.*

It also has a requirement for protection of the atmosphere and the public in the local vicinity:

> *7.2 The external atmosphere and the public in the vicinity of the facility should be protected from possible harm from hazardous substances.*

The above clause may be considered to apply to effluents and water streams near facilities, as their contamination with antimicrobials can have a public health impact. The literature contains several reports of effluents and water streams contaminated with potentially dangerous levels of antimicrobials (*8*, *10*, *12*).

The guidance also has a requirement for treatment of hazardous effluent before it is discharged:

> *7.3 If liquid effluent poses a safety or contamination risk, the effluent should be treated before being discharged to a municipal drain.*

However, it should be noted that the municipal drain may not be suitable to handle the large quantities of hazardous effluents such as those that are released by large pharmaceutical companies, and therefore manufacturers are requested to carefully consider this in their approach.

The guidance also contains a general statement about handling of liquid and solid waste effluent and another about safe disposal:

> ***13. Effluent treatment***
>
> *13.1 Liquid and solid waste effluent should be handled in such a manner as not to present a risk of contamination to the product, personnel or to the environment.*
>
> *13.2 All effluent should be disposed of in a safe manner, and the means of disposal should be documented. Where external contractors are used for effluent disposal they should have certification authorizing them to handle and treat hazardous products.*

As per the above clause, where external contractors are used for effluent disposal, they should have certification authorizing them to handle and treat hazardous products.

The management of waste that is obtained from quality control testing in a laboratory setting at a manufacturer's site or contract laboratory is covered by the following clause:

> ***Guidance on good practices for pharmaceutical quality control laboratories. Annex 1, WHO Technical Report Series, No. 957, 2010 (34)***
>
> ***7. Premises***
>
> *7.6 Procedures should be in place for the safe removal of types of waste including toxic waste (chemical and biological), reagents, samples, solvents and air filters.*

The amount of antimicrobial waste being generated by laboratory testing activities is generally considered to be negligible compared to the amounts that are being generated by manufacturing activities but should still be considered in exceptional cases, e.g. if very large amounts of sample are being tested by a quality control laboratory.

4. Expectations for manufacturers of antimicrobials

Application of the requirements outlined in the above-mentioned GMP clauses shall be verified during onsite inspections. In addition, manufacturers of APIs and FPPs should consider retaining documentation on the following:

- a risk assessment for all contaminants related to antimicrobial manufacturing, in the event that they are released into the environment, and the associated risk of development of resistant microorganisms;
- based on the above risk assessment, waste-stream analysis for each antimicrobial agent produced (at API sites and FPP sites). This analysis should be repeated whenever there is a change in production affecting waste streams;
- the quantity and nature of the waste generated, including the analytical data and documentation of analyses performed and their findings on the levels of antimicrobial agents or their precursors;
- regular reports on the collection, treatment and disposal of waste and wastewater; the frequency should be risk-based and in line with local, regional or international regulatory requirements, as applicable;
- information on the methods used to treat the waste should be documented to be effective for each specific antimicrobial or antimicrobial precursor. Analytical data demonstrating the conversion of these substances and their residues to non-hazardous waste materials should be available at the facility and kept up to date;
- if effective waste treatment is not yet implemented for all waste streams resulting from the manufacture of each API or FPP, documentation on a time-limited strategy should be in place, with specified milestones for that implementation, specifying actions towards achieving treatment that significantly reduces the concentration of the antimicrobial substance or its precursor (and its microbial source, when relevant); and
- a rationale and risk assessment as to why the manufacturer selected specific methods of decontamination of manufacturing waste containing antimicrobials and/or their mitigation strategy. Many decontamination methods already exist that reduce or remove antimicrobials (and microbes that have produced fermentative antimicrobials) from waste streams entering the environment from antimicrobial manufacturing: secondary and tertiary wastewater treatment; membrane filtration and ozonation; and ultraviolet disinfection and heat treatment, which are even more effective at

removing viable bacteria (*1*, *11*). Incineration may also be considered for solid or semi-liquid waste. The zero-liquid effluent approach or zero-discharge policy is encouraged, especially when the risk is assessed to be high or unclear, as it prevents any contamination of the environment. The level of effectiveness and by-products should be considered when adopting a particular approach.

It is recommended that this documentation be maintained at the manufacturing facility regardless of whether or not an external contractor has been used. These points to consider should be used by manufacturers as part of their self-audits, in order to verify their continued level of GMP compliance. Although the aim is not to reduce verification of the quality of products, the waste management practices and related documentation listed in this *Points to consider* document could be reviewed and scrutinized during regulatory inspections.

It should be noted that the above requirements will not be used to draw a conclusion on the level of GMP compliance of a manufacturing site. Their purpose is to guide/encourage manufacturers to apply all of the GMP principles. The application of these principles will help to tackle the emergence of AMR, by raising awareness of the preventative measures that manufacturers should take to adequately manage the waste and wastewaters that are generated while manufacturing antimicrobials.

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Annex 7

Good storage and distribution practices for medical products

1. Introduction

1.1 Storage and distribution are important activities in the supply chain management of medical products. Various people and entities may be responsible for the handling, storage and distribution of medical products. Medical products may be subjected to various risks at different stages in the supply chain, for example, purchasing, storage, repackaging, relabelling, transportation and distribution.

1.2 Substandard and falsified products are a significant threat to public health and safety. Consequently, it is essential to protect the supply chain against the penetration of such products.

1.3 This document sets out steps to assist in fulfilling the responsibilities involved in the different stages within the supply chain and to avoid the introduction of substandard and falsified products into the market. The relevant sections should be considered as particular roles that entities play in the storage and distribution of medical products.

1.4 This guideline is intended to be applicable to all entities involved in any aspect of the storage and distribution of medical products, from the premises of the manufacturer of the medical product to his or her agent, or the person dispensing or providing medical products directly to a patient. This includes all entities involved in different stages of the supply chain of medical products; manufacturers and wholesalers, as well as brokers, suppliers, distributors, logistics providers, traders, transport companies and forwarding agents and their employees.

1.5 The relevant sections of this guideline should also be considered for implementation by, amongst others, governments, regulatory bodies, international procurement organizations, donor agencies and certifying bodies, as well as all health-care workers.

1.6 This guideline can be used as a tool in the prevention of distribution of substandard and falsified products. It should, however, be noted that these are general guidelines that may be adapted to suit the prevailing situations and conditions in individual countries. National or regional guidelines may be developed to meet specific needs and situations in a particular region or country.

1.7 To maintain the quality of medical products, every party that is active in the supply chain has to comply with the applicable legislation and regulations. Every activity in the storage and distribution of medical products should be carried out according to the principles of good manufacturing practices

(GMP) (*1*) or applicable standard such as ISO 13485 for medical devices (*2*); good storage practices (GSP) (*3*); and good distribution practices (GDP) (*4*), as applicable.

1.8 This guideline does not deal with dispensing to patients, as this is addressed in the *Joint FIP/WHO* (International Pharmaceutical Federation/World Health Organization) *guidelines on good pharmacy practice* (GPP) (*5*).

1.9 This guideline should also be read in conjunction with other WHO guidelines, for example those listed at the end of the document under References and Further reading.

2. Scope

2.1 This document lays down guidelines for the storage and distribution of medical products. It is closely linked to other existing guidelines recommended by the WHO Expert Committee on Specifications for Pharmaceutical Preparations, for example those listed at the end of the document under References and Further reading.

2.2 Depending on the national and regional legislation, these guidelines may apply equally to pharmaceutical products for human and veterinary use, and other medical products, where applicable.

2.3 The document does not specifically cover GMP aspects of finished products in bulk, distribution of labels, or packaging, as these aspects are considered to be covered by other guidelines. The principles for the distribution of starting materials (active pharmaceutical ingredients [APIs] and excipients) are also not covered here. These are laid down in the WHO document *Good trade and distribution practices for pharmaceutical starting materials* (*6*).

3. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts and documents.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when used in the production of a drug, becomes an active ingredient of that drug. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

auditing. An independent and objective activity designed to add value and improve an organization's operations by helping it to accomplish its objectives, using a systematic, disciplined approach to evaluate and improve the effectiveness of risk management, control and governance processes.

batch. A defined quantity of pharmaceutical products processed in a single process or series of processes, so that it is expected to be homogeneous.

batch number. A distinctive combination of numbers and/or letters that uniquely identifies a batch, for example, on the labels, its batch records and corresponding certificates of analysis.

broker. A person or organization that arranges transactions in relation to the sale or purchase of medical products that consist of negotiating, independently and on behalf of another legal or natural person, and that do not include physical handling.

consignment. The quantity of medical products supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include pharmaceutical products belonging to more than one batch.

container. The material employed in the packaging of a medical product. Containers include primary, secondary and transportation containers. Containers are referred to as primary if they are intended to be in direct contact with the product. Secondary containers are not intended to be in direct contact with the product.

contamination. The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material, intermediate or pharmaceutical product during handling, production, sampling, packaging or repackaging, storage or transportation.

contract. Business agreement for the supply of goods or performance of work at a specified price; this may include quality elements in the agreement, or in a separate contract.

corrective and preventative actions (CAPA). A system for implementing corrective and preventive actions resulting from an investigation of complaints, product rejections, non-conformances, recalls, deviations, audits, regulatory inspections and findings and trends from process performance and product quality monitoring.

cross-contamination. Contamination of a starting material, intermediate product or finished pharmaceutical product or medical product with another starting material or product, during production, storage and transportation.

distribution. The procuring, purchasing, holding, storing, selling, supplying, importing, exporting or movement of medical products, with the exception of dispensing or providing medical products directly to a patient or his or her agent.

excipient. A substance, other than the active ingredient, which has been appropriately evaluated for safety and is included in a drug delivery system, to aid in the processing of the drug delivery system during its manufacture; protect, support or enhance stability, bioavailability, or patient acceptability; assist in product identification; or enhance any other attribute of the overall safety and effectiveness of the drug during storage or use.

expiry date. The date given on the individual container (usually on the label) of a medical product, up to and including the date on which the product is expected to remain within specifications if stored correctly. It is established for each batch by adding the shelf-life to the date of manufacture.

falsified product. A product that has been deliberately and/or fraudulently misrepresented as to its identity, composition or source. Such deliberate/fraudulent misrepresentation refers to any substitution, adulteration or reproduction of an authorized product, or the manufacture of a product that is not an authorized product.

"Identity" shall refer to the name, labelling or packaging or to documents that support the authenticity of an authorized product. "Composition" shall refer to any ingredient or component of the product in accordance with applicable specifications authorized/recognized by the national regulatory authority (NRA). "Source" shall refer to the identification, including name and address, of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable (*7*).

first expiry/first out (FEFO). A distribution procedure that ensures that the stock with the earliest expiry date is distributed and/or used before an identical stock item with a later expiry date is distributed and/or used.

forwarding agent. A person or entity engaged in providing, either directly or indirectly, any service concerned with clearing and forwarding operations in any manner to any other person; this includes a consignment agent.

good distribution practices (GDP). That part of quality assurance that ensures that the quality of a medical product is maintained by means of adequate control of the numerous activities that occur during the trade and distribution process, as well as providing a tool to secure the distribution system from falsified, unapproved, illegally imported, stolen, substandard, adulterated and/or misbranded medical products.

good manufacturing practices (GMP). That part of quality assurance that ensures that pharmaceutical products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

good pharmacy practice (GPP). The practice of pharmacy aimed at providing and promoting the best use of medicines and other health-care services and products by patients and members of the public. It requires that the welfare of the patient is the pharmacist's prime concern at all times.

good practices (GXP). The group of good practice guides governing the preclinical, clinical, manufacture, testing, storage, distribution and post-market activities for regulated medical products, such as good laboratory practices (GLP), good clinical practices (GCP), good manufacturing practices (GMP), good pharmacy practice (GPP), good distribution practices (GDP) and other good practices.

good storage practices (GSP). That part of quality assurance that ensures that the quality of medical products is maintained by means of adequate control throughout the storage thereof.

heating, ventilation and air conditioning systems. Heating, ventilation and air conditioning, also referred to as environmental control systems.

importation. The act of bringing or causing any goods to be brought into a customs territory (national territory, excluding any free zone).

intermediate product. Partly processed product that must undergo further manufacturing steps before it becomes a bulk finished product.

labelling. The process of identifying a medical product, including the following information, as appropriate: name of the product; active ingredient(s), type and amount; batch number; expiry date; special storage conditions or handling precautions; directions for use, warnings and precautions; and names and addresses of the manufacturer and/or supplier.

manufacture. All operations of purchase of materials and products, production, packaging, labelling, quality control, release, and storage of medical products and the related controls.

marketing authorization. A legal document issued by the NRA for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy, performance (where applicable) and quality. It must set out, inter alia, the name of the product, the pharmaceutical dosage form; the quantitative formula

(including excipients) per unit dose (using International Nonproprietary Names or national generic names where they exist); the shelf-life and storage conditions; and packaging characteristics, or other details as required by the product category. It specifies the information on which authorization is based (e.g. "The product(s) must conform to all the details provided in your application and as modified in subsequent correspondence"). It also contains the product information approved for health professionals and the public, the sales category, the name and address of the holder of the authorization and the period of validity of the authorization. Once a product has been given marketing authorization, it is included on a list of authorized products – the register – and is often said to be "registered" or to "have registration". Market authorization may occasionally also be referred to as a "licence" or "product licence".

material. A general term used to denote starting materials (APIs and excipients), reagents, solvents, process aids, intermediates, packaging materials and labelling materials.

medical products. Products including, but not limited to, finished pharmaceutical products, medical devices including in vitro diagnostic medical devices, and vaccines.

packaging material. Any material, including printed material, employed in the packaging of a medical product, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary, according to whether or not they are intended to be in direct contact with the product.

pedigree. A complete record that traces the ownership of, and transactions relating to, a medical product as it is distributed through the supply chain.

pharmaceutical product. Any product intended for human use, or veterinary product intended for administration to food-producing animals, presented in its finished dosage form, which is subject to control by pharmaceutical legislation in either the exporting or the importing state and includes products for which a prescription is required; products that may be sold to patients without a prescription; biologicals; and vaccines. It does not, however, include medical devices.

product recall. A process for withdrawing or removing a medical product from the distribution chain because of defects in the product, complaints of serious adverse reactions to the product and/or concerns that the product is or may be falsified. The recall might be initiated by the manufacturer, importer, wholesaler, distributor or a responsible agency.

production. All operations involved in the preparation of a medical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

quality assurance. A wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that medical products are of the quality required for their intended use.

quality risk management. A systematic process for the assessment, control, communication and review of risks to the quality of medical products in the supply chain.

quality system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product (or services) will satisfy given requirements for quality.

quarantine. The status of medical products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

retest date. The date when a material should be re-examined to ensure that it is still suitable for use.

sampling. Operations designed to obtain a representative portion of a medical product, based on an appropriate statistical procedure, for a defined purpose, for example, acceptance of consignments or batch release.

self-inspection. An internal procedure followed to evaluate the entity's compliance with GSP and GDP, as well as GXP in all areas of activities, designed to detect any shortcomings and to recommend and implement necessary corrective actions.

shelf-life. The period of time during which a medical product, if stored correctly, is expected to comply with the specification as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

standard operating procedure (SOP). An authorized written procedure giving instructions for performing operations that are not necessarily specific to a given product but of a more general nature (e.g. equipment operation, maintenance and cleaning, validation, cleaning of premises, environmental control, sampling and inspection).

storage. The storing of medical products up to the point of use.

substandard products. "Substandard" medical products (also called "out of specification") are authorized by NRAs but fail to meet either national or international quality standards or specifications – or, in some cases, both.

supplier. A person or entity engaged in the activity of providing products and/or services.

transit. The period during which medical products are in the process of being carried, conveyed or transported across, over or through a passage or route to reach their destination.

vehicles. Trucks, vans, buses, minibuses, cars, trailers, aircraft, railway carriages, boats and other means that are used to convey medical products.

4. General principles

4.1 There should be collaboration between all entities, including governments, customs agencies, law enforcement agencies, regulatory authorities, manufacturers, distributors and entities responsible for the supply of medical products to patients, to ensure the quality and safety of medical products; to prevent the exposure of patients to substandard and falsified products; and to ensure that the integrity of the distribution chain is maintained.

4.2 The principles of GSP and GDP should be included in national legislation and guidelines for the storage and distribution of medical products in a country or region, as applicable, as a means of establishing minimum standards. The principles of GSP and GDP are applicable to:

- medical products moving forward in the distribution chain from the manufacturer;
- medical products that are moving backwards in the chain, for example, as a result of the return or recall thereof; and
- donations of medical products.

5. Quality management

5.1 Entities involved in the storage and distribution of medical products should have a comprehensively designed, documented and correctly implemented quality system that incorporates GSP, GDP, principles of quality risk management and management review.

5.2 Senior management has the ultimate responsibility to ensure that an effective quality system is established, resourced, implemented and maintained.

5.3 The quality system should ensure that:

- GSP and GDP are adopted and implemented to ensure that the quality of medical products is maintained throughout their shelf-life in the supply chain; and medical products are appropriately procured, stored, distributed and delivered (in compliance with the legislation) to the appropriate recipients (see Section 18.1);
- operations are clearly specified in written procedures;
- responsibilities are clearly specified in job descriptions;
- all risks are identified and necessary, effective controls are implemented;
- processes are in place to assure the management of outsourced activities;
- there is a procedure for self-inspection and quality audits;
- there is a system for quality risk management;
- there are systems for managing returns, complaints and recalls; and
- there are systems to manage changes, deviations and corrective and preventive actions (CAPAs).

5.4 There should be an authorized, written quality policy describing the overall intentions and requirements regarding quality. This may be reflected in a quality manual.

5.5 There should be an appropriate organizational structure. This should be presented in an authorized organizational chart. The responsibility, authority and interrelationships of personnel should be clearly indicated.

5.6 Roles and responsibilities should be clearly defined and understood by the individuals concerned, and recorded as written job descriptions.

5.7 The quality system should include appropriate procedures, processes and resources.

6. Quality risk management

6.1 There should be a system to assess, control, communicate and review risks identified at all stages in the supply chain.

6.2 The evaluation of risk should be based on scientific knowledge and experience and ultimately be linked to the protection of the patient.

6.3 Appropriate controls should be developed and implemented to address all risks. The effectiveness of the controls implemented should be evaluated at periodic intervals.

7. Management review

7.1 There should be a system for periodic management review. The review should include at least:

- senior management;
- review of the quality system and its effectiveness by using quality metrics and key performance indicators;
- identification of opportunities for continual improvement; and
- follow-up on recommendations from previous management review meetings.

7.2 Minutes and related documentation from management review meetings should be available.

8. Complaints

8.1 There should be a written procedure for the handling of complaints. In the case of a complaint about the quality of a medical product or its packaging, the original manufacturer and/or marketing authorization holder should be informed as soon as possible.

8.2 All complaints should be recorded and appropriately investigated. The root cause should be Identified, and the impact (e.g. on other batches or products) risk-assessed. Appropriate CAPAs should be taken.

8.3 Where required, the information should be shared with the NRA and a recall initiated where appropriate.

8.4 A distinction should be made between complaints about a medical product or its packaging and those relating to distribution.

8.5 The relevant information, such as the results of the investigation of the complaint, should be shared with the relevant entities.

8.6 Medical product quality problems and suspected cases of substandard or falsified products identified should be handled according to relevant authorized procedures. The information should be shared with the manufacturer and appropriate national and/or regional regulatory authorities, without delay.

9. Returned goods

9.1 Returned medical products should be handled in accordance with authorized procedures.

9.2 All returned medical products should be placed in quarantine upon receipt. The status of the goods should be clear. Precautions should be taken to prevent access and distribution until a decision has been taken with regard to their disposition. The particular storage conditions applicable to the medical products should be maintained until their disposition.

9.3 Medical products returned should be destroyed unless it is certain that their quality is satisfactory, after they have been critically assessed in accordance with a written and authorized procedure.

9.4 The nature of the medical product, any special storage conditions it requires, its condition and history and the time lapse since it was issued, should all be taken into account in this assessment. Where any doubt arises over the quality of the medical product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

9.5 When handling returned goods, the following considerations at least should be taken:

- a risk-based process should be followed when deciding on the fate of the returned goods. This should include, but not be limited to, the nature of the product, storage conditions, condition of the product history, time-lapse since distribution and the manner and condition of transport while being returned;
- the terms and conditions of the agreement between the parties; and
- examination of the returned goods, with decisions taken by suitably qualified, experienced and authorized persons.

9.6 Where products are rejected, authorized procedures should be followed, including safe transport.

9.7 Destruction of products should be done in accordance with international, national and local requirements regarding disposal of such products, and with due consideration to the protection of the environment.

9.8 Records of all returned, rejected and destroyed medical products should be kept for a defined period, in accordance with national requirements.

10. Recalls

10.1 There should be a written procedure, in compliance with national or regional requirements, to effectively and promptly recall medical products.

10.2 The effectiveness of the procedure should be checked annually and updated as necessary.

10.3 The original manufacturer and/or marketing authorization holder, or other relevant contract party, should be informed in the event of a recall.

10.4 Information on a recall should be shared with the appropriate national or regional regulatory authority.

10.5 All recalled products should be secure, segregated, transported and stored under appropriate conditions. These should be clearly labelled as recalled products. The particular storage conditions applicable to the product should be maintained where possible.

10.6 All customers and competent authorities of all countries to which a given medical product may have been distributed should be informed promptly of the recall of the product.

10.7 All records, including distribution records, should be readily accessible to the designated person(s) responsible for recalls. These records should contain sufficient information on products supplied to customers (e.g. name, address, contact detail, batch numbers, quantities and safety features – including exported products).

10.8 The progress of a recall process should be recorded and a final report issued, which includes a reconciliation between delivered and recovered quantities of medical products.

11. Self-inspection

11.1 The quality system should include self-inspections. These should be conducted to monitor the implementation, compliance with and effectiveness of SOPs, as well as compliance with regulations, GSP, GDP and other appropriate guidelines.

11.2 Self-inspections should be conducted periodically, according to an annual schedule.

11.3 The team conducting the inspection should be free from bias and individual members should have appropriate knowledge and experience.

11.4 The results of all self-inspections should be recorded. Reports should contain all observations made during the inspection and presented to the relevant personnel and management.

11.5 Necessary CAPAs should be taken and their effectiveness should be reviewed within a defined timeframe.

12. Premises

General

12.1 Premises should be suitably located, designed, constructed and maintained, to ensure appropriate operations such as receiving, storage, picking, packing and dispatch of medical products.

12.2 There should be sufficient space, lighting and ventilation to ensure required segregation, appropriate storage conditions and cleanliness.

12.3 Sufficient security should be provided and access should be controlled.

12.4 Appropriate controls and segregation should be provided for products requiring specific handling or storage conditions, such as radioactive materials, products containing hazardous substances and products to be stored under controlled temperature and relative humidity conditions.

12.5 Where possible, receiving and dispatch bays should be separate, to avoid mix-ups. Bays should protect products from weather conditions.

12.6 Activities relating to receiving and dispatch should be done in accordance with authorized procedures. Areas should be suitably equipped for the operations.

12.7 Premises should be kept clean. Cleaning equipment and cleaning agents should not become possible sources of contamination.

12.8 Premises should be protected from the entry of birds, rodents, insects and other animals. A rodent and pest control programme should be in place.

12.9 Toilets, washing, rest and canteen facilities should be separate from areas where products are handled. Food, eating, drinking and smoking should be prohibited in all areas where medical products are stored or handled.

Receiving area

12.10 Each incoming delivery should be checked against the relevant documentation, to ensure that the correct product is delivered from the correct supplier. This may include, for example, the purchase order, containers, label description, batch number, expiry date, product and quantity.

12.11 The consignment should be examined for uniformity of the containers and, if necessary, should be subdivided according to the supplier's batch number should the delivery comprise more than one batch. Each batch should be dealt with separately.

12.12 Each consignment should be carefully checked for possible contamination, tampering and damage. A representative number of containers in a consignment should be sampled and checked according to a written procedure. Any suspect containers or, if necessary, the entire delivery, should be quarantined for further investigation.

12.13 Receiving areas should be of sufficient size to allow the cleaning of incoming medical products.

12.14 When required, samples of medical products should be taken by appropriately trained and qualified personnel and in strict accordance with a written sampling procedure and sampling plans. Containers from which samples have been taken should be labelled accordingly.

12.15 Following sampling, the goods should be subject to quarantine. Batch segregation should be maintained during quarantine and all subsequent storage.

12.16 Materials and products requiring transport and storage under controlled conditions of temperature and relative humidity, as applicable, should be handled as a priority. The transportation temperature data, where appropriate, should be reviewed upon receipt, to ensure that the required conditions had been maintained. Where applicable, cold-chain materials and products should be handled according to the approved conditions by the authority, or as recommended by the manufacturer, as appropriate.

12.17 Medical products should not be transferred to saleable stock until an authorized release is obtained.

12.18 Measures should be taken to ensure that rejected medical products cannot be used. They should be segregated and securely stored while awaiting destruction or return to the supplier.

Storage areas

12.19 Precautions should be taken to prevent unauthorized persons from entering storage areas.

12.20 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of medical products.

12.21 Storage areas should be appropriately designed, constructed, maintained or adapted. They should be kept clean and there should be sufficient space and lighting.

12.22 Storage areas should be maintained within acceptable and specified temperature limits. Where the labels show special storage conditions are required (e.g. temperature, relative humidity), these should be provided, controlled, monitored and recorded.

12.23 Materials and medical products should be stored off the floor, away from walls and ceilings, protected from direct sunlight and suitably spaced, to permit ventilation, cleaning and inspection. Suitable pallets should be used and kept in a good state of cleanliness and repair.

12.24 A written sanitation programme should be available, indicating the frequency of cleaning and the methods to be used to clean the premises and storage areas.

12.25 There should be appropriate procedures for the clean-up of any spillage, to ensure complete removal of any risk of contamination.

12.26 Where the status is ensured by storage in separate areas, these areas should be clearly marked and their access restricted to authorized personnel. Any system replacing physical separation and labelling or demarcation should provide equivalent security. For example, computerized systems can be used, provided that they are validated to demonstrate security of access (*8*).

12.27 Sampling should be done under controlled conditions and conducted in such a way that there is no risk of contamination or cross-contamination. Adequate cleaning procedures should be followed after sampling.

12.28 Certain materials and products, such as highly active and radioactive materials, narcotics and other hazardous, sensitive and/or dangerous materials and products, as well as substances presenting special risks

of abuse, fire or explosion (e.g. combustible liquids and solids and pressurized gases), should be stored in a dedicated area that is subject to appropriate additional safety and security measures, and in accordance with national legislation.

12.29 Materials and medical products should be handled and stored in such a manner as to prevent contamination, mix-ups and cross-contamination.

12.30 Materials and medical products should be stored in conditions that assure that their quality is maintained. Stock should be appropriately rotated. The "first expired/first out" (FEFO) principle should be followed.

12.31 Narcotic medical products should be stored in compliance with international conventions, national laws and regulations on narcotics.

12.32 Broken or damaged items should be withdrawn from usable stock and separated.

12.33 There should be a written procedure for fire control, including prevention of fire, fire detection and fire drills. Fire-detection and firefighting equipment should be available and should be serviced regularly.

Storage conditions

12.34 The storage conditions for medical products should be in compliance with their labelling and information provided by the manufacturer.

12.35 Heating, ventilation and air conditioning systems should be appropriately designed, installed, qualified and maintained, to ensure that the required storage conditions are upheld (*9*).

12.36 Mapping studies for temperature, and relative humidity where appropriate, should be done, for example in storage areas, refrigerators and freezers (*10*).

12.37 Temperature and relative humidity, as appropriate, should be controlled and monitored at regular intervals. Data should be recorded and the records should be reviewed. The equipment used for monitoring should be calibrated and be suitable for its intended use. All records pertaining to mapping and monitoring should be kept for a suitable period of time and as required by national legislation.

Note: See Appendix 1 for recommended storage conditions.

13. Stock control and rotation

13.1 Records of stock levels for all medical products in store should be maintained, in either paper or electronic format. These records should be updated after each operation (e.g. entries, issues, losses, adjustments). These records should be kept for a suitable period of time and as required by national legislation. Periodic stock reconciliation should be performed at defined intervals, by comparing the actual and recorded stock.

13.2 The root cause for stock discrepancies should be identified and appropriate CAPAs taken to prevent recurrence.

13.3 When damaged containers are received, this should be brought to the attention of the person responsible for quality. Any action taken should be documented. (These containers should not be issued unless the quality of the medical products has been shown to be unaffected.)

13.4 All stock should be checked at regular intervals, to identify those items that are close to their retest or expiry date. Appropriate action should be taken, such as removal of these items from useable stock.

14. Equipment

14.1 Equipment, including computerized systems, should be suitable for its intended use. All equipment should be appropriately designed, located, installed, qualified and maintained.

14.2 Computerized systems should be capable of achieving the desired output and results.

14.3 Where electronic commerce (e-commerce) is used, i.e. electronic means for any of the steps, defined procedures and adequate systems should be in place to ensure traceability and confidence in the supply chain and products concerned.

14.4 Electronic transactions (including those conducted via the Internet) relating to the distribution of medical products should be performed only by authorized persons, according to defined and authorized access and privileges.

14.5 Where GXP systems are used, these should meet the requirements of WHO or other appropriate guidelines on computerized systems (*8*, *11*).

15. Qualification and validation

15.1 The scope and extent of qualification, and validation where appropriate, should be determined using documented risk management principles.

15.2 Premises, utilities, equipment and instruments, processes and procedures should be considered.

15.3 Qualification and validation should be done following procedures and protocols. The results and outcome of the qualification and validation should be recorded in reports. Deviations should be investigated and the completion of the qualification and validation should be concluded and approved.

16. Personnel

16.1 There should be an adequate number of personnel.

16.2 Personnel should have appropriate educational qualification, experience and training relative to the activities undertaken.

16.3 A designated person within the organization, with appropriate qualification and training, should have the defined authority and responsibility for ensuring that a quality management system is implemented and maintained. This person should preferably be independent from the person responsible for operations and should ensure compliance with GSP and GDP.

16.4. Personnel should have the authority and resources needed to carry out their duties and to follow the quality systems, as well as to identify and correct deviations from the established procedures.

16.5 There should be arrangements in place to ensure that management and personnel are not subjected to commercial, political, financial or other pressures or conflict of interest that may have an adverse effect on the quality of service provided or on the integrity of medical products.

16.6 Safety procedures should be in place relating to all relevant personnel and property, environmental protection and product integrity.

16.7 Personnel should receive initial and continued training in accordance with a written training programme. The training should cover the requirements of GSP and GDP (as applicable), as well as on-the-job training. Other topics should be included, such as product security, product identification and the detection of falsified products.

16.8 Personnel dealing with hazardous products (such as highly active materials, radioactive materials, narcotics and other hazardous, environmentally sensitive and/or dangerous pharmaceutical products, as well as products presenting special risks of abuse, fire or explosion) should be given specific training.

16.9 Personnel should be trained in, and observe high levels of, personal hygiene and sanitation.

16.10 Records of all training, attendance and assessments should be kept.

16.11 Personnel handling products should wear garments suitable for the activities that they perform. Personnel dealing with hazardous pharmaceutical products, including products containing materials that are highly active, toxic, infectious or sensitizing, should be provided with protective garments as necessary.

16.12 Appropriate procedures relating to personnel hygiene, relevant to the activities to be carried out, should be established and observed. Such procedures should cover health, hygiene and the clothing of personnel.

16.13 Procedures and conditions of employment for employees, including contract and temporary staff, and other personnel having access to medical products, must be designed and implemented to assist in minimizing the possibility of such products coming into the possession of unauthorized persons or entities.

16.14 Codes of practice and procedures should be in place to prevent and address situations where persons involved in the storage and distribution of medical products are suspected of, or found to be implicated in, any activities relating to the misappropriation, tampering, diversion or falsification of any product.

17. Documentation

17.1 Documentation includes all procedures, records and data, whether in paper or electronic form. Documents should be appropriately designed, completed, reviewed, authorized, distributed and kept as required. Documents should be readily available.

17.2 Written procedures should be followed for the preparation, review, approval, use of and control of all documents relating to the policies and activities for the process of storage and distribution of medical products.

17.3 Documents should be laid out in an orderly fashion and be easy to complete, review and check. The title, scope, objective and purpose of each document should be clear.

17.4 All documents should be completed, signed and dated as required by authorized person(s) and should not be changed without the necessary authorization.

17.5 Documentation should be prepared and maintained in accordance with the national legislation and principles of good documentation practices (*11*).

17.6 Records should be accurate, legible, traceable, attributable and unambiguous. Electronic data should be backed-up in accordance with written procedures. Records should be maintained for the back-up and restoration of data.

17.7 Procedures for the identification, collection, indexing, retrieval, storage, maintenance, disposal of and access to all applicable documentation should be followed.

17.8 Documents should be reviewed regularly and kept up-to-date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version.

17.9 All records should be stored and retained using facilities that prevent unauthorized access, modification, damage, deterioration and/or loss of documentation during the entire life-cycle of the record. Records must be readily retrievable.

17.10 Comprehensive records should be maintained for all receipts, storage, issues and distribution. The records should include, for example:

- date (e.g. receipt or dispatch, as appropriate);
- name and description of the product;
- quantity received, or supplied;
- name and address of the supplier and customer;
- batch number(s);
- expiry date;
- suitability of the supplier;
- qualification of suppliers; and
- customer qualification.

17.11 All containers should be clearly labelled with at least the name of the medical product, batch number, expiry date or retest date, and the specified storage conditions.

18. Activities and operations

18.1 All activities and operations should be conducted in accordance with national legislation, GSP, GDP and associated guidelines.

18.2 Storage and distribution of medical products should be done by persons authorized to do so, in accordance with national legislation.

18.3 Activities and operations should be performed in accordance with documented procedures.

18.4 Automated storage and retrieval systems and operations should comply with current GSP, GDP and GXP guidelines, as well as the recommendations in this guideline.

Receipt

18.5 Medical products should be procured from appropriately authorized suppliers.

18.6 Deliveries should be examined for damage, seal intactness, signs of tampering, labelling, completeness of order and other related aspects (e.g. availability of a certificate of analysis, where applicable), at the time of receiving.

18.7 Containers and consignments that do not meet acceptance criteria at the time of receipt should be labelled, kept separate and investigated. This includes suspected falsified products.

Storage

18.8 Medical products requiring specific storage conditions, or controlled access (e.g. narcotics), should be processed without delay and stored in accordance with their requirements.

18.9 Appropriate controls should be implemented to prevent contamination and/or mix-ups during storage.

18.10 Controls and procedures should be in place to prevent and handle spillage and breakage.

Repackaging and relabelling

18.11 Repackaging and relabelling of materials and products are not recommended. Where repackaging and relabelling occur, these activities should only be performed by entities appropriately authorized to do so and in compliance with the applicable national, regional and international requirements, and in accordance with GMP.

18.12 Procedures should be in place for the controlled disposal of original packaging, to prevent re-use thereof.

Distribution and transport

18.13 Medical products should be transported in accordance with the conditions stated on the labels and described by the manufacturer. The risk to the quality of the medical product during transport and distribution should be eliminated or minimized to an acceptable level.

18.14 Product, batch and container identity should be maintained at all times.

18.15 All labels should remain legible.

18.16 Distribution records should be sufficiently detailed to allow for a recall when required.

18.17 Drivers of vehicles should be identified and present appropriate documentation to demonstrate that they are authorized to transport medical products.

18.18 Vehicles should be suitable for their purpose, with sufficient space and appropriately equipped to protect medical products.

18.19 The design and use of vehicles and equipment must aim to minimize the risk of errors and permit effective cleaning and/or maintenance, to avoid contamination, build-up of dust or dirt and/or any adverse effect on the quality of the products.

18.20 Where feasible, consideration should be given to adding technology, such as global positioning system (GPS) electronic tracking devices and engine-kill buttons to vehicles, which would enhance the security and traceability of vehicles with products.

18.21 Where possible, dedicated vehicles and equipment should be used for medical products. Where non-dedicated vehicles and equipment are used, procedures should be in place to ensure that the quality of the

products will not be compromised. Defective vehicles and equipment should not be used. These should either be labelled as such or removed from service.

18.22 There should be procedures in place for the operation and maintenance of all vehicles and equipment.

18.23 Equipment and materials used for the cleaning of vehicles should not become a source of contamination or have an adverse effect on product quality.

18.24 Vehicles used for transportation of medical products should be qualified, where applicable, to demonstrate their capability to maintain the required transport conditions. There should be a maintenance programme for the cooling/heating system.

18.25. Appropriate environmental conditions should be maintained, monitored and recorded. All monitoring records should be kept for a defined period of time, as required by national legislation. Records of monitoring data should be made available for inspection by the regulatory or other oversight body.

18.26 Instruments used for monitoring conditions, for example, temperature and humidity, within vehicles and containers should be calibrated at regular intervals.

18.26 Rejected, recalled and returned products, as well as those suspected as being falsified, should be securely packaged, clearly labelled and accompanied by the appropriate supporting documentation.

18.27 Measures should be in place to prevent unauthorized persons from entering and/or tampering with vehicles and/or equipment, as well as to prevent the theft or misappropriation thereof.

18.28 Shipment containers should have no adverse effect on the quality of the medical products and should offer adequate protection to materials and these products. Containers should be labelled indicating, for example, handling and storage conditions, precautions, contents and source, and safety symbols, as appropriate.

18.29 Special care should be taken when using dry ice and liquid nitrogen in shipment containers, owing to safety issues and possible adverse effects on the quality of medical products.

18.30 Written procedures should be available for the handling of damaged and/or broken shipment containers. Particular attention should be paid to those containing potentially toxic and hazardous products.

Dispatch

18.31 There should be documented, detailed procedures for the dispatch of products.

18.32 Medical products should only be sold and/or distributed to persons or entities that are authorized to acquire such products in accordance with the applicable national legislation and marketing authorization. Written proof of such authorization, or an import permit or equivalent where there is no marketing authorization, must be obtained prior to the distribution of products to such persons or entities.

18.33 Dispatch and transportation should be undertaken only after the receipt of a valid order, which should be documented.

18.34 Records for the dispatch of products should be prepared and should include information such as, but not limited to:

- date of dispatch;
- complete business name and address (no acronyms), type of entity responsible for the transportation, telephone number, names of contact persons;
- status of the addressee (e.g. retail pharmacy, hospital or community clinic);
- a description of the products, including, for example, name, dosage form and strength (if applicable);
- quantity of the products, i.e. number of containers and quantity per container (if applicable);
- applicable transport and storage conditions;
- a unique number to allow identification of the delivery order; and
- assigned batch number and expiry date (where not possible at dispatch, this information should at least be kept at receipt, to facilitate traceability).

18.35 Records of dispatch should contain sufficient information to enable traceability of the product. Such records should facilitate the recall of a batch of a product, if necessary, as well as the investigation of falsified

or potentially falsified products. In addition, the assigned batch number and expiry date of products should be recorded at the point of receipt, to facilitate traceability.

18.36 Vehicles and containers should be loaded carefully and systematically on a last-in/first-out (LIFO) basis, to save time when unloading, to prevent physical damage and to reduce security risks. Extra care should be taken during loading and unloading of cartons, to avoid damage.

18.37 Medical products should not be supplied or received after their expiry date, or so close to the expiry date that this date is likely to be reached before the products are used by the consumer (*12*).

18.38 Medical products and shipment containers should be secured in order to prevent or to provide evidence of unauthorized access. Vehicles and operators should be provided with additional security where necessary, to prevent theft and other misappropriation of products during transportation.

18.39 Medical products should be stored and transported in accordance with procedures such that:

- the identity of the product is not lost;
- the product does not contaminate and is not contaminated by other products;
- adequate precautions are taken against spillage, breakage, misappropriation and theft; and
- appropriate environmental conditions are maintained, for example, using cold-chain for thermolabile products.

18.40 Written procedures should be in place for investigating and dealing with any failure to comply with storage requirements, for example, temperature deviations. If a deviation has been noticed during transportation, by the person or entity responsible for transportation, this should be reported to the supplier, distributor and recipient. In cases where the recipient notices the deviation, it should be reported to the distributor.

18.41 Transportation of products containing hazardous substances or narcotics and other dependence-producing substances, should be transported in safe, suitably designed, secured containers and vehicles. In addition, the requirements of applicable international agreements and national legislation should be met.

18.42 Spillages should be cleaned up as soon as possible, in order to prevent possible contamination, cross-contamination and hazards. Written procedures should be in place for the handling of such occurrences.

18.43 Damage to containers and any other event or problem that occurs during transit must be recorded and reported to the relevant department, entity or authority and investigated.

18.44 Products in transit must be accompanied by the appropriate documentation.

19. Outsourced activities

19.1 Any activity relating to the storage and distribution of a medical product that is delegated to another person or entity should be performed by the appropriately authorized parties, in accordance with national legislation and the terms of a written contract.

19.2 There should be a written contract between the entities. The contract should define the responsibilities of each entity (contract giver and contract acceptor) and cover at least the following:

- compliance with this guideline and the principles of GSP and GDP;
- the responsibilities of all entities for measures to avoid the entry of substandard and falsified products into the distribution chain;
- training of personnel;
- conditions of subcontracting subject to the written approval of the contract giver; and
- periodic audits.

19.3 The contract giver should assess the contract acceptor before entering into the contract, e.g. through on-site audits, documentation and licensing status review.

19.4 The contract giver should provide to the contract acceptor all relevant information relating to the material and medical products.

19.5 The contract acceptor should have adequate resources (e.g. premises, equipment, personnel, knowledge, experience and vehicles, as appropriate) to carry out the work.

19.6 The contract acceptor should refrain from performing any activity that may adversely affect the materials or products handled.

20. Substandard and falsified products

20.1 The quality system should include procedures to assist in identifying and handling medical products that are suspected to be substandard and/or falsified.

20.2 Where such medical products are identified, the holder of the marketing authorization, the manufacturer and the appropriate national, regional and international regulatory bodies (as appropriate), as well as other relevant competent authorities, should be informed.

20.3 Such products should be stored in a secure, segregated area and clearly identified to prevent further distribution or sale. Access should be controlled.

20.4 Records should be maintained reflecting the investigations and action taken, such as disposal of the product. Falsified products should not re-enter the market.

21. Inspection of storage and distribution facilities

21.1 Storage and distribution facilities should be inspected by inspectors authorized by national legislation. This should be done at determined, periodic intervals.

21.2 Inspectors should have appropriate educational qualifications, knowledge and experience (*13*).

21.3 An inspection should normally be conducted by a team of inspectors.

21.4 Inspectors should assess compliance with national legislation, GSP, GDP and related guidelines (GXP), as appropriate.

21.5 Inspections should cover the premises, equipment, personnel, activities, quality system, qualification and validation and other related aspects, as contained in this guideline.

21.6 An inspection report should be prepared and provided to the inspected entity within a defined period of time from the last day of the inspection. Observations may be categorized based on risk assessment.

21.7 CAPA for observations listed as non-compliances in the inspection report, with the national legislation and guidelines, should be submitted for review by the inspectors within the defined period, as stated by the inspectors.

21.8 Inspections should be closed with a conclusion after the review of the CAPAs.

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Appendix 1

Recommended storage conditions

Note: Appropriate conditions should be provided for medical products during storage and distribution. Conditions should be maintained as stated on their labels (or as described by the manufacturers as applicable) during storage and distribution. Statements such as "store at ambient conditions" should be avoided. Where possible, actual limits should be specified by the manufacturers, such as "store below 25 °C". See Table A7.1 below.

Table A7.1
Recommended limits for descriptive storage conditions[a]

Label description	Recommended limits
Store at controlled room temperature	15 to 25 °C
Store in a cold or cool place	8 to 15 °C
Store in a refrigerator	5 ± 3 °C
Store in a freezer	–20 ± 5 °C
Store in deep freezer	–70 ± 10 °C
Store in a dry place	No more than 60% relative humidity
Protect from moisture	No more than 60% relative humidity
Store under ambient conditions	Store in well-ventilated premises at temperatures of between 15 °C and 30 °C and no more than 60% relative humidity. Extraneous odours, other indications of contamination and intense light must be excluded.
Protect from light	To be maintained in the original manufacturer's light-resistant containers.
Chilled	5 ± 3 °C

[a] These limits are recommended values and are based on pharmacopoeia limits and guidelines.

Annex 8

Points to consider for setting the remaining shelf-life of medical products upon delivery

1. Introduction

Following discussions relating to establishing a document for the remaining shelf-life of medical products upon delivery, and considering the discussion between the Interagency Pharmaceutical Coordination group (IPC) representatives, it was decided to initiate a project to establish a document on remaining shelf-life for procurement and supply of medical products.

The concept and project to establish such a document was also discussed during the meeting of the Fifty-third Expert Committee on Specifications for Pharmaceutical Products (ECSPP) in October 2018. It was noted that some guidance documents were available from different procurement agencies. It was agreed that the World Health Organization (WHO) would initiate the discussion and preparation of a document, while following the WHO process for the establishment of such a paper.

Information and policy on remaining shelf-life was collected from different agencies and interested parties and a first draft document was prepared after an informal discussion meeting in Geneva, Switzerland, in January 2019.

It was then agreed that the document should not cover only finished pharmaceutical products but should be extended to also cover other products, including, but not limited to, medical devices, vaccines and in vitro diagnostics (IVD) products. (These products are collectively referred to as "medical products" hereafter.)

A draft document was prepared and circulated to IPC members, as well as other interested parties, inviting comments. The comments received were reviewed during an informal discussion meeting in June 2019 and the draft document was updated.

The aims of this document are:

- to facilitate the national authorization of importation of medical products where applicable;
- to promote and support the efficient processing of medical products in the supply chain at all levels and thus prevent wastage because of delays;
- to assist in ensuring that there is sufficient stock of medical products, with acceptable remaining shelf life, in-country;
- to prevent dumping of medical products;
- to ensure that barriers to access and supply of medical products are addressed;
- to prevent out-of-stock situations;
- to prevent receipt of donations of medical products that are not in accordance with this guideline; and

- to prevent having expired stock of medical products.

The document is intended to provide guidance on setting the remaining shelf-life of medical products upon delivery and should be considered by all stakeholders in the supply chain of medical products. It is also recommended that the recommendations herein should be considered for inclusion in the national policy of countries.

2. Scope

The principles contained in this document should be applied to medical products in the supply chain. This includes donated products (*1*).

This document focuses on remaining shelf-life and does not address details contained in other guidelines, guides and agreements between different parties in the supply chain.

As "kits" are made up of different products, and owing to certain specifics related to the shelf-life of kits, these are not included in the scope of this guideline. The principles contained in this guideline may, however, be used in considering the remaining shelf-life of items in a kit, as the expiry date of the kit can be short because of a specific product in the kit.

All stakeholders, including national regulatory authorities, manufacturers, suppliers, donors and recipients, should consider the recommendations on remaining shelf-life contained in this document.

3. Glossary

The definitions given below are taken from existing WHO guidelines, where available, or alternatively from other recognized guidelines.

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

consignment (or delivery). The quantity of a medical product(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

expiry date (or expiration date). The date placed on the container or labels of a medical product designating the time during which it is expected to remain within established shelf-life specifications if stored under defined conditions, and after which it should not be used.

finished pharmaceutical product (FPP). A product that has undergone all stages of production, including packaging in its final container and labelling. An FPP may contain one or more active pharmaceutical ingredients.

install by date. The date by which an instrument, device or other has to be installed.

manufacture. All operations of purchase of materials and products, production, quality control, release, storage and distribution of medical products, and the related controls.

manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabelling of medical products.

marketing authorization (product licence, registration certificate). A legal document issued by the competent medicines regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.

manufacturer (IVD). Any natural or legal person with responsibility for design and/or manufacture of an IVD product with the intention of making it available for use, under his or her name, whether or not such an IVD product is designed and/or manufactured by that person him- or herself or on his or her behalf by (an)other person(s).

manufacturing date. The date of production of a batch is defined as the date that the first step is performed involving combination of the active ingredient with other ingredients. Where there are no other ingredients than an active ingredient, the date of the start of the processing or filling operation is considered as the date of production.

medical product. Products including, but not limited to, finished pharmaceutical products, medical devices, vaccines and IVD products.

pharmaceutical product. Any material or product intended for human or veterinary use presented in its finished dosage form, or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

production. All operations involved in the preparation of a product, from receipt of materials, through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

remaining shelf-life. Defined as the period remaining, from the date upon delivery, to the expiry date, retest date, install by date or other use before date established by the manufacturer.

retest date. The date when a material should be re-examined to ensure that it is still suitable for use.

shelf-life. The period of time, from the date of manufacture, that a product is expected to remain within its approved product specification while handled and stored under defined conditions.

upon delivery. The date the medical product is delivered as specified, e.g. at the port, at the point in country after customs clearance, or at the end-user – and as defined in the agreement between relevant parties.

4. The need for recommendations

As there was no harmonized approach on remaining shelf-life for medical products amongst procurers, donors and recipient countries, it was agreed that it will be beneficial to have a harmonized approach when considering remaining shelf-life. This will assist national regulatory authorities (NRAs), suppliers, donors, procurers, importers and distributors to manage medical products throughout the supply chain, thus ensuring the availability of quality medical products within their remaining shelf-life reaching the end-user. The authorization of importation of medical products by NRAs sometimes delays access to medical products. A harmonized approach among countries may facilitate authorization and release of medical products in the supply chain in a timely manner.

This is not a standalone document. It should be read with other documents, guides and guidelines, including, but not limited to, WHO guidelines such as *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (*2*), *Good storage and distribution practices* (*3*), *Guidelines for medicines donations* (*1*), *Model quality assurance system for procurement agencies* (*4*), *The International Pharmacopoeia* (*5*) and guidelines of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (*6*).

5. Remaining shelf-life

Note: The manufacturing date of a medical product should be defined by the manufacturer and be provided, if requested.

5.1 Principles

Decisions on remaining shelf-life for medical products should be defined realistically, contextualized and adapted to each importer, following a thorough risk assessment taking into account the criteria on page 195. It should be defined and be based on relevant factors, including but not limited to the category and type of product; inventory level; manufacturing and transit lead time; local release lead time; storage condition; delivery chain; and resources in the recipient country or region.

There should be agreements between suppliers, purchasers and recipients covering the relevant responsibilities of each party, including remaining shelf-life or expiry date.

Products should be transported, received, stored and distributed in accordance with WHO *Good storage and distribution practices* (*3*). Special attention should be given to temperature-, light- and moisture-sensitive products.

Products supplied by the manufacturer or supplier should meet the policy of national government and the recommendations in terms of remaining shelf-life prescribed in this document.

Products should be appropriately labelled. The label should include the expiry, retest or install by date, as appropriate. Products with an "install by" date should be installed prior to the date specified by the supplier.

Products received should be scrutinized in an attempt to identify possible substandard and falsified products. It should be ensured that, for example, the expiry date is not falsified (*7*).

Where different periods for remaining shelf-life have been defined for products, recipients should ensure that the products meet the remaining shelf-life requirement for the intended destination, e.g. central warehouse, regional warehouse, testing site or user point.

National authorization for importation, where required, should be obtained based on the available information, including the expiry date of the product, to allow for calculation of the remaining shelf-life and to assist in expediting approval.

Where so justified, suppliers, recipients and national authorities may negotiate deviations from the policy for remaining shelf-life, provided that:

- where the remaining shelf-life is shorter than stipulated in the policy, it is ensured that the stock will be consumed prior to expiry; and

- the medical product reaches end-users with adequate remaining shelf-life to permit confidence on the time to consume it before expiry.

Risk assessment to ensure that the parameters listed above are met should be done, taking into account the following considerations:

- assessment of need;
- type of product: different criticality for the safety of the patient between pharmaceutical products, vaccines, medical devices and IVD products;
- expiry date: with this the remaining shelf-life at delivery time can be estimated;
- compliance with WHO guidelines on *Good storage and distribution practices* (3);
- delivery time to storage facility;
- storage conditions;
- stock rotation;
- delivery time from storage to end-user;
- frequency of stock replenishment – order frequency (based on consumption): recipients and end-users should regularly verify that medical products in stock are rotated or used within their remaining shelf-life, and adjust the quantities ordered to make sure that the medical products will be used during their remaining shelf-life;
- assessment of the real needs, to ensure that the medical products can be used within their shelf-life;
- emergencies: during an emergency situation, the remaining shelf-life policy should be well balanced to ensure that life-saving medical products will be received on time; and that the needs will be covered if there is an increased demand.;
- the logistic setup: the location of the premises, the number of means/types of transportation and the number of e.g. vehicles, and its adaptability will have an impact on the speed of the delivery and, hence, on the confidence that products will be used before their expiry date;
- the activity specificities: similarly, whether the medical products will be used by the national programme, or are managed directly by the importer, outside of a national programme, will make a difference in terms of speed of delivery to the end-user; and

- the point of delivery: national warehouses, or importer or end-user facilities will also have an impact on the speed of delivery.

5.2 Expiry date

Products, such as pharmaceutical products, should have an expiry date allocated by the manufacturer. The expiry date should be established based on the results of stability testing obtained in the relevant packaging (primary and secondary packaging, where appropriate) and required stability conditions (*2*).

5.3 Retesting

Where a manufacturer or supplier has obtained approval from an NRA for a new or extended shelf-life, this may be applied.

Products with an expiry date should not be subjected to retesting by the purchaser or recipient for the purpose of extension of shelf-life. Only in exceptional cases, such as product shortages, should a recipient consider extending the expiry date of received batches, subject to certain conditions, such as availability of scientific data, the application of risk management principles, and NRA approval. The new expiry date should be reflected on the packaging.

Products with a retest date allocated by a manufacturer, e.g. chemicals and reagents, may be retested and used if the quality parameters are met.

An illustrative example of recommended remaining shelf-life of products is given in Appendix 1.

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Appendix 1

Example of minimum remaining shelf-life of medical products

Note: The total shelf-life of a product is based on results from testing during stability (and, where relevant, sterility) studies under specified conditions. The storage and transport conditions stipulated by the manufacturer should be followed, to ensure the product quality is maintained.

Table A8.1
Example of the minimum remaining shelf-life (RSL; at the time of dispatch and upon delivery) of medical products, based on the outcome of risk assessment

Total shelf-life (TSL)	RSL at time of dispatch from manufacturer's premises	RSL at time of delivery at port of entry of country	RSL at time of delivery at end-user level
48 months < TSL ≤ 60 months	40 months	30 months	12 months
36 months < TSL ≤ 48 months	30 months	24 months	12 months
24 months < TSL ≤ 36 months	20 months	15 months	6 months
12 < TSL ≤ 24 months	9 months	7 months	3 months
TSL ≤ 12 months	Special arrangements and conditions apply		

Annex 9

World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices

Background

The report of the Fifty-third meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in 2018 (*1*) stated the following:

> *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 we adopted by the ECSPP and published in 2008 (2, 3). The Expert Committee agreed to 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 existing 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.

As agreed at the ECSPP meeting in October 2018, UNFPA and WHO have separated out different aspects of the current procedure for contraceptive devices and condoms.

All related documents were restructured and revised in the first half of 2019, then sent out for public consultation in July 2019. Comments received were reviewed by a group of specialists in October 2019, before being presented to the ECSPP. This is one of the three adopted by the Fifty-fourth ECSPP meeting to replace the previous guidance document.

1. Introduction

The United Nations, through its procurement agencies, supplies medicines and other health products to countries throughout the world, in order to improve access to a choice of products of acceptable quality, safety and efficacy.

The World Health Organization (WHO), United Nations Population Fund (UNFPA) and other key partners developed an evidence-based list of essential medicines for reproductive health (2006) (*4*), which was subsequently approved by the WHO Expert Committee on Selection and Use of Essential Medicines. From this list, and the recommendations of members of the Reproductive Health Supplies Coalition, it was agreed that WHO would include a core group of contraceptive essential medicines in the Prequalification Programme, the implementation of which began in 2006. As part of this activity, it was agreed that UNFPA would take responsibility for the prequalification of copper-bearing intrauterine devices and male latex condoms, and that the UNFPA scheme would be harmonized with that of the WHO Prequalification Programme.

This document describes the implementation of the WHO/UNFPA Prequalification Programme for contraceptive devices (male latex condoms, female condoms and intrauterine devices).

The Prequalification Programme was approved in principle and subject to confirmation following an external review for publication by the Forty-second meeting of the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in October 2007 (*2*).

The Prequalification Programme is supported by a specific UNFPA management system with detailed standard operating procedures (SOPs).

The WHO/UNFPA Prequalification Programme involves the following key activities:

- the evaluation of documents submitted in response to an invitation for expression of interest (EOI);
- the inspection of each manufacturing site per product;
- product testing;
- the review of testing and inspection reports to make a decision about the acceptability of each product and its specific manufacturing site; and
- the periodic reassessment of the prequalification status of products and manufacturing sites.

1.1 Objectives

The overall objective is to implement a scheme to prequalify manufacturers of contraceptive devices of assured quality, at specific manufacturing sites, for

procurement by United Nations agencies and other bulk procurement agencies. Specific objectives are to:

- promote the procurement of contraceptive devices from manufacturing sites that have been ascertained to have the capacity to produce good quality products;
- establish a system that promotes the procurement of good quality products that retain their effectiveness throughout their stated shelf-life and conform to the latest edition of the relevant international standard for the product;
- broaden the base of suppliers for contraceptive devices that are deemed acceptable, in principle, for procurement by United Nations agencies and other bulk procurement agencies; and
- maintain and publish the list of prequalified suppliers.

2. The Prequalification Programme for reproductive health devices

2.1 Eligibility to participate

The Prequalification Programme is intended for manufacturers who carry out all key manufacturing steps, as specified by UNFPA in the call for an EOI referred to in Section 2.2.

For male latex condoms, this includes manufacturers that undertake the processes of formulation, compounding and dipping, lubrication, and testing, as well as manufacturers using pre-vulcanized latex and who undertake at least the final assembly, testing and packaging of the finished product.

For female condoms, this includes manufacturers that undertake the processes of formulation, compounding and dipping, lubrication, and testing, and who undertake at least the formation of the sheath, testing and packaging.

For intrauterine devices, this includes manufacturers that undertake the process of moulding, assembly, packaging and control of sterilization. One or more of these processes may be carried out on a contract basis but the manufacturer retains overall responsibility for product quality.

The Prequalification Programme does not apply to agents, distributors or suppliers engaged only in testing, lubricating and primary packaging.

2.2 Application for prequalification: expression of interest

2.2.1 Calls for and submission of expressions of interest

Invitations to interested parties to submit EOIs are published at regular intervals on the UNFPA website.

The invitation is open and transparent and invites manufacturers and/or their agents, as described in Section 2.1, to submit EOIs for the products listed in the invitation. The manufacturers should submit their EOIs to the UNFPA focal point, with the relevant information requested in the invitation. Manufacturers that are applying for a requalification/reassessment should submit the EOI the year before the re-inspection is to take place (see Section 2.9). If a manufacturer has more than one site, each site must submit a separate application. The manufacturers will be given a specified period from the time of publication of the advertisement to submit their responses. The information must be submitted in English (see Section 2.10).

UNFPA will receive and record the EOI from each manufacturer and issue an acknowledgement of receipt.

WHO and UNFPA will provide further guidance on the submission of documentation for prequalification and make such guidance available on the UNFPA and WHO websites.

When submitting an EOI, the manufacturer should send the following items to the UNFPA focal point:

- a covering letter expressing interest in participating in the WHO/UNFPA Prequalification Programme and confirming that the information submitted in the summary technical documentation (STED) is complete and correct; refer to Appendix 1 for a sample covering letter;
- an STED as specified in the WHO/UNFPA technical specification for male latex condoms, female condoms or intrauterine devices for submitting product data and information; and
- 10 product samples in their primary package, as examples of products produced, for each type mentioned in the STED (if applicable).

The STED must be accompanied by copies of all current certifications/accreditations; all manufacturing licences/registrations held; a copy of the company registration; copies of certificates and relevant documentation as applicable in the country of manufacture; documentation of the principal place of incorporation (for those that are corporations); specific certification/licences required in the country for manufacturing and exporting; and other legal documents, such as trading certificates.

The documentation must be submitted in English, as described in Section 2.11. Documents that are not in English must be submitted with certified translations. The manufacturer must provide an electronic version (CD or USB key to be sent by courier or registered mail or email) of this material.

2.2.2 Assessment of documents submitted

The aim of assessment of the submitted documentation is to determine whether the manufacturer is certified to ISO 13485 (*5*) and other appropriate ISO standards; has appropriate regulatory approvals, manufacturing capacity, factory documentation and legal status; and is capable, in principle, of meeting the WHO/ UNFPA specification with respect to product quality and safety, to warrant inspection by UNFPA.

2.2.2.1 Initial screening of documentation

UNFPA will aim to screen the documentation within 30 days of the closing date for receipt of responses, to ascertain whether or not it contains all the required information.

If the submission is incomplete, the manufacturer will be informed and requested to complete the STED within a specified time period. If the STED remains incomplete, it may be rejected.

STEDs that are considered complete following the administrative screening will be retained by UNFPA for evaluation.

UNFPA will exchange letters with the manufacturer covering provisions of confidentiality; the process of assessment of submitted information; and the scheduling and procedure of the site inspection.

2.2.2.2 Assessment of the summary technical documentation

UNFPA will appoint suitably qualified and experienced experts to complete the assessment of the STED within 90 days of the closing date for receipt of responses.

The assessment of the submitted documentation will be done in accordance with SOPs established by UNFPA for that purpose. To ensure uniformity in the evaluation and timeliness of assessment activities, UNFPA will, if needed, provide training to the assessors on the procedures that are specific to UNFPA.

In making its assessment, UNFPA may take into account information submitted by the manufacturer during previous applications that may be in UNFPA's possession, including results from previous site inspections and laboratory test results on the relevant products produced by the manufacturer.

UNFPA aims to advise the manufacturers of the outcome of their assessment of the documentation within 30 days after its completion. If applications are found to be in compliance with the requirements of UNFPA, as detailed in the operational guidance for the product and on the WHO and UNFPA websites, the manufacturing site will be scheduled for inspection.

2.2.2.3 Technical experts hired by UNFPA

Profile

Document assessments and inspections are carried out by technical experts appointed by UNFPA. The technical experts are selected through an international competitive bidding process to select individuals that have documented qualifications, detailed knowledge of the process for manufacturing contraceptive devices, experience in auditing and quality management systems, and specific experience inspecting sites manufacturing contraceptive devices.

The document assessment and inspection may include one or more experts. The assessor may be responsible for subsequent inspections of the manufacturing site, depending on the contraceptive device. The experts must comply with the confidentiality and conflict-of-interest rules of UNFPA, as laid down in Sections 3 and 4 of this guidance document.

2.3 Site inspection

UNFPA will plan and coordinate inspections at the manufacturing sites to assess:

- the manufacturing facilities;
- the manufacturing process;
- the quality management systems; and
- product quality

for compliance with the requirements of the WHO/UNFPA specification and good management practice, including the international standards relevant to the product.

2.3.1 Inspection team

The inspection will be performed by a team of inspectors consisting of experts appointed by UNFPA, who will conduct the assessment on behalf of UNFPA. The inspectors must have documented qualifications, detailed knowledge of manufacturing processes, expertise in auditing and quality management systems, and specific experience in inspecting condom and intrauterine device manufacturing sites. The inspectors must comply with the confidentiality and conflict-of-interest rules of UNFPA, as detailed in Sections 3 and 4 of this guidance document. To ensure uniformity in inspection procedures, UNFPA has prepared an SOP and, if necessary, can provide training to these experts.

Where possible, UNFPA will appoint at least one inspector who is able to communicate in and read the local language. Failing this, an interpreter selected by UNFPA will be used. One member of the team will be designated by UNFPA as the "lead inspector" and will be responsible for directing the on-site inspection

activities and production of the report. The team may include observers from UNFPA. UNFPA will advise and seek the involvement of the national competent body in the on-site inspection.

UNFPA will advise the manufacturer, in advance, of the composition of the team performing the site inspection and the identity of each inspector. The manufacturer has the opportunity to express possible concerns regarding any of the inspectors, to UNFPA prior to the visit. If such concerns cannot be resolved in consultation with UNFPA, the manufacturer may object to a team member's participation in the site visit. Such an objection must be made known to UNFPA by the manufacturer within 10 days of receipt of information on the composition of the proposed team. UNFPA will consider the objection and, if it is upheld, a replacement inspector will be appointed.

In order to ensure a standardized approach, each team will perform the inspections and report on its findings to UNFPA, in accordance with the SOPs established by UNFPA for that purpose.

Information submitted in response to the invitation for EOI and the assessment report will be made available to the inspectors. All inspectors must comply with the confidentiality and conflict-of-interest rules of UNFPA, as detailed in Sections 3 and 4.

2.3.2 Scope and scheduling

Prior to the inspection, the manufacturer will be informed of the scope of the inspectors' planned activities. The key components of the inspection are described in the operational guidance of the relevant technical specifications of the product (*6*–*8*) and on the WHO and UNFPA websites. The inspection may not be limited to these components. Manufacturers must be prepared to show the inspectors all aspects of the facility, including records and data that relate to the production of the condoms and intrauterine devices.

UNFPA aims to advise the manufacturer of the date of inspection at least 30 days in advance. UNFPA and the inspectors will make efforts to accommodate reasonable requests by the manufacturers and national regulatory authorities to change the date of inspection.

UNFPA will inform the manufacturer that the inspectors may request copies of specific documents for review during inspection and may request permission to take photographs during the inspection, subject always to considerations of confidential information as referred to in Section 3 of this document.

2.3.3 Transparency

The inspection team is paid by UNFPA to inspect the facilities and the members are reimbursed by UNFPA for their hotel and transport expenses.

The manufacturer will not pay for hotel accommodation or make any payments for or to the inspectors and/or UNFPA staff. The manufacturer may be requested to assist in making reservations at an appropriate hotel and arrangements for local transportation between the hotel and manufacturing facilities.

The members of the inspection team cannot accept any gifts from the companies they visit. UNFPA requires that manufacturers do not make any offers of gifts of whatever value to the inspectors and/or UNFPA staff.

By participating in the Prequalification Programme, the manufacturer agrees to allow full access to:

- any of the facilities that are in any way involved in the production, packaging and storage of the product(s) concerned; and
- all documentation related to that production.

If such access is not provided, the inspection will not be completed, and the manufacturing site and specific products cannot be prequalified.

Any evidence of fraud or serious omissions by the manufacturer in the initial assessment procedure or the inspection will lead to termination of the site inspection.

2.4 Product testing

Products will be sampled for independent testing according to the sampling requirements for prequalification testing specified in the WHO/UNFPA technical specification: *WHO/United Nations Population Fund technical specifications for male latex condoms* (6); *Female condom: generic specification, prequalification and guidelines for procurement* (*7*); or the *TCu380A intrauterine contraceptive device: WHO/UNFPA technical specification and prequalification guidance* (*8*).

Products will be sampled for independent testing before or after the inspection, under the supervision of, or by, an independent sampler appointed by UNFPA or by the inspectors at an appropriate point during the site inspection. As a component of their prequalification application, manufacturers shall submit a copy of their production plan for the coming year, to enable UNFPA to communicate the number of samples from each production lot. The manufacturers should retain samples for prequalification testing and/or schedule the inspection during a time when sample lots will be available for sampling. Sampling and testing will be conducted in accordance with the requirements detailed in the WHO/UNFPA technical specifications (*6*–*8*). All product testing will be undertaken by independent test laboratories selected by UNFPA, of defined and documented competence and experience, as demonstrated by accreditation to the current ISO 17025 standard (*9*) with testing of contraceptive product within the scope of its accreditation. The sample will be packed and sealed by the inspector or the independent sampler,

as appropriate. The inspectors may take the sample with them or arrange for the manufacturer to have the sealed box sent to the selected laboratory by courier, at UNFPA's expense.

The manufacturer will be provided with a copy of this test report.

2.5 Reporting and decision to prequalify

At the conclusion of the inspection, the inspectors will prepare a brief written summary report outlining the key findings and observations discussed with the manufacturer during the site inspection. A copy of this report will be provided to the manufacturer.

Manufacturers should not submit corrective actions to UNFPA in response to this summary report but only in response to the official inspection report that is issued. The official inspection report prepared by the inspection team will be issued to the manufacturer by UNFPA 4–6 weeks following the inspection.

The report will indicate one of the following recommendations:

- prequalify the product manufactured at a specific site without conditions. This will only be the case when there is no evidence that corrective action is required;
- require the manufacturer, where deemed necessary, to undertake specified corrective and preventive action(s) (CAPA(s));
- determine that the product and manufacturing site is ineligible for prequalification (without any requirement for corrective action being offered). This will not, however, preclude the manufacturer from resubmitting an application in response to future invitations for EOIs.

If any additional information is required, or corrective action has to be taken by the manufacturer(s), UNFPA will postpone its decision on the acceptability of the site(s) involved until such information has been evaluated, or the corrective action has been taken and found satisfactory in accordance with the time frame and recommendations made by the inspectors.

The inspection report may contain nonconformities and observations. The findings of the inspection may include non-mandatory observations aimed at highlighting potential for improved manufacturing and quality management practices. Nonconformities are classified as major or minor. A manufacturer that receives a major nonconformity cannot be prequalified and, if already prequalified, its status may be suspended. A major nonconformity will require submission of corrective and preventative actions and a possible re-inspection. Minor nonconformities require corrective and preventative action to be submitted

to UNFPA by the manufacturer in the stated period, in order to achieve or maintain prequalification. Observations made by the inspectors are intended to highlight opportunities to improve quality management practices. It is strongly recommended that manufacturers consider acting upon any observations made, but prequalification is not dependent upon this.

Where UNFPA recommends corrective action, the manufacturer must advise UNFPA within an agreed period of time that corrective action has been completed and provide the relevant evidence, if required. The recommendation for corrective action may include further independent product testing or re-inspection. After review of the evidence, UNFPA will decide whether or not to schedule a further inspection.

CAPA submissions should be submitted to UNFPA electronically, in response to the official inspection report. Evidence of action shall be provided. Evidence of actions taken should be supplied to UNFPA in the form of SOPs, pictures or other appropriate formats. The files submitted shall be organized and clearly labelled. Each manufacturer will normally be permitted two rounds of CAPA reviews. The first submission of corrective and preventive actions shall be in possession of UNFPA within 90 days of receipt of the official inspection report, unless otherwise agreed with UNFPA. If a manufacturer has not successfully addressed all nonconformities raised during the inspection following the second CAPA review, the manufacturer may be asked to submit a fresh EOI for prequalification. The EOI should only be submitted when the manufacturer demonstrates compliance with the requirements of the Prequalification Programme. Any exceptions to this will be evaluated on a case-by-case basis.

If a further inspection is deemed necessary, the inspection process and assessment will be implemented in accordance with the procedure detailed in Sections 2.3, 2.4 and 2.5 of this document. Any re-inspection may be at the expense of the manufacturer.

If evidence supporting mandatory improvement actions or additional information is required, or other corrective actions have to be taken by the manufacturer, UNFPA will postpone its final decision until such information has been evaluated or the corrective action has been taken and found satisfactory.

If the manufacturer has not submitted a satisfactory response within 12 months of submission of the report from UNFPA, the application will lapse and the manufacturer will need to reapply in response to a future invitation for an EOI.

UNFPA reserves the right to terminate the procedure of quality assessment of a specific product if:

- the manufacturer is not able to provide the required information; and/or

- the manufacturer is unable to implement the corrective actions in a specified time period; and/or
- the information supplied is inadequate to complete the quality assessment process.

Each manufacturer will receive a letter from UNFPA informing them of the outcome of the quality assessment process. UNFPA aims to inform the manufacturer of the results of the process within 30 days of receipt of all final reports. Manufacturers will verify the final report that is produced for accuracy. In the event of any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA detailing the handling of appeals and complaints will be followed, to discuss and resolve the issue. The ownership of any of the reports produced during the course of, or as the result of, the assessment of documentation, product testing and inspection of the manufacturing site, lies with UNFPA. Thus, UNFPA shall be entitled to use and publish such reports and/or a summary of a report, subject always, however, to the protection of any commercially confidential information of the manufacturer(s).

Confidential information may include:

- confidential intellectual property, "know-how" and trade secrets (including, e.g. formulas, processes or information contained or embodied in a product, unpublished aspects of trademarks and/or patents); and
- commercial confidences (e.g. structures and development plans of a company).

Provisions of confidentiality will be contained in the exchange of letters, to be concluded before the assessment of the STED or inspection of the manufacturing site(s), between UNFPA and each manufacturer.

Notwithstanding the foregoing, UNFPA and WHO may share a summary and/or the full evaluation and inspection reports with the relevant authorities of any interested Member State of United Nations and/or WHO. Confidential information submitted by the manufacturer that is marked "confidential" will not be included in the full evaluation and inspection reports without the permission of the manufacturer.

2.6 Listing of prequalified contraceptive devices and manufacturing sites

Once UNFPA is satisfied that the quality assessment process is complete and where the STED and corresponding manufacturing site have been found to meet the prequalification requirements, the product produced at the specified

manufacturing site(s) will be listed on the WHO and UNFPA prequalification websites.

The list of prequalified contraceptive devices and corresponding manufacturing sites will be compiled and updated in accordance with an SOP established by UNFPA for this purpose.

2.7 Maintenance of prequalification status

Once the product and the corresponding manufacturing sites are included in the list of prequalified manufacturers, the manufacturer is required to advise UNFPA, within 30 days, of any matter that affects the information on which the approval was based. This includes but is not limited to:

- change of premises;
- change in production and testing equipment;
- change in senior management;
- product recalls;
- change in certifications or licences held by the manufacturer;
- reports of adverse events;
- change in device design;
- change in suppliers' key raw materials and components not previously listed in the STED;
- change in specification of raw materials, components and primary packaging materials;
- change in packaging;
- change in formulation;
- change in process and/or technology;
- change in production capacity; and
- new information about shelf-life.

It is the manufacturer's responsibility to provide UNFPA with the appropriate documentation (referring to relevant parts of the STED) to prove that the implementation of any intended variation will not have an adverse impact on the quality of the product that has been prequalified. UNFPA will undertake an evaluation of variations according to established UNFPA guidelines and SOPs, and communicate the outcome to the manufacturer. Compliance with the requirement to report changes will be checked during the reassessment inspection and processes carried out by UNFPA.

2.8 Periodic monitoring of the quality of products produced by prequalified manufacturing sites

At periodic intervals, UNFPA may, through an independent sampler, take random samples of contraceptive devices produced by listed manufacturers. Samples will be taken from intact lots stored in the manufacturer's or distributor's warehouse. The sample size will be in accordance with the current international standard for the contraceptive devices. The range of tests to be conducted will be in accordance with lot-by-lot pre-shipment compliance testing, as detailed in the WHO/UNFPA technical specification for the product.

All product testing will be undertaken by an independent test laboratory, selected by UNFPA, of defined and documented accreditation to the current ISO 17025 (*9*) international standard. In the event of failure to meet the established requirements for testing, UNFPA will investigate the problem and communicate this to the manufacturer.

UNFPA may request reports from consumer or regulatory authorities, or from other procurement agencies relating to the quality and supply of the prequalified contraceptive device.

Complaints communicated to UNFPA concerning contraceptive devices procured through this Prequalification Programme will be investigated in accordance with an SOP established by UNFPA for that purpose. After investigation, UNFPA will provide a written report of the complaint investigations, including recommendations for action, to the /manufacturer. UNFPA will require evidence of effective action taken, where relevant.

UNFPA will make the report available to the appropriate authorities of the country where the manufacturing site is located, when necessary in the interest of public health, subject always to consideration of commercially confidential information, as referred to earlier in this document. UNFPA reserves the right to make such reports public if it considers this to be of public health importance. In addition, UNFPA reserves the right to share the full report and/or recommendations for action with WHO and relevant authorities of interested Member States of the United Nations and/or WHO. At periodic intervals, UNFPA may request a summary of the statistical analysis of product production from the manufacturer, for demonstration of continued capability to manufacture to the WHO/UNFPA technical specification. This may be accompanied by a request for selected evidence from management review, risk management, production, measurement and analysis and other records.

2.9 Reassessment of prequalified manufacturing sites – reassessment

UNFPA aims to undertake a reassessment of products manufactured at a specific site, at intervals of at least 3 years and no more than 5 years. Such reassessments

will consist of a comprehensive evaluation of documentation, site inspection and product testing, similar to the initial prequalification assessment, as determined by a risk-based assessment. Prequalified manufacturers should submit a EOI (application) for reassessment 12 months before expiry of their current prequalification status.

Reassessment may also be required in the following situations:

- if the contraceptive devices supplied by the manufacturer are considered by UNFPA or by one or more of the other United Nations agencies not to be in compliance with the agreed WHO/ UNFPA specification and requirements for pre-shipment compliance testing;
- if a complaint that is considered serious in nature has been received by UNFPA or one or more of the other United Nations agencies or organizations; and
- if there is a significant change in the manufacturing process in respect to one or more of the items listed in Section 2.7.

All relevant information, including the reassessment of submitted documentation and site inspection reports, together with monitoring information, will be considered by the designated UNFPA official, and a decision will be made to:

- maintain the contraceptive device and its manufacturing site on the list of prequalified products without need for corrective actions;
- maintain the prequalification status of the contraceptive device and its manufacturing site with a requirement for corrective actions and, where agreed to by UNFPA, further product testing and/or a site inspection; or
- suspend the prequalified status.

UNFPA aims to advise the manufacturer of the result of the reassessment and make any necessary amendments to the list of prequalified manufacturing sites and products within 30 days of receipt of the data on the basis of which the decision is made. The updated list will be published on the WHO and UNFPA prequalification websites.

UNFPA will de-list any prequalified product and manufacturing site if the submitted information is subsequently found to be incorrect or fraudulent. UNFPA will issue a notice of listing and de-listing and inform the appropriate authorities.

2.10 Language

The official language of the programme is English. All documents submitted as part of an application for prequalification will be in English. If the original of any required document is not in English, the manufacturer must submit a copy of the original plus a certified translation into English. All correspondence between UNFPA and the manufacturer should be in English. All reports issued by the assessors, inspectors and UNFPA on the assessment and inspections will be in English.

Inspections will be conducted in English, with the aid of an interpreter where necessary. It is the responsibility of the manufacturer to advise UNFPA and for UNFPA to agree whether or not an interpreter is required for the inspection.

2.11 Fees

To ensure sustainability of the Prequalification Programme, UNFPA has introduced prequalification fees to contribute to the expenses of the assessments, inspections and product testing. The fees were introduced in 2019 after several consultations with manufacturers.

2.12 Resolution of disputes

If there is any disagreement between a manufacturer and UNFPA, an SOP established by UNFPA for the handling of appeals and complaints will be followed, to discuss and resolve the issue.

3. Confidentiality undertaking

The assessors and inspectors will treat all information to which they gain access during the evaluations and inspections, or otherwise in connection with the discharge of their responsibilities in regard to the above-mentioned project, as confidential and proprietary to UNFPA and parties collaborating with UNFPA, in accordance with the terms set out below.

Assessors and inspectors will take all reasonable measures to ensure that:

- confidential information is not used for any other purpose than the evaluation/inspection activities described in this document; and
- confidential information is not disclosed or provided to any person who is not bound by similar obligations of confidentiality and non-use as contained herein.

Assessors and inspectors will not, however, be bound by any obligations of confidentiality and non-use to the extent they can clearly demonstrate that any part of the confidential information:

- was known to them prior to any disclosure by or on behalf of UNFPA (including disclosure by manufacturers);
- was in the public domain at the time of disclosure by or on behalf of UNFPA (including by manufacturers);
- has become part of the public domain through no fault of theirs; or
- has become available to them from a third party not in breach of any legal obligations of confidentiality.

4. Conflict of interest

Before undertaking the work, each assessor and inspector will also (in addition to the above-mentioned confidentiality undertaking) be required to sign a declaration of interest.

If, based on this declaration of interest, it is felt that there is no risk of a real or perceived conflict of interest (or it is felt that there is only an insignificant and/or irrelevant conflict of interest), and it is thus deemed appropriate for the evaluator or inspector in question to undertake this work, he or she will discharge his or her functions exclusively as adviser to UNFPA. In this connection, each assessor and inspector is required to confirm that the information disclosed by him or her in the declaration of interest is correct and complete, and that he or she will immediately notify UNFPA of any change in this information.

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8. TCu380A intrauterine contraceptive device: WHO/UNFPA technical specification and prequalification guidance 2016. Geneva: World Health Organization and United Nations Population Fund; 2016 (https://www.unfpa.org/sites/default/files/resource-pdf/TCu380A_IUD_WHO_UNFPATechnicalSpec_Guidance_updated2017.pdf, accessed 17 December 2019).
9. ISO 17025:2017(en). General requirements for the competence of testing and calibration laboratories (https://www.iso.org/obp/ui/#iso:std:iso-iec:17025:ed-3:v1:en, accessed 17 December 2019).

Appendix 1

Letter of application for prequalification of contraceptive devices

All product summary technical documentation (STED) submitted must be accompanied by a covering letter expressing interest in participating in the United Nations Population Fund (UNFPA) prequalification process and confirming that the information submitted in the STEFD summary is complete and correct. Below is an example of such a letter.

Letter of application

Date _____

To: United Nations Population Fund
Procurement Services Branch
Marmorvej 51
DK 2100 Copenhagen
Denmark

Sir/Madam:

Being duly authorized to represent and act on behalf of [name of manufacturer] (hereinafter referred to as the "Applicant") and having reviewed and fully understood all the information on prequalification provided, the undersigned hereby applies to be prequalified by UNFPA as a potential supplier of [indicate relevant device].

Attached to this letter are copies of original documents defining:

- the Applicant's legal status
- the summary technical documentation (STED)
- sample products [if applicable].

UNFPA and its authorized representatives are hereby authorized to conduct any enquiries or investigations to verify the statements, documents and information submitted in connection with this application and to seek clarification from our bankers and clients regarding any financial and technical aspects. This letter of application will also serve as authorization to any individual or authorized representative of any institution referred to in the supporting documentation to provide such information deemed necessary and requested by yourselves to

verify statements and information provided in this application or with regard to the resources, experience and competence of the Applicant.

The Applicant declares that all the information provided with the application is valid.

Name of Applicant [Organization] _____

Name of Responsible Officer _____

Signature _____

Position/Title _____ Date _____

Annex 10

World Health Organization/United Nations Population Fund technical specifications for male latex condoms

Background

The report of the Fifty-third meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in 2018 (*1*) stated the following:

> *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 we adopted by the ECSPP and published in 2008 (2, 3). The Expert Committee agreed to 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 existing 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.

As agreed at the ECSPP meeting in October 2018, UNFPA and WHO have separated out different aspects of the current procedure for contraceptive devices and condoms.

All related documents were restructured and revised in the first half of 2019, then sent out for public consultation in July 2019. Comments received were reviewed by a group of specialists in October 2019, before being presented to the ECSPP. This is one of the three adopted by the Fifty-fourth ECSPP meeting, to replace the previous guidance document.

1. Introduction

This annex contains the World Health Organization (WHO)/United Nations Population Fund (UNFPA) specification that is suitable for the bulk procurement of male latex condoms for use in social marketing and public-sector programmes for family planning and prevention of sexually transmitted infections.

A specification is a statement of the buyer's requirements and covers all the attributes and features of the product. Many of these requirements, particularly the design features, may be unique to the buyer and not specified in the International Organization for Standardization (ISO) standard ISO 4074. The buyer's specification must be a detailed and unambiguous statement of the buyer's requirements and describe the means by which those requirements can be measured and assessed. The specification is generally attached to the bidding documents and forms part of the supply contract.

The WHO/UNFPA specification is based on the performance requirements for male latex condoms specified in the international standard ISO 4074 Natural latex rubber male condoms – requirements and test methods. This standard specifies the essential performance requirements that latex condoms are expected to meet and the test methods that are used to assess compliance with these requirements. This standard is based on extensive research and an ongoing consultation process, involving leading experts from around the world in all aspects of condom manufacturing, testing, research and use. The WHO/UNFPA specification described here incorporates the performance requirements of ISO 4074.

The WHO/UNFPA specification has been developed by consensus and is based on available evidence, details of which are given in Appendix 1. The WHO/UNFPA specification describes the general, design, performance and packaging requirements for the product and the methods of verification. It can be used unchanged, or adapted to the specific requirements of programmes. However, it is important to understand the points listed next.

- **General requirements** specify the safety of constituent materials and other characteristics, such as shelf-life. These properties should not vary from lot to lot and therefore do not need testing on a regular basis. Retesting is required following any significant change to the formulation, manufacturing process, equipment used or packaging. The general requirements detailed in the WHO/UNFPA specification **should not be changed**. They are listed in Section 3.1 of this document.
- **Performance requirements** specify the essential performance attributes of the condoms, established in accordance with ISO 4074. These must be tested on a lot-by-lot basis, since the quality of these

attributes may vary due to the manufacturing process. Laboratory tests are carried out to assess the barrier properties of the package, the integrity of the product and its ability to resist breakage. Performance requirements detailed in the WHO/UNFPA specification **should not be changed**. The only exceptions are:

- the possibility to include or exclude bursting volume and pressure testing after oven conditioning;
- the packaging integrity requirements, where the purchaser may choose to apply more stringent testing, especially if the condoms are to be delivered by air or to high-altitude locations (refer to the alternate package seal integrity test in Appendix 2).

The performance requirements are listed in Section 3.2 of this document.

- **Design requirements** are mainly concerned with the acceptability of the product to the end-user. These can be varied within certain limits to meet specific programmatic requirements. Special boxes have been provided in the WHO/UNFPA specification for changes to such design requirements as colour, length and width. For each design requirement, there is a means of verification. These are listed in Section 3.3 of this document.
- **Packaging requirements** are detailed in the WHO/UNFPA specification. Packaging materials and package shape should not be changed unless the impact on the shelf-life of the product has been confirmed by accelerated stability studies and real-time stability studies are in progress according to clause 11 of ISO 4074:2015. If consumer packaging is required, it is important to include detailed instructions in the specification and to discuss the design requirements with the manufacturer. The packaging requirements are listed in Section 3.2 of this document.

The WHO/UNFPA specification is based on:

- the international standard ISO 4074;
- a literature review of the available evidence;
- the recommendations of the WHO/UNFPA/Joint United Nations Programme on HIV/AIDS(UNAIDS)/Family Health International (FHI360) Male Latex Condom Technical Review Committee (May 2002, August 2007 and July 2008); and
- feedback from participants attending the WHO/UNFPA workshops to introduce the male latex condom specification and procedures for prequalification and procurement.

Where appropriate, reference is made to the current edition and corrigenda of the published international standard, ISO 4074 *Natural latex rubber male condoms* – requirements and test methods.

This WHO/UNFPA specification should not be considered nor used as a standard for regulatory purposes. For regulatory purposes, the applicable standard is ISO 4074 or the relevant local standard, depending on the country.

If used in conjunction with the WHO/UNFPA Prequalification Programme, the WHO/UNFPA specification will ensure that a quality-assured product is prequalified and later purchased and distributed to the end-user.

2. Glossary

acceptance quality limit (AQL). The quality level that is the worst tolerable process average when a continuing series of lots is submitted for acceptance sampling (ISO 2859-1). *Note*: Manufacturers should be consistently achieving a process average that is better than the AQL.

bead. The thickened ring formed at the open end of the condom.

bioburden. The population of microorganisms on a raw material, component, product, packaging or equipment.

CE mark. On condom packaging, a mark certifying that the product conforms to the essential requirements of the European Commission Directive 93/42/EEC on medical devices (*4*).

colony-forming units (cfu). A unit of measure of the level of microbial contamination of a product.

compliance testing. A regime of testing to verify that a lot complies with the specification.

condom. A medical device that is intended to be worn on the penis during sexual activity, for purposes of contraception and to prevent the spread of sexually transmitted infections. Condoms are usually made from natural rubber latex but may also be made from synthetic materials, such as polyurethane.

consumer pack. A wallet or carton into which one or more foil packages are inserted for marketing purposes.

date of manufacture. The date on which the condoms were dipped.

design requirements. Characteristics of the condom that are specified according to the buyer's requirements.

expiry date. The date at which the product is no longer considered acceptable for use.

exterior shipping carton. The container into which a number of inner boxes are packed.

general requirements. The general quality characteristics of condoms that are verified before supply commences and that are not expected to vary from lot to lot.

inner box. A box used to contain a convenient number of condoms in packages or consumer packs. Inner boxes typically contain 100–200 condoms; where a gross (144 condoms) is used as the unit of purchase, inner boxes are usually specified to contain one gross.

inspection level. The degree of examination of the lot, as specified in ISO 2859-1. The higher the inspection level, the more samples will be tested and, hence, the lower the risk of faulty products reaching the end-user.

length. The length of the condom measured from the open end to the tip, excluding any reservoir.

lot. A collection of condoms of the same design, colour, shape, size and formulation. A lot must be manufactured at essentially the same time, using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing, and be packed in the same type of individual container, using the same packaging materials.

lot number or code. A unique identifying alphanumeric code assigned to a lot.

Lowry method. A method for determining the water-extractable protein levels in latex products.

national regulatory authority. A regulatory body with authority in a specific country to control the importation and distribution of medical products. *See also* **regulatory authority**.

package. The foil sachet in which the condom is sealed after manufacture.

performance requirements. The critical tests of quality that all lots must pass in order to provide adequate consumer protection.

prequalification. The steps taken by the buyer to verify a manufacturer's suitability to provide condoms of the required quality. The WHO/UNFPA Prequalification Programme includes periodic assessment of manufacturing dossiers, testing of samples and factory inspection.

pre-shipment compliance testing. A regimen of compliance tests carried out before a shipment leaves the supplier's factory.

regulatory authority. A national or international body set up to oversee the safety, efficacy and quality of medical devices, including condoms, imported and distributed within a country or region.

reservoir. A narrow portion of the condom at the closed end, designed to contain ejaculate. The reservoir is sometimes called the teat.

shelf-life. The period of time after manufacture that the product is considered acceptable for use.

social marketing. The use of commercial marketing techniques to distribute, promote and sell products and services of social importance, often at a subsidized price.

specification. A detailed statement of a product's requirements as established by the buyer. Usually, a specification is based on an established standard.

standard. A detailed statement of the minimum acceptance requirements, as established by a national or international regulatory authority.

viscosity. The resistance to flow of a fluid.

wall thickness. The thickness of the latex film.

width. The mean lay-flat width of 13 condoms measured in accordance with the relevant annex of ISO 4074 at a point 75 ± 5 mm from the closed end, rounded to the nearest 0.5 mm.

3. WHO/UNFPA specification

3.1 General requirements

Manufacturers shall include in their summary of technical documentation evidence to confirm that the condoms comply with the general requirements listed in Table A10.1. Verification of conformance to these requirements is assessed during prequalification.

General requirements cover the selection and safety of materials and the shelf-life of the product.

Table A10.1
General requirements for condoms

General requirements	Description
Lot definition	A lot is a collection of condoms of the same design, colour, shape, size and formulation. A lot must be manufactured at essentially the same time, using the same process, same specification of raw materials, common equipment, same lubricant and any other additive or dressing, and be packed in the same type of individual container, using the same packaging materials. All condoms comprising a lot will: • have an identical formulation; • have the same design, dimensions, colour, shape and surface texture; • be manufactured on the same production line; • be vulcanized under identical conditions; • be in the same packaging; • have the same lubricant; and • have the same date of expiry printed on the package. Lot sizes over 500 000 are not permitted.
Date of manufacture	The date of manufacture is generally the date that the condoms were dipped. The date of manufacture may be the date of packaging (i.e. sealing the condoms into the individual containers), as long as the storage period between dipping and packaging does not exceed 6 months and the unpackaged condoms are stored under controlled conditions as specified in Clause 11.1 of ISO 4074:2015. Storage conditions will be subject to assessment as part of the prequalification inspection.
Materials	The condoms shall be made of natural rubber latex. The condoms shall not liberate toxic or otherwise harmful substances in amounts that can be irritating, sensitizing or otherwise harmful to the user of the condom under normal conditions of use.

Table A10.1 *continued*

General requirements	Description
Biocompatibility	Biocompatibility assessments shall be conducted on the whole condom, including any lubricants and dressing materials, in accordance with ISO 10993-1. Specifically, evaluations shall be conducted for cytotoxicity according to ISO 10993-5 and for irritation and skin sensitization according to ISO 10993-10. Manufacturers should choose accredited laboratories for these tests, and the results shall be interpreted by an accredited toxicologist or other suitably qualified expert. Expert reports should be available for review. The expert review report can be a separate document or can be included in the test report. Extraction conditions shall be at a temperature of 37 ± 1 °C, according to ISO 10993-12. Many latex products that have been established as safe, including condoms and medical gloves, can exhibit a positive cytotoxic response when tested according to ISO 10993-5. While any cytotoxic effect can be of concern, it is primarily an indication of potential for in vivo toxicity and a condom cannot necessarily be determined to be unsuitable for use based solely on cytotoxicity data. Manufacturers are advised to confirm local requirements for safety testing with appropriate regulatory authorities in the countries in which the condoms are to be distributed. In accordance with ISO 10993-1, manufacturers may provide data on equivalent products. The International Agency for Research on Cancer (IARC, WHO) has classified 2-mercaptobenzothiazole (MBT) as probably carcinogenic to humans (*5*). MBT shall not be used as an accelerator in condom formulations
Water-extractable protein levels	It will be verified during prequalification that manufacturers determine the water-extractable levels of proteins in their products. The recommended levels for soluble protein, as determined by the modified Lowry method, should be less than 200 µg/g. Manufacturers should take steps not to exceed this level and should monitor production periodically, at least once a year and following any significant change to the latex formulation. The recommended interval is every 3 months.

Table A10.1 *continued*

General requirements	Description
	There is no specific standard for determining the protein levels in condoms. The methods described in ISO 12243 (*6*), EN 455-3 (*7*) or ASTM D5712 (*8*) for determining the protein levels in medical gloves can be modified for condoms.[1] Documentation recording protein levels should be available for review.
Bioburden levels	Condoms are not sterile devices, but nevertheless manufacturers should take steps to minimize the risk of contamination of the products with microorganisms. It will be verified during prequalification that manufacturers periodically determine bioburden levels. Documentation recording bioburden levels should be available for review. For prequalification, the manufacturer should be able to demonstrate that they are able to maintain bioburden levels on packed condoms below 100 cfu (colony-forming units)/condom and not exceeding 500 cfu/condom. There should be an absence of *Staphylococcus aureus* and Enterobacteriaceae, including *Escherichia coli* and *Pseudomonas aeruginosa*. For prequalification, bioburden levels should be determined periodically, e.g. at least quarterly (and following any significant change to the latex formulation), by extracting the condoms with a neutralizing medium and determining the total viable aerobic count using appropriate test methods. Further information on the rationale for the bioburden limits, methods of determining bioburden levels and general guidelines on controlling bioburden contamination during manufacture is given in ISO 4074:2015 Annex G.
N-nitrosamines	It will be verified during prequalification that manufacturers take steps to minimize the formation of *N*-nitrosamines. For prequalification purposes, the manufacturer should be able to demonstrate they are able to achieve levels below 50 ppb (parts per billion) measured as per ISO 29941 (*9*). Levels should be monitored periodically and at least once a year, and following any significant change to the latex formulation.

[1] For further information about latex allergy and protein levels, refer to the list of Further reading.

Table A10.1 *continued*

General requirements	Description
	Minimization of the formation of *N*-nitrosamines can be achieved by ensuring that condoms are adequately leached and washed; and by using minimum amounts of accelerators. It is recommended that, where possible, accelerators, such as zinc dibutyldithiocarbamate, that have a preferred safety profile (*10*),[2] are used in the formulation.
Dusting powder	A suitable dusting powder should be used to prevent the condoms from sticking together during manufacture. Acceptable powders are: • cornstarch; • magnesium or calcium carbonate; and • silica. Manufacturers may use other dusting powders, as long as they do not compromise the biocompatibility and safety of the condom. Talc or lycopodium spores shall not be used. It is recommended that manufacturers not use excess powder (maximum recommended is 50 mg per condom).
Shelf-life and stability studies	
Shelf-life	ISO 4074 describes the minimum stability requirements for condoms. These are considered the minimum requirements for placing condoms on the market. It can be assumed that condoms meeting these requirements have a minimum shelf-life of 2 years. Condoms shall comply with the performance requirements of this WHO/UNFPA specification throughout the stated shelf-life of the condom. The manufacturer shall determine the shelf-life based on the outcome of stability studies and measured from the date of manufacture. The claimed shelf-life shall be not less than 3 years and not more than 5 years.

[2] For further information about *N*-nitrosamines, refer to the list of Further reading.

Table A10.1 *continued*

General requirements	Description
	Variations Textured condoms made using the same latex formulation and processes as untextured condoms that have an established shelf-life based on real-time stability studies should be subjected to comparative accelerated stability studies extending out to 90 days and 180 days at 50 °C. Subject to satisfactory results, the specified shelf-life of the textured condoms may be assumed to be the same as for the equivalent untextured condom after 90 days, and confirmed after 180 days, without the need for a real-time stability study.
Stability studies – real time	Manufacturers **must** determine the shelf-life by real-time studies conducted at 30 +5/–2 °C (i.e. between 28 °C and 35 °C but with a target temperature of 30 °C), according to the relevant clause in ISO 4074. Pending the outcome of real-time studies, manufacturers may use accelerated ageing studies at 50 ± 2 °C to estimate a provisional shelf-life, as described in ISO 4074. The results of an accelerated ageing study, according to ISO 4074, must be available at the time of submitting an application for prequalification, and a real-time study must also be in progress.
Sampling	Condoms for stability studies shall be taken from three normal production lots. Sampling shall be done according Annex A or Annex B (preferred) of ISO 4074:2015. The sample size should be adequate for at least six separate tests for the three tests from ISO 4074.
Conditioning	Samples should be incubated in their individual sealed containers, according to the relevant annex of ISO 4074: one set for 168 ± 2 hours at 70 ± 2 °C, and another set for 90 ± 1 days at 50 ± 2 °C. At the end of the incubation periods, the condoms should be withdrawn and tested for airburst properties, freedom from holes and package seal. The incubation period at 50 ± 2 °C can be extended to 120 days or 180 days, in order to estimate a provisional shelf-life by accelerated ageing, in which case testing at 90 days is not necessary.

Table A10.1 *continued*

General requirements	Description
Testing requirement	Compliance with the requirements for bursting properties should be assessed at least annually for the full shelf-life of the product, and for freedom from holes and package integrity, as specified in the relevant clauses of ISO 4074, by the end of the testing period. All three lots of condoms shall remain in compliance with the requirements for bursting properties, freedom from holes and visible defects, including visibly open packaging seals and package integrity, as specified in the relevant clauses of ISO 4074, for the duration of the stability study. If all three lots of condoms remain in compliance with the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074 for a period of 120 days at (50 ± 2) °C, a provisional shelf life of 3 years may be assigned. If all three lots of condoms remain in compliance with the requirements for bursting properties, freedom from holes and package integrity specified in the relevant clauses of ISO 4074 for a period of 180 days at (50 ± 2) °C, a provisional shelf life of 5 years may be assigned. If at any time during the real-time studies, the manufacturer becomes aware that the shelf-life estimates made using the accelerated ageing studies are incorrect, the manufacturer must notify the procurers and regulators immediately.
Provisional shelf-life	Pending the outcome of the real-time studies, manufacturers may estimate a provisional shelf-life, using an accelerated ageing study.
Minimum stability requirements	Condoms shall comply with the minimum stability requirements defined in the relevant clause of ISO 4074. Condoms meeting these minimum stability requirements can be assumed to have a provisional shelf-life of 2 years.
Stability study report	The stability study report should indicate the time between dipping and foiling for the lots used for the study. If a manufacturer has not recorded the required information in the stability study report, then the default position will be that the manufacturer must use the dipping date as the date of manufacture.

3.2 Performance requirements

The performance requirements specified in Table A10.2 are based on the requirements of ISO 4074. These requirements cannot be altered. Verification of compliance with these requirements must be done as part of prequalification and the lot-by-lot pre-shipment compliance testing of the product. For prequalification purposes, the sampling plans specified in Annex B of ISO 4074 shall be used. Testing after oven conditioning may be required as part of prequalification, following a risk-based assessment.

Information on methods of monitoring quality is given in the condom quality assurance guidance document (*10*).

Table A10.2
Performance requirements

Performance requirements	Description
Bursting volume and pressure	
Sampling	In accordance with ISO 2859-1 General Inspection Level I (*11*). For prequalification testing, at least code letter M as specified in Annex B of ISO 4074:2015 shall be used.
Testing	In accordance with test method in the relevant annex of ISO 4074 and the relevant clause in ISO 4074.
Requirement	Minimum bursting requirements as listed below: **Acceptance quality limit (AQL) 1.5** **Volume:** • 16.0 dm^3 for condoms with mid-body widths ≥ 45.0 mm and < 50.0 mm • 18.0 dm^3 for condoms with mid-body widths ≥ 50.0 mm and < 56.0 mm • 22.0 dm^3 for condoms with mid-body widths ≥ 56.0 mm and < 65.0 mm • 28.0 dm^3 for condoms with mid-body widths ≥ 65.0 mm and < 75.0 mm **Pressure:** 1.0 kPa (for all widths) The width is defined as the mean lay-flat width of 13 condoms measured in accordance with the relevant annex of ISO 4074 at a point 75 ± 5 mm from the closed end, rounded to the nearest 0.5 mm.

Table A10.2 *continued*

Performance requirements	Description
Freedom from holes and visible defects	
Sampling	ISO 2859-1 General Inspection Level I, but at least Code Letter M (*11*). For prequalification testing, at least Code Letter N as specified in Annex B of ISO 4074:2015 shall be used.
Testing	In accordance with the relevant annex of ISO 4074.
Requirement	In accordance with the test method in the relevant annex of ISO 4074. • **Freedom from holes: AQL 0.25** • **Critical visible defects: AQL 0.4** • **Visibly open package seals: AQL 0.4** ISO 4074 describes a limited number of critical visible defects. WHO/UNFPA specifies an extended list of critical visible defects and imperfections in Section 3.2.1 of this document. It is not possible to define all critical defects and imperfections, and it may be necessary to exercise some judgement about whether or not a particular visible defect is critical. (If you need assistance, contact qa-team-group@unfpa.org) If the visible defect may affect the performance of the condom, the defect is considered critical. If a defect not listed in Table A10.3 is considered critical by any party, then the procurer, test laboratory and manufacturer must consult with each other to agree on the classification of the defect concerned. Exact definitions of critical defects and imperfections should be reviewed and agreed upon during the contractual process.
Package seal integrity	
Sampling	ISO 2859-1 Inspection Level S-3 (*11*)
Testing	In accordance with the package integrity test method in the relevant annex of ISO 4074
Requirement	**AQL 2.5**

Table A10.2 *continued*

Performance requirements	Description
Alternative package seal integrity method (for condoms to be delivered by air shipment or to high-altitude destinations), to be specified in contracts; to be adopted and manufacturers given a transition period of 6 months to 1 year of publication of this specification	
Sampling	ISO 2589-1 Inspection Level S-4 (*11*), Minimum Code Letter H (80 samples)
Testing	Use the alternative package seal test specified in Appendix 2
Requirement	**AQL 0.65**

3.2.1 Types of visible defects

Some visible defects may adversely affect the performance of the condom, for example by increasing the risk of it breaking or slipping off in use. These defects are classified as critical and an AQL of 0.4 is applied to nonconforming condoms.

The most common critical visible defects are covered by ISO 4074. These defects include broken, missing or severely distorted beads and permanent creases with adhesion of the film. They are evaluated by visual inspection, as part of the procedure for testing for freedom from holes.

Other types of critical visual defects are occasionally seen, and they should be assessed for their potential effect on the performance and acceptability of the condom.

Some of the more common critical visible defects are described in Table A10.3 and imperfections that are not critical are listed in Table A10.4.

Table A10.3
Critical visible defects

Defect	Description
Pleat/crease	The film sticks to itself and the pleat/crease cannot be removed by gentle stretching of the adjacent film.
Blister/bubble	An obvious circular or teardrop-shaped thin area with a well-defined border in the film (such defects may break under pressure).
Embedded and surface particles	Any particle with any dimension of 1 mm or greater. These may be dirt, hair, insects, powder granules, coagulum, etc.

Table A10.3 *continued*

Defect	Description
Bead defects	Faulty, missing or severely distorted beads (as in ISO 4074).
Crack marks	Lines that penetrate the surface of the film, formed by shrinkage of the latex during drying. These do not include flow lines or marks from the mould.
Delamination	Areas where the individual layers of latex separate (condoms are formed by two or more dips in the liquid latex).
Thin areas	Small areas of the condom (including the teat) that are visibly thin. These can show up as bulges with well-defined edges on the freedom-from-holes test. Condoms that look asymmetrical when filled with water are not in this category (see Table A10.5).
"Cupping" (a concave region at the end of the teat)	An apparent indentation at the end of the teat, which is often caused by significant thickness variations around the teat. Very small concave areas (<2 mm) shall be treated as non-critical visible defects.

Table A10.4
Imperfections that are not regarded as defects

Phenomenon	Description
Micro-coagulum	Particles of rubber with dimensions <1 mm.
Flow lines	Lines of denser material in the film.
Small concave spot at the end of the teat	An apparent indentation caused during the withdrawal of the former (dipping mould) from the latex. Large concave spots (e.g. >2 mm) at the end of the teat shall be treated as thin areas (critical visible defect).
Distortion due to rolling	Apparent variations in condom width due to stretching during rolling.
Distortion when testing for freedom from holes	Distortion of the condom during the freedom-from-holes test that are due to small differences in thickness around the wall of the condom, caused by relative movement of the latex and the former (dipping mould) during dipping (bulges with well-defined edges should be treated as critical visible defects).
Uneven lubricant	The open end of the condom may appear dry, especially on new condoms. The lubricant penetrates the roll slowly.

Table A10.4 *continued*

Phenomenon	Description
Embedded and surface particles (small)	Particles with dimensions < 1 mm that are visible to the naked or corrected eye.
Faulty bead (minor)	Uneven and partially distorted beads.
Uneven colour	Minor streaking.

3.2.2 Packaging defects and ISO 4074

The main packaging defects are listed in Box A10.1. Additional defects are sometimes detected only after shipment. This section summarizes common types of packaging defects, including those detailed in the WHO/UNFPA specification.

Individual packages

The quality of the individual foil packages shall be assessed by visual inspection using a sampling plan in accordance with ISO 2859-1 Inspection Level S-3 (*11*). An AQL of 2.5 shall be applied to these defects collectively. Packaging defects are summarized in Box A10.1.

Consumer packs

There are no requirements for consumer packs included in the WHO/UNFPA specification. Procurers should fully specify requirements in accordance with programme needs. Compliance should be assessed by visual inspection, using a sampling plan in accordance with ISO 2859-1 Inspection Level S-3 (*18*). It is recommended that an AQL of 2.5 be applied to consumer pack requirements.

In cases where organizations repack condoms into consumer packaging, the quality of the consumer packaging is entirely at the discretion of the organization doing the repacking. The only requirements that can be specified are the labelling requirements for the consumer pack and information to be supplied to the user. These requirements are detailed in ISO 4074, although local requirements may apply as well.

Cartons and marking

Packaging requirements should be agreed in the purchase order. Compliance should be assessed by visual inspection, using a sampling plan in accordance with ISO 2859-1 Inspection Level S-3 (*11*). It is recommended that an AQL of 4.0 be applied to carton requirements.

Box A10.1
Packaging defects

Individual foil packaging defects, ISO 2859-1 Inspection Level S-3, AQL 2.5
- Empty package
- No lubricant
- Lubricant leakage
- Delamination of the packaging film
- Discoloured film and labels
- Missing manufacturer's name
- Incorrect/missing lot number
- Incorrect/missing date of manufacture
- Incorrect/missing expiry date

Consumer packs, ISO 2859-1 Inspection Level S-3, AQL 2.5
- Empty or partially filled packs
- Discolouration
- Delamination
- Missing manufacturer's name
- Incorrect/missing lot number
- Incorrect/missing date of manufacture
- Incorrect/missing expiry date
- Incorrect format of expiry date

Cartons and markings, ISO 2859-1 Inspection Level S-3, AQL 4.0
- Non-permanent marking
- Empty or partially filled cartons
- Damaged cartons that may affect the integrity or quality of the condoms inside
- Missing manufacturer's name
- Incorrect/missing lot number
- Incorrect/missing manufacture date
- Incorrect/missing expiry date

3.3 Design requirements

The design properties listed in Table A10.5 may be adapted, where appropriately indicated, to reflect the specific needs of the programme and population of intended users. Modification should be based on information about the target population. Verification of compliance with these requirements is to be done as part of the lot-by-lot compliance testing of the product.

If specific design changes are agreed between the manufacturer and procurer, then any appropriate testing procedures, sampling plans and compliance levels (AQLs) should also be agreed. Changes in condom design, such as different

shapes or the inclusion of pigments, can affect airburst properties and, in some circumstances, freedom from holes.

It is recommended that, where changes to the specification are made, dimensional requirements and design features should be subject to ISO 2859-1 Inspection Level S-2 (*11*) with an AQL of 1.0.

Appropriate reference samples should be maintained by the manufacturer and testing laboratory. The national regulatory authority and/or purchaser may also retain reference samples.

Table A10.5
Design requirements

Design requirements	Description
Shape and texture	
Verify by visual inspection	The surface of the condoms can be textured or non-textured. Texturing typically consists of a number of ribs or dots formed onto the surface of the condom. Condoms may be of any shape consistent with normal commercial practice and client requirements. If the condom is not parallel-sided and smooth, attach a dimensioned drawing with detailed description, which should be agreed with by manufacturer and procurer.
Integral bead	
Verify by visual inspection	The open end of the condom shall have a rolled ring of latex, called an integral bead, "rim" or "ring".
Colour, to be evaluated at prequalification	
Verify by visual inspection	Condoms can be translucent, pigmented or unpigmented. Pigments used with coloured condoms shall be suitable for use in medical devices and shall not degrade the rubber. The shelf-life of coloured condoms is to be verified by accelerated stability studies verified at 90 days and 180 days at 50 °C. If a pigment is required, indicate the colour and provide full details of the pigment, including a material safety data sheet (MSDS). Pigments and pigment dispersions or flavours used with coloured condoms shall be suitable for use in medical devices. A condom incorporating pigment, flavours and/or fragrances shall be subject to biocompatibility evaluation according to the relevant parts of ISO 10993.

Table A10.5 *continued*

Design requirements	Description
Odour and fragrance to be evaluated at prequalification	
Verify by visual inspection and smell	The condoms shall not give off an unpleasant odour when the package is opened at any time after manufacture and for the shelf-life of the product. It is recommended that manufacturers include odour assessment as part of their shelf-life studies. (Condoms have a characteristic odour of rubber, which tends to dissipate quickly once the package is opened. A mild odour that dissipates quickly is acceptable.) Procurers may specify the addition of a suitable fragrance. Such fragrances must be non-toxic, non-irritant and not degrade the rubber. The manufacturer shall supply details of the fragrance used and the amount added to the procurer. Fragrances used with condoms shall be suitable for use in medical devices. The condom and fragrance shall be subject to biocompatibility evaluation according to ISO 10993-1. The shelf-life of any fragranced condom shall be verified as described in Section 3.1. If a fragrance is desired, the manufacturer should specify it and provide full details of the fragrance, including an MSDS.
Testing	If a masking agent or fragrance is used, odour testing should become part of the lot-by-lot pre-shipment compliance testing. Odour testing should be included in ageing studies.
Width	
Sampling	In accordance with ISO 2859-1 Inspection Level S-2 (*11*)
Testing	In accordance with the test method in the relevant annex of ISO 4074
Requirement	The width is defined as the mean lay-flat width of 13 condoms measured in accordance with the relevant annex of ISO 4074 at a point 35 ± 15 mm from the open end, rounded to the nearest 0.5 mm. Standard widths within the public sector are 49 mm and 53 mm, with a tolerance of ±2 mm. **AQL 1.0** Other widths are available and may be more appropriate for specific target populations described in the list of Further reading. Users should select the appropriate width based on the best available data on the target population.

Table A10.5 *continued*

Design requirements	Description
Length	
Sampling	In accordance with ISO 2859-1 Inspection Level S-2 (*11*)
Testing	In accordance with the test method in the relevant annex of ISO 4074
Requirement	A minimum of 165 mm for condoms with nominal widths of < 50.0 mm A minimum of 180 mm for condoms with nominal widths from 50.0 mm up to 55.5 mm A minimum of 190 mm for condoms with nominal widths ≥ 56.0 mm **AQL 1.0**
Thickness	
Sampling	Test a sample of 13 condoms.
Testing	In accordance with the test method in the relevant annex of ISO 4074
Requirement	Unless otherwise specified, the nominal thickness will be 0.065 mm. If a different thickness is specified, then this must be agreed between the procurer and manufacturer. The thickness shall be stated in the specification and any purchase orders. The average single-wall thickness calculated for the 13 condoms tested shall be equal to the specified nominal thickness subject to a tolerance of: • ± 0.008 mm for condoms with nominal specified thickness of < 0.05 mm; • ± 0.01 mm for condoms with nominal claimed thickness ≥ 0.05 mm. **AQL 1.0** If a micrometer gauge is used, the thickness measurements are taken at three locations around the circumference of the condom at 30 ± 5 mm from the open end, 30 ± 5 mm from the closed end (excluding the reservoir tip), and at the mid-distance between those two points. The condom thickness is reported as the mean of the nine measurements.

Table A10.5 *continued*

Design requirements	Description
	For partially textured condoms, the thickness shall be measured at points closest to those specified above where the surface is smooth. The locations of the points of measurement shall be noted. If it is not possible to locate a smooth region on the condom where thickness can be measured, then thickness shall be measured at the points specified above and the specification should be adjusted to allow for the effect of the texturing – for example, by reference to the manufacturer's specification. In such cases, the method of measurement should be specified (gauge or ring weight). It should be noted that, when used for textured condoms, the mass method gives the approximate average for thickness, as opposed to the micrometer method, which gives an estimate. *Condoms thicker than 0.080 mm are usually considered to be extra thick, whereas condoms that are thinner than 0.060 mm are usually considered to be thin. There is no evidence that extra thick condoms (sometimes called extra strong) provide additional protection.*
Quantity of lubricant including powder	
Sampling	In accordance with ISO 2859-1 Inspection Level S-2 (*11*)
Testing	In accordance with the test method in the relevant annex of ISO 4074
Requirement	The condom shall be lubricated with a quantity of silicone fluid having a nominal viscosity between 200 and 350 centistokes. *Other lubricants such as glycols and water-based lubricants may be used by agreement between the manufacturer and procurer. Oil-based lubricants* ***should NOT*** *be used.* The nominal quantity of lubricant, including powder, in the package should be in the range 350 mg to 600 mg. The quantity of lubricant may be varied depending upon local requirements. UNFPA recommends 450 mg as the nominal dose but lower quantities may be appropriate for some markets. The nominal quantity of lubricant must be agreed between the procurer and manufacturer. The agreed nominal quantity of lubricant shall be stated in the specification and any purchase orders.

Table A10.5 *continued*

Design requirements	Description
	The amount of lubricant, including any dusting powder, shall be equal to the specified nominal amount, within a tolerance of ± 100 mg. If no amount is indicated, the nominal amount of lubricant shall be 450 mg. **AQL 4.0**
Individual package materials and markings	
Definition	Sometimes referred to primary packaging, individual packaging or individual containers
Packaging requirement	The colour, print design and identification markings, including Pantone references and font sizes, shall be as specified by the buyer and annexed to the specification for the purchase order. Unless otherwise specified, the individual packages shall be square or circular and shall not distort the rolled condom. The package shall be hermetically sealed and shall protect the product from oxygen, ozone, water vapour and ultraviolet and visible light. The package shall be hermetically sealed and shall protect the product from oxygen, ozone, water vapour and ultraviolet and visible light. If an alternative package shape is specified, then the shelf-life of the product in that package shall be confirmed as described in Section 3.1. **AQL 2.5**
Labelling requirement	The individual package shall have the following markings: • manufacturer's name; and identification(address) of manufacturing site* • lot number or lot identification code (printed at the time of packaging, not pre-printed); • expiry date: month and year in language(s) to be specified by the procurer. The year shall be written as a four-digit number and the month as a two-digit number (YYYY-MM) (printed at the time of packaging, not pre-printed). Other information, including texture, colour and fragrance can be agreed on between the manufacturer and procurer. In such cases, it is recommended that pre-printed foil is used. Manufacturing date: month-and-year manufacturing date can be added if required by procurer.

Table A10.5 *continued*

Design requirements	Description
	The lot numbers on packages must be printed at the time of packaging. * *Note*: If dipping of the condoms is done on one site and the naked condoms are packed and released for testing on another site, it is the manufacturer name and manufacturing site that did the final release testing that should be printed.
Sampling	In accordance with ISO 2859-1 Inspection Level S-2 (*11*)
Testing	The sample of condom packages is visually inspected to verify the required aspects of package quality.
Verified by visual inspection	Shape: unless otherwise specified, the individual packages shall be square or circular and shall not distort the rolled condom. The printing requirements, packaging and labelling can be verified by visual inspection.
Verified by supplier's data or independent test	Material: verified by manufacturer's data If it is not specified, packages should be constructed of a laminate that includes a layer of suitable impermeable flexible aluminium foil (recommended minimum thickness of 8 µm) and layers of plastic materials suitable for the mechanical protection of the metal foil and for printing and sealing. The lot numbers on packages must be printed at the time of packaging. In addition, the following shall apply: • there shall be no evidence of leakage; • the outside surface of the package shall be clean; • there shall be no separation of the layers of laminate; • if the sealed packages are in strips, the individual packages are separated by perforations or other means that allow the packages to be separated by hand without interfering with the seals; • the package must be easy to open without damaging the condom.

Table A10.5 *continued*

Design requirements	Description
Alternative package materials	Alternative package materials can be accepted if they have barrier and strength properties comparable to those of the packaging recommended above or if there are real-time stability data to show that the condom in its pack has adequate shelf-life. If an alternative material is required, append the full specification. The lot numbers on packages must be printed at the time of packaging. In addition, the following shall apply: • there shall be no evidence of leakage; • the outside surface of the package shall be clean; • there shall be no separation of the layers of laminate; • if the sealed packages are in strips, the individual packages are separated by perforations or other means that allow the packages to be separated by hand without interfering with the seals; • the package must be easy to open without damaging the condom.

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Appendix 1

International standards relevant to the Prequalification Programme for male latex condoms

Various external documents form part of the WHO/UNFPA Technical Specification and Prequalification Programme and the buyer may wish to mention them in any invitation to bid or order sent to the supplier. In every case, the edition of the document is the one in force on the date of the invitation to bid. These are standards published by the International Organization for Standardization (ISO). The latest version of the standard should be used by manufacturers.

- ISO 4074. Natural latex rubber male condoms – requirements and test methods (2015; https://www.iso.org/obp/ui/#iso:std:iso:4074:ed-3:v1:en).
- ISO 16038. Male condoms – guidance on the use of ISO 4074 and ISO 23409 in the quality management of natural rubber latex condoms (2017; https://www.iso.org/obp/ui/#iso:std:iso:16038:ed-2:v1:en).
- ISO 13485. Medical devices – quality management systems – requirements for regulatory purposes (2016; https://www.iso.org/obp/ui/#iso:std:iso:13485:ed-3:v1:en).
- ISO 2859-1. Sampling procedures for inspection by attributes. Part 1. Sampling schemes indexed by acceptance quality levels (AQL) for lot-by-lot inspection (1999; https://www.iso.org/obp/ui/#iso:std:iso:2859:-1:ed-2:v1:en).
- ISO 10993-1. Biological evaluation of medical devices. Part 1: Evaluation and testing within a risk management process (2018; https://www.iso.org/obp/ui/#iso:std:iso:10993:-1:ed-5:v2:en).
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- ISO 10993-10. Biological evaluation of medical devices. Part 10: Tests for irritation and skin sensitization (2010; https://www.iso.org/obp/ui/#iso:std:iso:10993:-10:ed-3:v1:en).
- ISO 10993-12. Biological evaluation of medical devices. Part 12. Sample preparation and reference materials (2012; https://www.iso.org/obp/ui/#iso:std:iso:10993:-12:ed-4:v1:en).

- ISO 14155. Clinical investigation of medical devices for human subjects – good clinical practice (2011; https://www.iso.org/obp/ui/#iso:std:iso:14155:ed-2:v1:en).
- ISO 14971. Medical devices – application of risk management to medical devices (2019; https://www.iso.org/obp/ui/#iso:std:iso:14971:ed-3:v1:en).

Appendix 2

Alternate package seal integrity test

1. Principle of the dry vacuum method

The condom packs are washed and dried, wrapped in coloured tissue, and put into U-shaped holders that prevent them from expanding. The U-shaped holders are placed in a vacuum chamber, which is evacuated for 20 minutes. The coloured tissue is examined for signs of staining. The packs are then examined, repacked and passed through the vacuum again, and the tissue re-examined.

Packs are considered to be leaking if:

a. a stain appears on the first examination, and the stain is found to be larger on the second examination; or
b. no stain appears on the first examination, and one appears on the second examination.

2. Equipment required for the dry vacuum

The following equipment is required:

a. ultrasonic cleaners with baths long enough to hold strips of 3 condoms (say, 200 mm). If the bath is not long enough, the strips can be gently folded to fit;

Note: It is necessary to ensure that the strips are submerged in the bath. This may be done by weighting the samples with a piece of metal (e.g. a large nut) or by using a frame that is part of the bath.

b. towels or tissues suitable for drying the packs;
c. isopropanol for washing (technical grade);
d. U-shaped holders for the condom strips;
e. coloured tissue suitable for wrapping the strips, in order to show leakage stains;
f. vacuum chamber (e.g. desiccator) capable of holding multiple U-shaped holders; and
g. vacuum pump capable of evacuating the vacuum chamber to 20 kPa (absolute).

Note: Manual washing may be used instead of the ultrasonic baths, provided that the process is shown to remove lubricant, which can be embedded in the stamping of the seals or in the serrations between packs.

3. Dry vacuum method

a. Select sufficient strips of 2 or 3 condoms from the lots to be tested, to give the required sample size (minimum 80).
b. Wash the strips in isopropanol in an ultrasonic bath for 10 minutes, and ensure they are submerged.

Note: The isopropanol can be re-used until it looks dirty on visual examination.

c. Remove the strips from the bath, and dry them with a paper towel.
d. Place the strips on a clean dry paper towel for to air-dry for at least 10 minutes.
e. Ensure the strips are dry.
f. Wrap each strip in coloured tissue then slide it into a U-shaped holder.
g. Place the U-shaped holders in a vacuum chamber and apply a vacuum of 20 ± 5 kPa (absolute). Hold at 20 ± 5 kPa (absolute) for 20 minutes and release the vacuum.

Note: if the laboratory is close to sea level, then 20 ± 5 kPa absolute is about –80 kPa gauge.

h. Remove the strips from the U-shaped holders one by one and check each tissue for stain marks.
   - Using a fine pen, mark the perimeter of each stain on the tissue.
   - Re-wrap the strip with the same tissue in the same place as before. Use the folds on the tissue to re-align the pack, or, if necessary, put guide marks on the tissue with a pen. Replace the strip in exactly the same orientation as it was before.
   - Record the leaking packages and the location of strip leaks.

Annex 11

World Health Organization/United Nations Population Fund specifications for plain lubricants

Background

The report of the Fifty-third meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in 2018 (*1*) stated the following:

> *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 we adopted by the ECSPP and published in 2008 (2, 3). The Expert Committee agreed to 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 existing 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.

As agreed at the ECSPP meeting in October 2018, UNFPA and WHO have separated out different aspects of the current procedure for contraceptive devices and condoms.

All related documents were restructured and revised in the first half of 2019, then sent out for public consultation in July 2019. Comments received were reviewed by a group of specialists in October 2019, before being presented to the ECSPP. This is one of the three adopted by the Fifty-fourth ECSPP meeting to replace the previous guidance document.

1. Introduction

The following guidelines give the specifications for procurement of additional lubricants to be used with male and female condoms in reproductive health programmes.

These guidelines have been updated following a detailed technical review conducted at the United Nations Population Fund (UNFPA) Global Consultation on Lubricants in November 2016 in Bangkok, Thailand, and a follow-up meeting, primarily with lubricant manufacturers, held in conjunction the Thirty-fourth ISO/TC 157 (International Organization for Standardization, Technical Committee 157 for Non-Systemic Contraceptives and STI Barrier Prophylactics) meeting in George Town, Penang, Malaysia in September 2017.

The Global Consultation on Personal Lubricants was convened to review the safety of personal lubricants, as research has shown users may experience irritation, burning and damaging effects to vaginal and rectal tissue, and to examine the ways to produce, procure and distribute safer products for all. Hosted by UNFPA, the United States Agency for International Development (USAID), the World Health Organization (WHO) and the International Planned Parenthood Federation (IPPF), the meeting brought together more than 80 manufacturers, researchers and technical experts, sexual health advocates and educators, as well as international organizations that procure lubricants for governments or local organizations.

The status of the WHO/UNFPA/FHI360 (Family Health International) advisory note on *Use and procurement of additional lubricants for male and female condoms* published in 2012 (4, was also reviewed at the Global Consultation. It was agreed that the majority of the recommendations made in that note are still valid and they have been incorporated in this specification. The recommendation that polyquaternary compounds should be avoided was found to be no longer supportable and has not been included in this specification.

2. Requirements

Manufacturers shall include in their product dossier evidence to confirm that the lubricant complies with the requirements listed in Table A11.1. Verification of conformance to these requirements is assessed by review of the product dossier.

Table A11.1
Generic requirements

Requirements	Description
Definition and general properties	**Description** Water-based lubricants shall be clear, translucent or white gels or viscous liquids. They shall be free from lumps and foreign matter and be non-staining and water washable. Silicone lubricants shall be clear, translucent or white gels or viscous liquids free from lumps and foreign matter and be non-staining. **Ingredients** Lubricants shall contain only ingredients that are safe for human use in contact with vaginal mucosa and skin during sexual intercourse. The ingredients shall be non-irritant and non-toxic and shall not liberate any toxic or harmful substance during storage and use. Lubricants shall be free from added fragrance, colour, spermicides, herbal ingredients and special ingredients that claim specific pleasure-enhancing properties. Silicone lubricants shall contain a minimum of 30% polydimethylsiloxane (dimethicone), with a viscosity of 5 cps (centipoise) and above (mixtures of polydimethylsiloxanes with different viscosities are permitted). **Compatibility with condoms** Lubricants shall be compatible with male and female condoms (any exceptions shall be noted in the labelling). Testing shall be conducted according to ASTM D7661 (*5*) and ISO 19671:2018 (6). When testing silicone lubricants containing volatile cyclomethicone, the conditioning of the condoms in the presence of the lubricants should be done under occlusive conditions, to prevent evaporative loss of the cyclomethicone. **Preservatives** Water-based lubricants shall be preserved against microbial contamination and shall contain suitable preservatives. The lubricant shall be manufactured under suitable conditions, to maintain control of bioburden. **Sterility** Lubricants may be supplied sterile in unit-dose containers.

Table A11.1 *continued*

Requirements	Description
	Manufacturer Lubricant shall be manufactured in accordance with certified quality management systems (QMS) and in compliance with national and regional regulatory requirements. The QMS shall comply with ISO 13485 (*7*). Lubricant shall have regulatory approval such as a CE Mark or United States Food and Drug Administration (US FDA) 510(k) clearance (*8*). **Lubricity** There are currently no specification requirements for lubricity, nor are there any recommended methods for measuring lubricity. Manufacturers who specify lubricity requirements should submit details of the specification and test method to UNFPA. Similarly, manufacturers who test for the retention of lubricity over the time of use should submit details of the test method and requirement.
Composition	The manufacturer shall submit to procurement agencies full composition details of the lubricant, with the quantities and specifications of individual ingredients used. Wherever available, the ingredients shall comply with corresponding pharmacopoeia specifications. When specific proprietary ingredients are used, their material safety information shall be submitted. Water-based lubricants shall be formulated to comply with the requirements listed next. • Osmolality shall be less than 1200 mOsm/kg.[1] This osmolality limit can be achieved by keeping the total glycol content below about 8.3 mass fraction (%w/w).[2] • pH shall be in the range 5.0 to 7.0.[3] • Viscosity shall be within the tolerance of ±10% of the value specified by the manufacturer. The manufacturer shall submit the method of determination of viscosity, giving details of equipment, temperature conditions, spindle speed, spindle number and shear rate. Silicon-based lubricants shall be formulated to comply with the requirements listed next.

[1] This requirement is under review and might be revised at a future date.

[2] This limit may be varied depending on the specific glycols used.

[3] *Note*: Lubricants with a low buffering capacity that do not disturb the pH of the vagina or rectum are preferred.

Table A11.1 *continued*

Requirements	Description
	• Viscosity shall be within a tolerance of ±10% of the value specified by the manufacturer. The manufacturer shall submit the method of determination of viscosity, giving details of equipment, temperature conditions, spindle speed, spindle number and shear rate.
Biocompatibility	Lubricants shall comply with the requirements of biocompatibility assessments conducted in accordance with ISO 10993-1 (*9*), for specific parameters of cytotoxicity (ISO 10993-5) (*10*) and skin irritation and sensitization (ISO 10993-10) (*11*).[4] The toxicity study reports shall be reviewed and interpreted by a qualified toxicologist or other suitably qualified expert. Full reports of biocompatibility assessments shall be submitted as part of the product dossier.
Bioburden levels	Lubricants need not be sterile. However, they shall be subjected to control of microbial contamination by appropriate measures taken in formulation, manufacturing and packing operations. In the finished product, bioburden levels shall be maintained below 100 cfu (colony-forming units) per gram (USP 1111) (*12*). There shall be an absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Escherichia coli*. These requirements apply to both water-based and silicone-based lubricants. Bioburden levels shall be maintained at the above levels during storage and repeated opening of a container during multiple use. Lubricants shall comply with the evaluation of preservative efficacy, performed as per the requirements of a relevant pharmacopoeia. If the lubricant is supplied sterile in unit-dose containers, the sterility assurance level shall be 10^{-6}.

[4] *Note*: Some regulatory authorities require acute systemic toxicity to be assessed. For example, USFDA requires acute toxicity testing by intraperitoneal administration.

Table A11.1 *continued*

Requirements	Description
Shelf-life and stability	Lubricants shall have a minimum shelf-life of 3 years from the date of manufacture. To ensure compatibility with condom-storage recommendations and shelf-life estimates, real-time studies shall be conducted within the temperature range of 28 °C to 35 °C. The humidity shall be maintained at (75 ± 5%) relative humidity (RH), to ensure conformity with Zone IVb (hot, higher humidity) requirements. In line with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q1A(R2) (*13*), accelerated studies shall be conducted at 40 ± 2 °C and 75 ± 5% RH. Manufacturers may elect to use higher temperatures such as 50 °C and 60 °C, providing the results can be correlated with real-time shelf-life estimates at 28 °C to 35 °C. For water-based lubricants, manufacturers should include freeze/thaw cycling in their stability studies, to confirm that the lubricants can tolerate freezing. Manufacturers should also confirm that osmolality remains within specifications at the end of the stability study and undertake intermediate osmolality measurement if any significant changes occur to the water content and/or viscosity of the lubricant, and, in the case of lubricants packed in sachets, the weight of the sachets during the course of the study. Critical parameters, including pH, bioburden, viscosity, odour, physical condition, etc., shall be monitored during stability studies. For water-based lubricants, preservative assays and microbiological challenge tests shall be conducted during stability studies. Silicone lubricants containing cyclomethicone should be monitored for weight loss due to any loss of volatile material through the packaging. Lubricants shall remain within the manufacturer's specification for the duration of the shelf-life period. The data and report on accelerated stability studies and ongoing real-time studies shall be submitted as part of the product dossier.

Table A11.1 *continued*

Requirements	Description
Compatibility with condoms	The manufacturer should submit reports of compatibility studies conducted on the use of lubricant with male and female condoms made from natural rubber latex and synthetic materials. The toxicity study reports shall be reviewed and interpreted by an appropriately qualified person to assess toxicology reports, e.g. a pharmacologist, pharmacist, microbiologist or a laboratory medicine specialist. If any biocompatibility or toxicity risks are identified, a risk/benefit analysis shall be included in the report. Full reports of biocompatibility assessments shall be submitted as part of the product dossier Any exceptions from testing or incompatibilities shall be noted.
Packaging	**Individual containers** Lubricants shall be packed in tamper-evident containers that facilitate multiple delivery of lubricant. Examples are collapsible/squeeze tubes and containers with a suitable delivery system for application of lubricant. It is recommended that containers should be made of recyclable materials that are compatible with the lubricant, as substantiated by stability studies and shelf-life claims. The containers shall not have sharp edges. They shall not liberate any toxic or harmful substance during storage and use of the product. The individual containers shall be free from leakage of lubricant. The recommended nominal contents for multi-dose containers are 35 g, 50 g and 82 g. Other sizes may be considered, depending upon programme requirements. The recommended nominal contents for a single-dose sachet is 3 g for silicone lubricants and 4–5 g for water-based lubricants. Pack contents are based on the amount of lubricant that can be expressed from the pack under normal use. This will be evaluated by weighing 20 full primary containers individually and weighing them again after squeezing out their contents. Alternatively, the weight of lubricant expressed may be determined directly by collecting it in a tared container or dish.

Table A11.1 *continued*

Requirements	Description
	Secondary packing The individual containers shall be packed in secondary distribution packages of an appropriate size as per programme requirements (e.g. 25 units per secondary pack). Cardboard boxes shall be Forest Stewardship Council (FSC; or equivalent) marked/certified. They shall only contain paper/cardboard. Plastic coating shall not be used. **Shipper cartons** Shipper cartons shall be FSC (or equivalent) marked/certified. They shall be made of a minimum of 40% recycled/post-consumer material. The shipper carton should only contain paper/cardboard. Plastic coating shall not be used. By 2020, the plastic carton liner shall be made from recycled material/plastic and biodegradable plastic. The recommendations relating to packaging in this specification may be varied depending on the intended use of the lubricant. Full details of the required packaging should be agreed in advance and specified in purchase orders.
Labelling	**Individual containers** Labelling requirements may be subject to local regulatory requirements. Subject to any local requirements, the individual containers shall be marked with the details listed next. • Contents (specify if it is water- or silicone-based lubricant) • The quantity of lubricant that can be expressed from the container in normal use • If in a multi-dose container, advice on the amount of lubricant to be used • Manufacturer's name and address • Batch/lot number • Expiry date (in YYYY-MM format) • Storage conditions – store at an average temperature below 30 °C and avoid exposure to direct sunlight • Warnings/special notes, if any • Maximum time period in which the contents can be used after the container was first opened • A list of any ingredients that may be an irritant or that could cause allergic reactions

Table A11.1 *continued*

Requirements	Description
	• A statement that the lubricant is compatible with male and female condoms (any exceptions, such as male polyurethane condoms, shall be stated on the package) • A statement that lubricant is not a contraceptive and does not protect against pregnancy, sexually transmitted infections and HIV. **To protect against pregnancy and sexually transmitted infections, the lubricant must be used with a condom.** **Secondary packaging** • Contents • Quantity • Manufacturer's name and address • Batch/lot number • Date of manufacture and expiry date (in YYYY-MM format) • Storage conditions • Warnings/special notes, if any **Shipper cartons** (or as per UNFPA shipping instructions to be provided by the buyer) • UNFPA logo • UNFPA project number • UNFPA purchase order (PO) number • Country of destination • Contents as water-based lubricants • Quantity • Manufacturer's name and address • Batch/lot number • Date of manufactue (in YYYY-MM format) • Expiry date (in YYYY-MM format) • Weight • Volume • Storage conditions text: "Store in well-ventilated, dry storage conditions with an average temperature of less than 30 °C away from direct sources of heat including sunlight" • Warnings/special notes, if any, to be defined by the manufacturer • Any special shipping instructions defined by the manufacturer

2.1 Lot-by-lot testing requirements

The manufacturer shall submit a certificate of analysis for each batch/lot of lubricant supplied, confirming conformance to the requirements specified in this section. This section may also be used by accredited/approved laboratories for the independent testing of lubricants.

Parameter	Requirements	Verification
Description	Water-based lubricant shall be clear, translucent or white gel or viscous liquid, free from lumps and foreign matter, and water washable. Silicone lubricants shall be clear, translucent or white gels or viscous liquids free from lumps and foreign matter and be non-staining.	Visual inspection on samples weighing about 5 g, drawn from five individual containers from each lot
pH	5.0 to 7.0	Inspection of a composite sample weighing about 10 g, drawn from five individual containers
Viscosity	Shall be within tolerance of ±1 % of the specified viscosity value	The manufacturer's method of giving equipment, temperature condition, spindle, speed, etc., shall be used. Testing is to be completed on a representative sample from each lot, either from the bulk immediately before packaging or from sufficient individual containers in order to provide an adequate sample size for the viscometer.
Bioburden	Bioburden levels shall be maintained below 100 cfu per gram. There shall be an absence of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Candida albicans* and *Escherichia coli*. Sterility (if claimed) shall be to the sterility assurance level of 10–6.	Testing as: per *The International Pharmacopoeia* (*14*), United States Pharmacopeia *(USP) (15) or* European Pharmacopoeia (*16*). Recommended testing frequency: • for the first 10 production lots, every lot shall be tested; • subject to all 10 lots conforming to specification, the testing frequency may be reduced to one in every 10 lots. If a lot fails, then full testing shall be reinstated until 10 consecutive lots have passed.

Table *continued*

Parameter	Requirements	Verification
Packaging and labelling	Shall comply with requirements of packaging and labelling as given in Section 2, except for material of construction.	Visual observation on samples of 13 containers per lot/batch

References

1. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1019; https://apps.who.int/iris/bitstream/handle/10665/312316/9789241210287-eng.pdf?ua=1, accessed 17 December 2019).
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6. ISO 19671:2018(en). Additional lubricants for male natural rubber latex condoms – effect on condom strength or equivalent (https://www.iso.org/obp/ui/#iso:std:iso:19671:ed-1:v2:en, accessed 19 December 2019).
7. ISO 13485:2016(en). Medical devices – quality management systems – requirements for regulatory purposes (2016; https://www.iso.org/obp/ui/#iso:std:iso:13485:ed-3:v1:en, accessed 19 December 2019).
8. US Food and Drug Administration. 510(k) clearances (https://www.fda.gov/medical-devices/device-approvals-denials-and-clearances/510k-clearances, accessed 19 December 2019).
9. ISO 10993-1. Biological evaluation of medical devices. Part 1: Evaluation and testing within a risk management process (2018; https://www.iso.org/obp/ui/#iso:std:iso:10993:-1:ed-5:v2:en, accessed 19 December 2019).

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12. United States Pharmacopoeia. USP 35<111>. Design and analysis of biological assays (https://www.drugfuture.com/Pharmacopoeia/usp35/PDF/0106-0117%20%5b111%5d%20DESIGN%20AND%20ANALYSIS%20OF%20BIOLOGICAL%20ASSAYS.pdf, accessed 19 December 2019).
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15. USP (https://www.usp.org/, accessed 19 December 2019).
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Annex 12

WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms

1. Introduction and background

The World Health Organization (WHO) recognizes the possibility to waive in vivo bioequivalence studies for immediate-release, solid oral dosage forms with active pharmaceutical ingredients (APIs) belonging to Class I and III according to the Biopharmaceutics Classification System (BCS), using comparative dissolution studies as surrogate proof of bioequivalence (*1*).

The WHO solubility classification, also referred to as the "WHO Biowaiver List", is a tool for national regulatory authorities (NRAs) and pharmaceutical manufacturing companies, suggesting medical products that are eligible for a waiver from in vivo bioequivalence studies, which are usually necessary to establish the therapeutic equivalence with the originator (comparator).

As part of its 2006 guidance on the waiving of bioequivalence requirements for immediate-release, solid oral dosage forms on the *WHO Model List of Essential Medicines* (*2*), WHO had provided a list of APIs based on data extracted from the public domain (i.e. solubility data published by different authors using inconsistent experimental conditions) (*3*).

2. WHO solubility classification for biowaiver

In 2017, the Fifty-second Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat revise the existing list using verifiable laboratory data that are generated according to consistent WHO criteria. Acting on this directive from the ECSPP, the WHO Secretariat initiated a multicentre research project, the Biowaiver Project, aimed at experimentally determining the equilibrium solubility profile of medicines listed in the EML, using a harmonized approach (*4*).

To classify APIs according to the BCS framework, two critical properties are usually evaluated: (i) an API's aqueous solubility; and (ii) its absorption/permeability. The initial phase of the WHO Biowaiver Project centres on unambiguous experimental assessment of the solubility parameter, as only highly soluble APIs are eligible for biowaiver. Once experimental solubility data are available, the exact BCS-class assignment can be determined by utilizing quantitative absorption/permeability data. However, since high solubility within an aqueous environment is a necessary prerequisite for an API to be eligible for a waiver from bioequivalence studies, the current focus on solubility is justified to guide the regulatory decision.

The WHO classification should be considered a living document and is meant to be regularly updated in accordance with new quality requirements

and progress in scientific development. The list replaces the existing literature-based compilation that is reported in the *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (*3*).

3. Scope

The aim of the WHO Biowaiver List is to enable an informed decision on whether or not a waiver from in vivo bioequivalence studies could be granted safely according to the WHO guidance *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*).

The WHO Biowaiver List is expected to promote access to standard quality essential medicines, by shortening the time required develop a multisource (generic) product supporting an optimized pharmaceutical development.

The WHO Biowaiver List has been recognized by WHO Regional and Country Offices as a "global good"; a normative work essential to strengthening global health in WHO Member States.

4. Methodology

The WHO *Protocol to conduct equilibrium solubility experiments for the purpose of biopharmaceutics classification system-based classification of active pharmaceutical ingredients for biowaiver* (*4*) is a tool available to all participants in this research. It was developed with the purpose of providing a harmonized methodology for the equilibrium solubility experiments, thereby minimizing the variability among centres and studies.

To date, all APIs studied in Cycles I and II are received as in-kind donations from pharmaceutical manufacturers supporting WHO in this scientific work. Equilibrium solubility experiments were conducted by universities, official national control laboratories, and WHO Collaborating Centres.

5. Results

Table A12.1 provides an overview of the APIs studied by WHO during Cycles I and II.

Table A12.1
WHO solubility classification of active pharmaceutical ingredients prioritized from the *WHO Model List of Essential Medicines* (*2*)

Medicine	Therapeutic area	Indication[a]	Highest therapeutic dose (mg)[b]	API PQ EOI / PQ	2019 WHO classification
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	No	II/IV
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	No	II/IV
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
codeine (sulfate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of *P. vivax* and *P. ovale* infections)	15	No	I/III

Table A12.1 *continued*

Medicine	Therapeutic area	Indication[a]	Highest therapeutic dose (mg)[b]	API PQ EOI / PQ	2019 WHO classification
pyrimethamine	Antiprotozoal medicines	Antimalarial medicines	75	Yes	II/IV
raltegravir (potassium)	Antiviral medicines	Antiretrovirals (HIV in pregnant women and in second-line)	400	Yes	II/IV
rifampicin	Antibacterials	Antituberculosis/ antileprosy medicines	750	Yes	II/IV
tenofovir disoproxil (fumarate)	Antiviral medicines	Antiretrovirals (HIV)	300	Yes	I/III

API: active pharmaceutical ingredient; PQ: prequalification; PQ EOI: expression of Interest for prequalification (*2*); WHO: World Health Organization.

[a] 21st *WHO Model List of Essential Medicines* (2019) (*2*).

[b] According to the WHO guidelines, *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*1*), APIs belonging to Classes I and III are eligible for biowaiver. Once experimental permeability data are available, the exact class attribution will be possible (i.e. either Class I or Class III). The present solubility characterization is already sufficient to provide an indication on whether or not an API is eligible for biowaiver.

Note. For exemption from an in vivo bioequivalence study, an immediate-release, multisource (generic) product should exhibit very rapid or rapid in vitro dissolution characteristics that are comparable to those of the reference product. A risk-based evaluation should also account for the excipients used in the formulation of the finished pharmaceutical product.

Establishing a new WHO Biowaiver List that is based on unambiguous verifiable experimental solubility data is a critical project with a tremendous public health impact on patients; procurement/United Nations agencies; national and regional regulatory authorities; payers; ethics committees; and manufacturers worldwide. The involvement and support from WHO stakeholders and partners is highly encouraged and appreciated.

References

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3. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fortieth report. Geneva: World Health Organization; 2006: Annex 8 (WHO Technical Report Series, No. 937; https://apps.who.int/medicinedocs/documents/s19640en/s19640en.pdf, accessed 18 November 2019).
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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; http://apps.who.int/medicinedocs/documents/s22406en/s22406en.pdf, accessed 18 November 2019).
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Annex 13

WHO guideline on the implementation of quality management systems for national regulatory authorities

Abbreviations

CREAM	clear, relevant, economic, adequate and monitorable
EDQM	European Directorate for the Quality of Medicines and HealthCare
GBT	*WHO Global Benchmarking Tool* (*4*)
GRP	good regulatory practices
ICT	information and communication technology
IT	information technology
ISO	International Organization for Standardization
M&E	monitoring and evaluation
NRA	national regulatory authority
PDCA	plan–do–check–act
QA	quality assurance
QMS	quality management system
RCA	root cause analysis
SMART	specific, measurable, attainable, realistic and time-bound
SWOT	strengths, weaknesses, opportunities and threats
WHO	World Health Organization

1. Background

Implementation of the Thirteenth World Health Organization (WHO) General Programme of Work (2019–2023) (*1*), as adopted by the Seventy-first World Health Assembly (2018), and the WHO Leadership priorities (*2*), has attracted much international public health attention to the theme of universal health coverage and to increased access to safe and effective medical products.

Several World Health Assembly resolutions, including WHA67.20 (2014) (*3*), mandate WHO to provide support to its Member States in strengthening national regulatory systems for medical products. It recognizes 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" (*3*).

Accordingly, to facilitate access to these products, WHO's vision is for all Member States to have an effective regulatory system that ensures medical products and other health technologies in the market meet internationally recognized standards of quality, safety and efficacy.

National regulatory authorities (NRAs) are responsible for ensuring the safety, quality and efficacy of medical products within their respective Member States; demonstrating that the services they provide consistently meet legal and regulatory requirements; delivering effective and efficient services; evaluating performance; and making improvements. An effective quality management system (QMS) can help to ensure that the products or services an NRA provides consistently meet statutory and regulatory standards and meet customers' expectations. A QMS provides opportunities to enhance customer satisfaction; address context-associated risks and opportunities for continued improvement; demonstrate conformity to specific QMS requirements; and assure the quality, safety and efficacy of medical products.

In 2015, WHO developed and launched the *WHO Global Benchmarking Tool* (GBT) (*4*). This tool assists WHO and regulators worldwide in evaluating the maturity and performance of regulatory systems and related functions. The GBT includes one indicator that assesses the NRA's level of development with respect to a QMS (*4*). Benchmarking results of low- and middle-income countries indicate that the majority of NRAs need to establish and implement a QMS or, if already established, enhance and maintain the QMS.

QMS implementation is challenging for NRAs, owing to the diversity of NRA legal mandates and organizational structures; the different levels of NRA development; and the number of regulatory functions that need to be implemented. WHO has developed this guideline to respond to requests by Member States for an international guideline on implementation of QMSs by NRAs.

2. Objectives

The aim of this guideline is to assist NRAs to develop, implement and improve their QMSs, based on principles from International Organization for Standardization (ISO) document ISO 9001 standard requirements (*5*). It provides recommendations on what NRAs should implement and maintain under each QMS to effectively and efficiently support the execution of NRA functions as mandated by national laws and regulations. The guideline is expected to promote consistency in regulatory practices within and across NRAs, to facilitate harmonization, mutual reliance and recognition mechanisms among Member States.

Therefore, the objectives of the guideline are as listed next.

1. Describe principles for implementing a QMS to support planning, execution, monitoring and evaluation (M&E) of the performance of all applicable functions and activities of an NRA.
2. Provide requirements for the QMS to support and facilitate systematic linkages and integration of different processes and systems of the regulatory functions and activities within an NRA.
3. Provide requirements that NRAs should consider for evaluating the performance of the QMS and measures that the NRA should implement for continually improving the QMS.

3. Scope

This is an overarching guideline that should be applied across all regulatory functions and activities, including registration and marketing authorization; vigilance; market surveillance and control; licensing establishments; regulatory inspections; laboratory access and testing; clinical trials oversight; national lot release; and others, as applicable to the implementing NRA. The guideline should be implemented to cover all types and categories of medical products and other health technologies under the responsibility of an implementing NRA. All other existing or future guidelines for QMSs for specific regulatory functions will complement this guideline.

The guideline can also be used for other regulatory activities that are mandated by the national laws and regulations to ensure public health safety, by assuring the quality, safety and effectiveness of medical products. This extends to areas of medical products such as pricing, professional training and regulation, as well as to other areas within the legislative mandates and functions of the NRA.

This guideline on QMS implementation can also be used for all models of NRA. NRAs can be legally, organizationally and operationally structured as follows:

- **discrete:** two or more institutions involved in partial or full enforcement of national laws and regulations for medical products in a country (e.g. one institution with legal mandates to enforce marketing authorizations and another one within the same country for licensing establishments' regulatory function);
- **decentralized:** one NRA with full legal mandates to enforce national laws and regulation of medical products within the country. A legally defined amount of enforcement, authority and operations is executed in localized zones or geopolitical zones of the country, while the rest is enforced at country level. This model exists in Member States with a federal governance system where laws and regulations are enforced at state/province and national levels; and

- **centralized:** one NRA with full legal mandates to enforce national laws and regulation of medical products within the country. The enforcement, authority and operations are executed, managed and controlled centrally for all applicable regulatory functions and activities.

The guideline is equally applicable to small, medium and large NRAs, as the principles and intended results of a QMS remain the same, regardless of the complexity of NRA. Therefore, this guideline describes the requirements that should be implemented; the MS and respective NRAs reserve the right to decide on how to address these requirements within the existing contexts and provisions of the laws. The guideline can be utilized by institutions that are responsible for single or multiple specific regulatory functions related to medical products.

Although the use of this guideline is voluntary, NRAs are encouraged to use it to facilitate implementation of their QMS. The implemented QMS should be demonstrated by documented evidence to have systematic processes that are controlled, maintained and evaluated for continuous improvement. NRAs are free to use any appropriate national or international standard or guideline on QMSs as a basis for the implementation.

Where different units within the NRA have already implemented a QMS for specific regulatory functions (such as laboratory testing and/or regulatory inspection), this guideline could be used by the NRA for those functions and processes that have not been addressed by the management systems already implemented. This is to avoid duplications and overlaps of management systems. It is expected that NRAs will gradually integrate all existing management systems within the overall QMS of the NRA. The implementing NRA could determine the extent to which this guideline should be implemented, without omitting any of its processes and activities that are mandated by national laws and regulations.

Effective implementation of this guideline will not lead to any WHO certifications and WHO will not conduct any audits for verification of implementation of a QMS. However, as part of the regulatory systems strengthening programme, WHO will conduct the benchmarking of the Member State's regulatory system and functions, including QMS-related processes, using the GBT (*4*) to determine the strengths and gaps, if any, for capacity-building and continuous improvement. This guideline should be implemented to cover regulatory functions that are part of the GBT, and other functions and activities of the NRA that are addressed by national laws and regulations but that are not part of the GBT. References to GBT revision VI (*4*) provides a linkage between GBT indicators and the relevant sections of this guideline (see Appendix 1).

The QMS using this guideline should be implemented on the foundation of the principles and recommendations on *Good regulatory practices* (GRP) (*6*). The implementation of the QMS should ensure that the GRP are integrated to the

extent possible without affecting the effectiveness and efficiency of the NRA to execute its functions.

4. Glossary

The definitions given below apply to the terms used in this guideline that are not defined in existing WHO terms and definitions databases. They may have different meanings in other contexts.

competence. Knowledge, skills and attitude required for successful work performance.

correction. Any action that is taken to eliminate a nonconformity. However, corrections do not address causes.

corrective actions. Steps that are taken to eliminate the causes of existing nonconformities in order to prevent recurrence. The corrective action process tries to ensure that existing nonconformities and potentially undesirable situations do not happen again.

customer. A person or organization that could or does receive a product or a service that is intended for or required by this person or organization. Customers of an NRA include individuals or parties who receive or could receive and use products and services that are provided and offered by the NRA. These parties include the general public, patients, manufacturers, distributors, health practitioners, researchers, the ministry of health and other individuals and institutions that rely on the NRA's products and services to make public health decisions.

customer satisfaction. A customer's perception of the degree to which the customer's expectations have been fulfilled. This relates to the expectations that different parties have of the NRA. The expectations include assurance that safe, efficacious and high-quality medical products will be available under the NRA mandate to regulate, and that the NRA will provide other products such as guidelines, public reports and related regulatory services that meet the expectations of different types of customers.

internal audit. An examination and assessment of all or part of a QMS with the specific purpose of improvement. An internal audit should be conducted by an independent (i.e. of the function to be audited) team of competent auditors as designated by the management for this purpose.

process. A set of interrelated or interacting activities that use inputs to deliver an intended result. In the context of NRAs, the production and service provision processes should coincide with basic regulatory functions.

product. Output of an organization that can be produced without any transaction taking place between the organization and the customer. They are also called regulatory products in this guideline. Products of NRAs relate to the tangible items that the NRA produces for its customers. These items include regulatory guidelines; public health notices; guidance notes; alerts; databases; mobile phone applications; reports; and other materials that are intended to provide regulatory information and communications to customers. Before their production, some of these products may require lengthy consultations for designing them.

quality. The total set of characteristics of an entity that affect its ability to satisfy stated and implied needs and to ensure the consistent and reliable performance of services or products in conformity with specified requirements.

quality management system. An appropriate infrastructure, encompassing the organizational structure, procedures, processes, resources and systematic actions necessary to ensure adequate confidence that a product or service will satisfy given requirements for quality.

quality policy. A brief statement that describes the organization's purpose, overall intentions and strategic direction; provides a framework for quality objectives; and includes a commitment to meet applicable requirements.

senior (top) management. Person(s) who direct and control an organization at the highest levels and who have the authority and responsibility to mobilize resources within the organization. In NRAs, the terms "senior management" or "top management" can be used interchangeably.

services. Output of an organization with at least one activity necessarily performed between the organization and the customer. Services of NRAs are also called regulatory services in this guideline. This includes, for example, activities such as evaluation of applications for market authorizations, inspections of facilities, testing of health product samples, etc.

5. Quality management system requirements for national regulatory authorities

5.1 Quality management system concepts

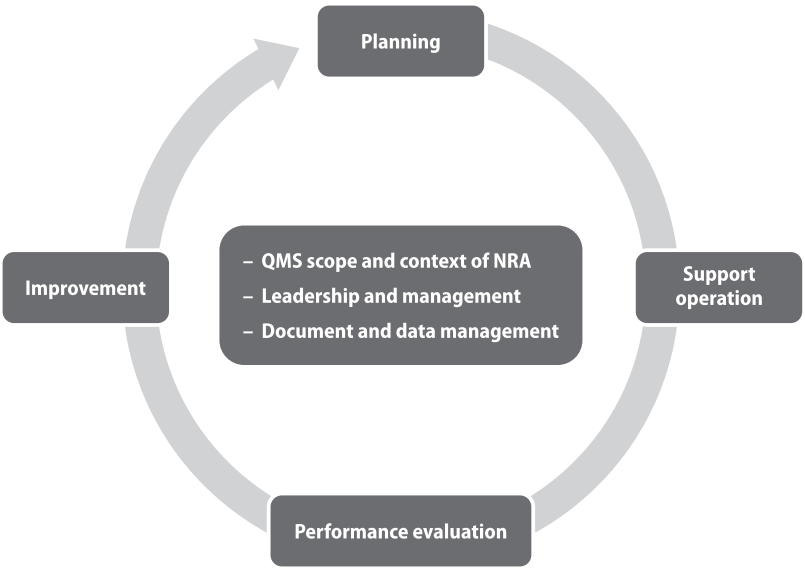
NRAs should implement a QMS that is supported by the process approach concept, plan–do–check–act (PDCA) cycle and risk-based thinking. NRAs should ensure that the implemented QMS meets its needs without making it unnecessarily complex, to avoid a negative effect on the NRA's effectiveness and efficiency. The QMS should be simple, fit for purpose and understandable.

The PDCA cycle requires NRAs to carry out planning, performing (implementing), checking (evaluating) and acting (to improve) processes in the QMS. The applied PDCA cycle covering the chapters in this guideline is provided in Fig. A13.1. The ISO 9001 standard (*5*) provides a brief description of the PDCA as follows:

- **Plan:** establish the objectives of the system and its processes, obtain the resources needed to deliver results in accordance with customers' requirements and the NRA's policies, and identify and address risks and opportunities;
- **Do:** implement what was planned;
- **Check:** monitor and, where applicable, measure processes and the resulting products and services against policies, objectives, requirements and planned activities and report the results;
- **Act:** take actions to improve performance, as necessary.

Fig. 1
Applied PDCA cycle

NRA: national regulatory authority; PDCA: plan–do–check–act;
QMS: quality management system.



The scope of the QMS and context of the NRA are placed in the middle, to provide the limitations to which the QMS should be implemented.

Leadership and management are centrally indicated, as they are important requirements for effective QMS implementation. Top management should commit and support all QMS processes, from planning up to acting for continuous improvement.

Document and data management are centrally indicated, because they should be part of every step of the PDCA cycle, in the form of procedures, forms and records that facilitate the consistent implementation of QMS processes and record retention.

Applying risk-based approaches (included in planning stages) enables NRAs to identify factors that could cause QMS processes to deviate or that could prevent the planned results from being achieved; to put in place proactive measures and controls to minimize the impact of negative effects; and to leverage opportunities as they arise. Risk-based thinking is applicable and should be implemented throughout the PDCA cycle.

NRAs should implement a QMS that identifies and integrates other management system standards that are applicable to the processes. The management systems that are for specific areas and processes should be documented. The NRA should ensure that the management systems do not create duplications, overlaps or inconsistencies within the overall QMS. While other WHO guidelines have been implemented for management systems of specific regulatory functions such as inspections and quality control testing, the overall QMS should be consistently implemented throughout the organization across different regulatory functions and other supporting areas.

QMSs are influenced by the different policies, objectives, diverse work methods, resource availability and administrative practices specific to each NRA. NRAs are free to decide the mode and routes to use when implementing this guideline, as long as the implemented QMS yields effective, consistent, transparent and reliable results in the regulation of medical products.

The QMS requirements that are described in this guideline are based upon the quality management principles presented next, as provided in ISO 9000 (*7*).

- **Customer focus:** the primary focus of a QMS is to meet customer requirements and to strive to exceed customer expectations. In this guideline, customer focus means meeting the needs and expectations of the public, patients, health-care practictioners, manufacturers, researchers and procurers, by providing regulatory products and services that assure access to high-quality, safe, effective and affordable medical products and health technologies.

- **Leadership:** leaders at all levels establish unity of purpose and direction and create conditions in which people are engaged in achieving the NRA's planned objectives.
- **Engagement (involvement) of people:** competent, motivated, empowered and engaged people at all levels throughout the organization are essential to enhance the organization's capability to create and deliver valued services.
- **Process approach:** consistent and predictable results are achieved more effectively and efficiently when activities are understood and managed as interrelated processes that function as a coherent system. This is critical, as it avoids having systems that are based on individuals within the NRA.
- **Improvement:** successful organizations have an ongoing focus on improvement. The NRA should ensure that it strives continously to improve its processes, products and services and the QMS.
- **Evidence-based decision-making:** decisions based on the analysis and evaluation of data and information are more likely to produce the desired results. This requires NRAs to implement measures for monitoring, analysing and evaluating the collected data, to assess whether the processes are delivering the desired results.
- **Relationship management:** for sustained success, organizations should manage their relationships with relevant interested parties. Implementing an effective QMS requires the NRA to ensure that its relationships are managed strategically for continous operations. The relationships include management of contractual agreements for activities subcontracted to individuals and institutions. The areas with subcontract agreements would either be technical or administrative and, if not managed properly, may have negative effects on the effective implementation of the QMS.

5.2 Quality management system requirements

The QMS requirements described in the subsequent subsections describe what NRAs should implement as part of their overall QMS. Table A13.1 provides a summary and focus for each subsection.

Table A13.1
Summary of quality management system requirements for each subsection

Subsection	Summary of requirements for implementation of a quality management system
5.2.1 Introduction	The requirements of this subsection focus on the NRA describing and documenting the setup of its QMS. The setup includes: • legislative mandates and scope (functions) of the NRA; • standards and guidelines used in QMS implementation; • QMS implementation history; • integration (as applicable) with other management and software systems for personnel performance appraisals, finances and accounting, environment, occupational health and safety, workflow, customer relationship management, ministry of health policies and strategic action plans; • identification of the functions and processes that are already covered by other QMSs.
5.2.2 Scope of the quality management system	This subsection describes the requirements for NRAs to document the processes that are covered by the implemented QMS. All processes and activities that are done by the NRA as mandated by national laws and regulations should be included in the QMS. Implementation can be done at once or in phases.
5.2.3 Organizational context of the national regulatory authority	The focus of this subsection is to provide guidance regarding what should be indicated when describing and documenting the setup of the NRA with its regulatory system, functions and activities within the QMS. This extends to the model type (discrete, decentralized or centralized) and to the relationships with other institutions providing regulatory services for medical products and other health technologies. The context should also specify what to implement in the QMS to support the NRA in handling and managing internal and external issues within its regulatory mandates and functions, as well as meeting the needs and expectations of interested parties (i.e. customers and stakeholders).
5.2.4 Leadership, management and organization	This subsection describes requirements for what should be expected from top management for effective implementation of the QMS. It also includes the roles, responsibilities and authorities that should be part of the implemented QMS.

Table A13.1 *continued*

Subsection	Summary of requirements for implementation of a quality management system
5.2.5 Document and data management	This subsection provides requirements that should be applicable to internally generated documents and to those of external origins, including data. The requirements include development, review, approval, distribution, version and access control, storage, retrieval and disposition of documents.
5.2.6 Planning	This subsection focuses on planning requirements for achieving the set objectives, managing risks and opportunities across the NRA, and planning changes to the QMS for continuous improvement.
5.2.7 Support and resources	This subsection includes requirements for input resources (technical and non-technical), personnel and infrastructure needed for effective implementation of the QMS.
5.2.8 Operation	This subsection addresses the requirements for QMS implementation in core processes and activities that are within the mandates of the NRA. It also provides guidance on documenting operational linkages of processes and systems for effective and efficient QMS implementation.
5.2.9 Performance evaluation	This subsection provides methodologies and recommendations regarding what should be implemented by the NRA to facilitate accurate, objective and efficient performance monitoring, analysis and evaluation of operations indicators, QMS effectiveness, resources and customer satisfaction.
5.2.10 Improvement	This subsection presents requirements for NRAs to implement in the QMS to support continuous improvements based on collected, analysed and evaluated data.

5.2.1 Introduction

NRAs should have documented, available and accessible legislative laws and regulatory policies on medical products that describe the regulatory functions and activities that should be included in the QMS.

NRAs should list and maintain current versions and copies of national, regional and international management system standards and guidelines that are used for the QMS implementation.

NRAs should document the history and evolution of their QMS, to demonstrate the controls and management of changes in the system to ensure

that it is effective for the institution. The evolution and changes should be justified and related to any changes to the adopted national, regional and/or international management system standards and guidelines (e.g. the case of the *Compendium of quality management system (QMS) technical documents for harmonization of medicine regulation in the East African Community* (*8*)).

NRAs should ensure that all existing and already implemented management systems are integrated in the QMS. The integration should ensure that there are systematic, adequate and appropriate linkages between the overall QMS and the management systems for specific technical or administrative functions. The QMS should be integrated into the regulatory processes, to ensure that it helps the NRA to achieve its legal mandates and functions.

The NRA should identify the functions and processes that are already covered by other QMSs. This should be done to identify gaps and align specific management systems with the overall QMS of the NRA as much as possible, to ensure consistency and facilitate effective performance M&E. The management systems for specific technical and administrative functions and processes are described in the next subsections.

5.2.2 Scope of the quality management system

This guideline aims to provide guidance on implementing a sustainable and effective QMS based on adapted ISO 9001 standard (*5*) requirements, to address the needs of NRAs with respect to all regulatory functions, including administrative and supporting processes. The scope of the QMS should include functions, processes and the facilities where they are undertaken.

NRAs should ensure that the implemented QMS provides a clear statement of scope that specifies the functions and processes that are covered as mandated by the national legal framework. The scope should include all applicable regulatory functions that are provided in the current version of the GBT (*4*). In addition, the QMS should also cover all additional technical and administrative functions and processes that are part of the NRA's routine operations.

Where there is more than one institution that is partially or fully involved in the regulatory activities of medical products of a country, the QMS for each institution should support consistency, effectiveness, efficiency and systematic collaboration, to improve and strengthen coordination between institutions. The QMS should also include the technical and administrative functions and processes that are interrelated and interdependent for the effective undertaking of the affected regulatory function(s). The QMS should be clear on the scope for each involved institution, to ensure that there are neither gaps nor overlaps of the processes and activities.

When a specific unit of an NRA has implemented a QMS (e.g. a quality control laboratory, inspectorate or province/zone/state), the scope should be

clear on the inclusions and exclusions (with justifications as applicable), without weakening operational linkages and interdependencies for timely and effective regulatory decision-making.

The scope statement of the implemented QMS should be documented and supported by a relevant national legal framework and by current best practices of the affected functions and processes.

5.2.3 Organizational context of the national regulatory authority

5.2.3.1 Understanding the national regulatory authority organization and its context

The NRA should demonstrate that it understands its organizational and operational context within the country's regulatory framework as part of national health system. The organization should understand the context under which it provides the regulatory products and services, which may be through using a discrete, decentralized or centralized type of organizational structure. This understanding facilitates the identification and management of internal and external issues relevant to its ability to achieve the objectives as defined in the NRA's strategic plans.

The NRA should document the context in which it exists and in which it has been given the legal mandate to perform regulatory functions that are within the scope of the QMS. The context should indicate the limitations of the NRA and the relationships with other institutions that are part of its routine operations.

The documented context of the NRA should clearly indicate the technical and administrative areas that are not exclusively under the control and management of the NRA. This could include areas such as personnel recruitment, management of finances, procurement, and management of equipment and infrastructure.

Determination and documentation of internal and external issues should be integrated in the regulatory processes of the NRA, based on the needs and expectations of customers and stakeholders. The determination of internal and external issues should also be linked to the development of a strategic plan to ensure that the implemented QMS helps the NRA achieve the objectives.

Internal and external issues can change (e.g. changes to laws or regulations, or procurement, changes in national labour laws, or changes to professional practice regulations), and therefore they should be monitored and reviewed. The NRA should conduct and document reviews of its organizational context at planned intervals, and whenever there are changes to the legal framework or when there are organizational or structural changes.

NRAs should understand the context, as well as the internal and external issues that provide the foundation and inputs for determining a strategic plan; scope of the QMS; quality policy; quality objectives; and related risks and opportunities.

NRAs may use national legal provisions to identify different types of interested parties (customers and other stakeholders) for the regulatory products and services that are provided. Where customers and other stakeholders are defined in the national laws and regulations, this would be sufficient, as long as all outputs and services provided by the NRA are addressed. This identification helps NRAs to separate other stakeholders from customers who should also be the focus of the QMS. NRAs should focus on all interested parties that can affect its ability to achieve the quality objectives. In addition, these interested parties should be categorized, along with their respective needs and expectations of the NRA that the implemented QMS is designed to support.

NRAs should have a robust and defined system in place to monitor, review and document the relevant requirements of interested parties at planned intervals.

5.2.3.2 Quality management system processes

NRAs should ensure that inputs and resources that are required to perform the processes and functions covered in the QMS scope, with expected outputs, are determined, documented and provided. NRAs should document the sequences and interactions of regulatory processes, together with related measures and criteria for their control (e.g. key performance indicators). The level and type of controls that are applied to the regulatory processes should be determined and documented with a risk-based approach and should utilize the available opportunities. The QMS should provide procedures for evaluating the processes and allow for the implementation of corrective actions under a controlled and managed change process. This should facilitate continuous improvements of the processes and the entire QMS.

The QMS should be integrated in the regulatory functions and processes, to ensure that the personnel who are assigned with responsibilities and authorities in performing regulatory and administrative activities have the required competencies.

5.2.4 Leadership, management and organization

5.2.4.1 Commitment of top management

Top management of the NRA should demonstrate leadership and commitment towards the effective implementation and sustainability of the QMS within the national legal framework, through continual identification of the needs and expectations of its customers. The following are responsibilities of top management with respect to a QMS:

- providing needed resources for the implementation of an effective QMS that is consistently implemented across the NRA units, functions and processes;

- integrating QMS requirements into the regulatory processes and aligning the quality policy and quality objectives with the strategic plans of NRAs;
- implementing a QMS that incorporates a risk-based approach and that is based on functions and processes rather than being built around individual personnel or specific activities;
- communicating the importance of the QMS, to maintain consistency in NRA functions and to improve the effectiveness and efficiency of the QMS;
- engaging, supervising and supporting all NRA personnel to contribute to the implementation and effectiveness of the QMS and to ensure that the NRA achieves the intended expectations; and
- reviewing the performance of the QMS and promoting improvements.

Top management should ensure that the risks and opportunities that can affect the ability of the NRA to provide products and services of the quality expected by customers are determined and documented. Top management should also ensure that the NRA implements measures to enhance customer satisfaction. To increase customer satisfaction, innovation and best practices may be introduced into the NRA's processes, with the appropriate determination of related risks and practicality.

5.2.4.2 Quality policy

Top management of NRAs should establish, implement and maintain a documented quality policy that contains actionable and practical statements that:

- take into consideration the organizational context and strategic directions and plans and provide a framework for setting quality objectives;
- include a commitment to comply with applicable national legislation, as well as regional and global regulatory requirements and best practices;
- include a commitment to continual improvement of the QMS; and
- include a commitment to adopt and implement GRP, as provided in the *WHO good regulatory practices: guideline for national regulatory authorities for medical products* (*6*).

Top management should communicate the quality policy to all NRA personnel and ensure that the personnel have read, understood and applied it within their respective activities. Where applicable and appropriate, controlled

copies of the quality policy should be available to customers and stakeholders, through established document control procedures as per QMS requirements.

5.2.4.3 Roles, responsibilities and authorities

To effectively implement the QMS, top management should assign and document roles, responsibilities and authorities, and should ensure that this information is communicated and understood within the NRA. Depending on the organizational context of the NRA and on the scope and complexity of the QMS, top management should assign the following responsibilities and authorities to one or more job function:

- ensuring that the QMS of the NRA conforms to the requirements of the adopted standards and guidelines;
- ensuring that the integrated QMS and regulatory processes are delivering their intended results as per action and strategic plans of the NRA;
- monitoring and reporting on the performance of the QMS and proposing opportunities for improvements to top management;
- ensuring the promotion of customer focus throughout the NRA, while assuring the quality, safety and efficacy/effectiveness of health products; and
- ensuring that the integrity of the QMS is maintained when changes (e.g. legislative, process, organizational or structural) to the QMS are planned and implemented.

Top management should ensure that the job function(s) to be assigned the above responsibilities and authorities have the necessary competencies and have direct access to and are accountable to top management.

5.2.5 Document and data management

NRAs should have the guidelines, policies and procedures that are necessary for the effective implementation of the QMS within the legislative provisions.

QMS documents should include, but are not limited to, internally and externally generated hard copy and/or soft copy formats of regulations, drawings, policies, guidelines, strategic plans, action/work plans, manuals, procedures, registers, logbooks, databases, spreadsheets, templates and forms, codes of ethics and professional conduct, inventories, checklists and all other documents that are used in the technical and administrative activities of NRAs.

QMS documents should include internally and externally generated evidential documents (e.g. records, files and reports) in hard copy and/or soft copy formats, which are retained by NRAs.

NRAs should consider all published materials, either on intranets or websites or in newsletters and other forms of publication, to be part of QMS documents and covered by the requirements of this guideline.

Within the QMS, NRAs should implement policies and procedures for identifying, describing, formatting, reviewing, approving, controlling (e.g. distribution, access and version control, retrieval and use), retaining and disposing of internally generated documents. QMS documents of external origin (e.g. regulations, standards, pharmacopoeia and WHO guidelines) should be subjected to the same requirements as for those that are internally generated, to the extent possible and practical, depending on the nature and intended use.

Where information technology (IT) is utilized to optimize regulatory processes for technical and administrative functions, NRAs should ensure that the system templates, forms and software that are used are identified, reviewed, approved, controlled and maintained under the same QMS policies and procedures that apply for other documents.

NRAs should implement a data management, protection (i.e. confidentiality, loss and integrity) and retention policy/procedure, to define clearly the types and categories of collected, analysed, evaluated and retained data. The policy/procedure should provide clear requirements for the format, medium and duration of retention for data and documents. In addition, there should be a policy/procedure for NRAs covering the maintenance and retention of all documents and data.

5.2.6 Planning

5.2.6.1 Quality management system planning

NRAs should plan and document how they will meet the needs and expectations of their customers and stakeholders, as stipulated in the national laws and regulations. The plan should include all technical and administrative functions, processes and activities of the NRA and their respective objectives.

5.2.6.2 Action to address risks and opportunities

When planning for the QMS, the NRA should consider the issues (internal and external) and requirements of the stakeholders and determine the risks and opportunities that need to be addressed in the context of the organization. The NRA should plan actions to address these risks and opportunities, with assigned roles, responsibilities and authorities. The planned actions should include a framework for monitoring and evaluating the effectiveness of the actions taken. The NRA can choose the methods of risk management that suit its needs. Depending on the size, complexity and regulatory functions of the NRA,

principles can be based on the WHO guidelines on quality risk management (*9*) and the ISO 31000 standard (*10*).

5.2.6.3 Quality objectives and planning to achieve them

NRAs should establish quality objectives for relevant regulatory and administrative functions, for all levels and sections of the NRA and for all processes needed for the QMS. Where quality objectives are established for multiple levels within the NRA (e.g. directorate, department, unit or zone), the objectives should be consistent, to ensure that all levels contribute towards achieving the overall expectations from legal mandates and of customers. The quality objectives should be integrated with regulatory objectives, to ensure that the QMS supports the consistency, effectiveness and efficiency of the NRA.

Quality objectives of the NRA should be consistent with its quality policy; should contribute to customer satisfaction; and should be relevant to the regulatory products and services as mandated by the national legal framework.

To the extent possible, quality objectives should be specific, measurable, attainable, realistic and time-bound (SMART). The QMS should provide the measures for the NRA to communicate the objectives to designated audiences within the NRA and the means to monitor and update the objectives.

The QMS should include a plan to ensure that the set objectives will be met. The planning exercise includes determining the actions that will need to be taken; the resources that will be required (e.g. human and financial to purchase equipment and the required supplies); the responsibilities that will be assigned to staff for specific tasks; the timelines that will be defined for completion of each step; and the means that will be used for monitoring and evaluating whether or not the objectives have been achieved.

5.2.6.4 Planning of changes

The NRA should plan for changes to the QMS. The purpose of planning changes is to maintain the integrity of the QMS and ensure the NRA's ability to provide conforming regulatory products and services during any changes. For any change, the NRA should consider the availability of resources and necessary allocation or reallocation of responsibilities. This could be done by implementing an effective change management process within the QMS.

The need for changes can result from changing needs of customers and other relevant interested parties, for example, new products to be evaluated to grant market authorization; availability of new information and communication technologies (ICTs) for a service or process; a move to outsourcing of important processes; departure of persons in key roles (e.g. due to retirement or job change); or a move to online service provision.

5.2.7 Support and resources

5.2.7.1 Resources

NRAs should determine, document and provide the resources that are needed to establish, implement, maintain and continuously improve the QMS. The determination should be done within the organizational context of the NRA and the scope of the legal mandates on the functions and activities. NRAs should also determine and document those technical and administrative resources that need to be provided by external providers (companies and individual experts).

5.2.7.2 Personnel

NRAs should determine, provide and document the personnel and their required minimum competencies necessary for effective implementation of the QMS and for effective operation and control of its processes. A focal person or lead may be appointed to coordinate and monitor the implementation of the QMS at appropriate levels and functions.

The competencies of all personnel should include a combination of appropriate education, professional training, experience and behavioural attitude, as deemed necessary by the NRA. Where the assigned personnel with defined responsibilities and authorities do not have all the competencies, training plans should be developed and implemented, with appropriate evaluation criteria for acquired competencies.

For the purposes of consistency of the QMS, NRA training plans for the rest of the technical and administrative personnel and functions should be based on the competency framework or matrix and/or performance appraisal system coordinated by human resources departments.

Records of evidence of an employee's competence, including educational diplomas or degrees; completion of training certificates; resumés; performance reviews; licences; and other documents should be retained.

The competency framework or matrix should be used in assigning official and non-official job function hierarchies and relationships (e.g. junior officer, senior officer or head of unit). The framework should also include the procedure for designation or qualification of technical officers (e.g. senior or lead assessor, senior or lead inspector, senior or lead analyst); these should be supported by requalification procedures.

5.2.7.3 Infrastructure and work environment

NRAs should determine, provide and maintain a documented list of infrastructures needed for technical and administrative processes in the execution of the legal mandates. Lists of the following should be maintained to allow for identification, location, type, quantities, versions, operational status

(i.e. in use versus not in use) and plans for qualification, validation, calibration and maintenance (as applicable):

- buildings and associated utilities;
- technical (e.g. inspection and testing equipment) and administrative equipment (e.g. servers, computers, and printers), including hardware and software;
- transportation and logistical resources; and
- ICT.

NRAs should determine, provide and maintain the human and physical factors of the work environment necessary for the operation of technical and administrative processes and activities within the context of the organizational structure and national legislation. To the extent that it is practical, the environment should address social, psychological and physical (i.e. workspace) conditions to promote work–life balance. Depending on the activities of the NRA, applicable occupational, health and safety policies and procedures should be considered for implementation, as provided in ISO 45001 (*11*).

The NRA and its units should implement and document a policy and procedure on the management of waste that is generated. The waste management should be conducted within the recommendations and applicable requirements of the current version of ISO 14001 (*12*).

5.2.7.4 Monitoring and measuring resources and equipment

NRAs should determine and document a list of monitoring and measuring resources and equipment used, to ensure that the regulatory products and services meet the expected requirements. The equipment should be suitable for the measurement activity to be undertaken, and maintained to ensure continued fitness.

For the equipment, including software, that is used in technical measurements (e.g. inspection and laboratory equipment), NRAs should ensure that the results obtained from such equipment are valid and that the calibration of equipment is traceable to national or international measurement standards. The calibrated equipment should be identified with its calibration status and safeguarded from adjustments, damage or deterioration.

In the event of measuring equipment being found to be out of calibration, NRAs should evaluate and document the validity of previous measurement results obtained from the equipment, and take appropriate actions.

5.2.7.5 Organizational knowledge management and awareness

The NRAs should consider how to determine and manage the organizational knowledge required to meet the NRA's present and future needs. Individuals

and their experience are the foundation of organizational knowledge. Capturing their experience and knowledge can generate synergies leading to the creation of new or updated organizational knowledge. In determining, maintaining and making organizational knowledge available, NRAs can benefit by (i) learning from failures and successes; (ii) gathering knowledge from stakeholders, experts and partners; and (iii) capturing existing internal knowledge.

The tools for maintenance and distribution of organizational knowledge can include the intranet, libraries, awareness sessions, newsletters and others.

NRAs should ensure that all personnel (both full-time and part-time) have read and understood the quality policy and the quality objectives that are relevant to their level in the organization. This should be documented to verify that personnel understood their contributions to the effectiveness of the QMS and the benefits of improved performance. NRA personnel should be aware of the implications of not following policies and procedures established under the QMS, for example, the release to customers of non-conforming regulatory products.

5.2.7.6 Internal and external communication

NRAs should determine, implement and document internal and external communication policies and procedures within the QMS. The policy should clearly describe "what" to communicate, and define responsibilities and authorities for communication to the assigned competent personnel. Depending on the context, nature and intent of the communication, the policy should describe the level, audience and frequency of the communication, including the format and medium (e.g. verbal, letter, mail, website or intranet). Social media and mobile applications are additional tools for communicating with interested parties.

The communication policy and procedure should be implemented within the legal framework of the NRA and related national (governmental) procedures and practices.

5.2.8 Operation

NRAs should ensure that planning of technical and administrative processes is done effectively, as provided under Section 5.2.6 for all operations within the scope of the QMS.

5.2.8.1 Customer communication and review of the regulatory products and services requirements

NRAs should ensure that there is a process of consistent communication with customers and stakeholders to collect their feedback, inputs and other inquiries that may be useful for reviewing the pertinence of the offered regulatory products

and services. The details of the regulatory products and services offered, including contingency requirements (such as those applied during natural disasters or epidemics), should be publicised (e.g. through the NRA website, pre-submission meetings, or scientific advice), so that customers are aware of the requirements for submissions to the NRA relating to regulatory products and services.

NRAs should ensure that the requirements and expectations for the products and services are determined and defined within the applicable national laws and regulations. To promote public transparency and accountability, the product and service requirements may include fee schedules and delivery timelines for product market authorizations, licences, reference standards (e.g. pharmacopoeia), permits and certificates. This information may be included in the national guidelines and guidance notes and should be publicly available to customers and stakeholders.

NRAs should ensure through a review process that requests for services received from customers are complete and in conformity with service requirements. A checklist used for such reviews should be documented. When there is a difference between the requirements for products or services as requested by the customer and the requirements prescribed by the NRA, this should be communicated to the customer and resolved before processing the request. Any verbal request or change in the requirements, either by the NRA or by the customer, should be confirmed before services are processed.

When the requirements for products and services are changed for any reason, NRAs should take measures to inform all relevant interested parties. They should retain evidence of the results of the revisions to the requirements of products and services, and any new requirements for the products and services that are provided.

5.2.8.2 Design and development of new products and services

When NRAs plan on implementing new regulatory function(s) due to revision of the national legal framework, or wish to introduce new regulatory products and/or services (such as through mobile phone application), the following process steps should be followed:

1. Determine and document the process(es) that will form part of the new function, including the stages, steps and control measures needed through implementation roadmaps or projects. The determination should include expected reviews, verifications and validations that the processes are sufficiently robust for the intended function. NRAs should also determine and document the competencies, responsibilities and authorities of the project development team. Where the NRA would not be able to provide all the required resources, the NRA should document those

resources that will be externally sourced. NRAs should determine the need to involve customers, stakeholders and internal personnel to ensure that key inputs are collected. NRAs should also assess whether any of the existing requirements (e.g. timelines or schedule of fees) are applicable to the new regulatory function, or whether there is a need to establish additional ones. All documents used and generated out of these roadmaps should be retained in an appropriate format and medium.

2. Once the implementation roadmap has been completed, NRAs should determine and document the inputs, such as performance indicators, national legal requirements for compliance, and codes of ethics and professional conduct, as well as the potential consequences of failure, using a risk-based approach.
3. As defined in the implementation roadmaps, intermediate reviews (where practical and possible), verification steps (i.e. comparing the new application/process with a similar proven application/process) and validation exercises (i.e. testing under intended user conditions) should be conducted by NRAs, to ensure that the resulting function or product meets the requirements for the intended use.
4. The expected outputs of the design and development process will be in the form of standard operating procedures or service provision manuals that give the information necessary for all the processes required to provide intended products and services, including information to be provided by the customers.
5. Where changes are to be made in the new application or to the developed products or process(s), these changes will be identified, reviewed and controlled. A risk-based change management procedure should be documented and implemented.

5.2.8.3 Externally provided products and services

NRAs should ensure that externally provided products and services (e.g. subcontracted ICT support, purchased reference standards, or subcontracted quality control laboratory testing) required for technical and administrative functions and activities of the NRA, conform to the QMS requirements. Where national laws and regulations exist for managing the use of public NRA funds in procurement, for example, a national public procurement act, with procedures based on amount thresholds for either single sourcing or open/closed bid competitions and decision levels (i.e. director-general, council, or board level), the QMS should not duplicate any procedures that are provided for public

procurements. However, the NRA should ensure that the public procurement procedure conforms to the requirements described in the subsequent paragraphs of this subsection and should close gaps, if any. The NRA should also implement these requirements when it performs direct procurement.

NRAs should ensure that competence criteria are defined, documented and implemented for the evaluation, selection, performance monitoring and re-evaluation of external providers and suppliers (e.g. NRAs having documented, well-defined and transparent criteria for the selection and performance monitoring of external non-staff experts).

When NRAs must perform in-house prequalification of providers, there should be a documented procedure and policy on the competence criteria for evaluation, selection, performance monitoring, and requalification. The prequalification and requalification should focus on the competence of the individual persons and the institution or company to provide the products and/or services that meet applicable QMS requirements.

NRAs should implement measures for ensuring that the externally provided products and services do not adversely affect the organization's image and ability to consistently deliver the products and services to the customers.

The NRA should determine which specific controls are to be implemented for an external provider, and for incoming products and services provided by them. Control activities that may be considered include inspections, certificates of analysis or testing, second party audits, evaluation of statistical data and key performance indicators.

The NRA should clearly communicate the requirements and controls to be applied to the external provider, and both parties should agree as to what is required. This understanding of requirements is usually reflected in a technical service agreement, or through a purchase order or contract. The NRA should ensure that the requirements communicated to the external providers are complete and clear and address any potential issues.

5.2.8.4 Service provision

NRAs should carry out their technical and administrative functions for processing requests for services under controlled conditions. The controlled conditions should include, as applicable, the points listed next:

- use of guidelines, policies and procedures that provide the requirements for the regulatory products and services, including those for performance of activities;
- NRAs should document and implement measures for reviewing (peer-review or quality assurance [QA] review), approving and releasing the output of intermediate processes, to ensure that

there are adequate controls for those activities that are involved in providing conforming products and services. For this purpose, the following guidelines should be considered for adoption and implementation, as applicable and to the extent necessary:

  - for technical processes involving review of application documents for marketing authorization for the assurance of quality, safety and efficacy, procedures and recommendations this includes, among others: *Good review practices: guidelines for national and regional regulatory authorities* (*13*); *Regulation and licensing of biological products in countries with newly developing regulatory authorities* (*14*) and *WHO guidelines on evaluation of similar biotherapeutic products (SBPs)* (*15*);
  - where the NRA has a unit responsible for good practices inspections, recommendations and technical requirements: WHO *Quality management systems requirements for national inspectorates* (*16*);

- as required, monitoring and measuring resources and equipment should be available and in use, to ensure that the processes are effective and controlled. Where measuring equipment must be used in providing regulatory services of the NRA laboratory, technical requirements and recommendations from the following guidelines should be considered for adoption and implementation, as applicable and to the extent necessary:
  - *WHO good practices for pharmaceutical quality control laboratories* (*17*) for physicochemical testing and *WHO good practices for pharmaceutical microbiology laboratories* (*18*) for microbiological testing. These two WHO guidelines can be supported and complemented with the current ISO/IEC 17025 standard (*19*) and the European Directorate for the Quality of Medicines and HealthCare (EDQM) *Quality management documents* (*20*);
- NRAs should ensure that the provided infrastructure and working environment are suitable for the operation of both technical and administrative processes and activities and for the performance of applicable regulatory functions; and
- NRAs should ensure that the appointment of personnel is based on the required competencies and qualifications and is described and documented in respective units. This should include the implementation of control measures to avoid or reduce human errors through peer- and QA reviews.

NRAs should document and implement policies and procedures on the unique identification and traceability of released regulatory products and services. As far as practical and possible, these should also be supported by systematic measures to facilitate traceability of the products and services to the equipment, software, personnel and location used by the NRA.

5.2.8.5 Property belonging to customers or external providers

NRAs should implement measures to verify, protect and safeguard properties that belong to customers and stakeholders, including providers, and avoid their loss, damage and any effects that would make them unsuitable for use. This can include properties, for example, that may have been seized and quarantined or used as input for making regulatory decisions. Examples of property include marketing authorization product dossiers, quarantined products, samples for testing, intellectual property and personal data.

The NRAs should determine those products and services (e.g. seized drugs, drug samples collected for analysis, vaccines under release, licences, market authorizations, permits or certificates to be issued) that can deteriorate or degrade, and implement appropriate storage conditions.

5.2.8.6 Release and compliance control of products and services

NRAs should document and implement practical procedures on the release of regulatory products and services through all stages up to and including the customer. The release process includes defining the responsibilities and authorities of the involved job functions. These processes should provide an internal QA procedure to ensure that the released products and services comply with all planned requirements.

NRAs should document and implement procedures for control of nonconformances and deviations that are observed or reported. If the nonconformity is discovered after the product has been delivered to the customer, the NRA should take appropriate actions to prevent unintended use or undesired consequences, and take measures such as issuing a recall or suspension. The QMS should not duplicate any existing procedures in technical units, such as a laboratory or inspectorate.

5.2.9 Performance evaluation

5.2.9.1 Monitoring and measurement

NRAs should conduct monitoring, measurement, analysis and evaluation of all planned technical and administrative activities, to determine whether the intended results, as defined in action plans, workplans or strategic plans, are being achieved. NRAs should define what needs to be monitored and measured

(e.g. characteristics of processes, products, services and potential risks) and the methods to be used for monitoring, measurement, analysis and evaluation of the performance and effectiveness of the QMS. The monitoring, measurement, analysis and evaluation of the NRA performance should be linked to the planned key performance indicators (or simply indicators), as applicable. The establishment and implementation of the indicators should be as practical as possible, to ensure that value is added through monitoring, measurement, analysis and evaluation activities. Therefore, the indicators or key performance indicators should have clear, relevant, economic, adequate and monitorable (CREAM) attributes. NRAs should determine and document the frequency of M&E of the indicators, from the implemented action and activity plans, as well as from the performance and evaluation of the QMS. NRAs should ensure that the M&E framework is consistent across different units, levels and functions of the organization. The framework should be documented and aligned with the relevant quality objectives (strategic objectives) of the NRA.

5.2.9.2 Monitoring of customer satisfaction

The NRA should develop methods to systematically seek feedback from a selected population of customers, or from every customer at planned intervals. Means to obtain feedback is provided by social and published media such as websites and message boards, opinion surveys and compliments, suggestions or complaints. The NRAs should determine the degree of customer satisfaction after the results of feedback are analysed and evaluated and then act based on this information.

NRAs should document, implement and publish comprehensive policies and procedures on handling of complaints, in order to provide guidance to customers and stakeholders on complaint submission, investigation, resolution, appeal and communication within the national legislations. The procedures should define the roles and responsibilities of a complainant and the NRA and specify timelines to effectively manage complaints related to regulatory products and services.

5.2.9.3 Analysis and evaluation

NRAs should analyse and evaluate monitoring and measurement data and information, to determine summary performance results of the following:

- compliance of regulatory products (e.g. guidelines and software applications) to quality and validity requirements;
- compliance of regulatory services to quality and timeline commitments and requirements;
- degree of customer satisfaction;

- performance and effectiveness of the QMS for the overall NRA and/or the QMS for NRA units or functions and the need for improvements to the QMS;
- level of implementation of action or activity plans and strategic plans at the time of reporting;
- effectiveness of the actions taken to address risks and opportunities (such as strengths, weaknesses, opportunities and threats (SWOT) analysis); and
- performance of external providers (including external technical experts).

5.2.9.4 Internal audit

NRAs should plan and conduct internal audits (at least once a year), to verify compliance to the QMS requirements across the organization and to verify that the QMS is effectively implemented and maintained. An internal audit programme should have defined planning requirements, frequencies, methodologies, responsibilities, competencies and reporting. Each internal audit programme should take into consideration the importance and associated risks of the processes to be audited, the internal and external changes affecting the NRA, and the results of previous audits, in order to:

- define the audit requirements for the criteria (QMS requirements) of compliance; scope (functions and departments to be audited); and methodology (interviews, examination of records, results, and trends) for each audit. The criteria for compliance may add and implement a scale for reporting observations (critical, major and minor), which should be clearly and objectively defined within the internal audit programme;
- select appropriately trained, qualified and competent auditors who can conduct the audit objectively and impartially. The impartiality can be achieved by employing auditors that audit those processes in which they are not involved while serving in the NRA;
- ensure that the internal audit reports are submitted to top management for actions;
- take appropriate corrections and corrective actions without delay and within timelines defined by top management. Where corrective actions are delayed due to unavailability of required resources, appropriate risk management plans should be implemented and documented; and

- retain records of internal audit programmes and internal audit reports, including records of corrections and corrective actions.

Further technical guidance on managing and performing internal audits can be adopted from the current version of ISO 19011 (*21*).

5.2.9.5 Management review

Top management of NRAs should review the QMS at planned intervals (i.e. at least once a year), to ensure its suitability, adequacy, effectiveness and alignment with the strategic direction of the organization as per strategic plans. Ideally, top management should review the QMS alongside the review of the NRA's regulatory plans (activity, action or strategic plans). This will ensure that the QMS remains integrated into regulatory processes effectively.

QMS reviews should consider inputs as provided in Table A13.2, with the listed expectations of the outputs to be presented in the minutes of the meeting (report).

Table A13.2
Inputs and outputs for review meetings

Inputs (to be reviewed)	Outputs
Status of actions from previous reviews Changes in internal and external issues that are relevant to the QMS Information on the performance and effectiveness of the QMS, including trends in: • customer satisfaction and feedback from stakeholders; • the extent to which quality objectives have been achieved; • performance on compliance to commitments and requirements for regulatory products and services; • nonconformances and deviations, and the status of implemented corrective actions; • results of M&E of indicators/key performance indicators; • results of internal and external audits; and • performance of external providers (including external technical experts) Adequacy of resources (financial, human, equipment and infrastructure)	• Decisions and actions related to opportunities for improvements • Decisions and actions related to changes required to the QMS • Actions on additional resources needed to implement improvement initiatives and suggested changes in the QMS and in other areas where resources (including human resources) are not adequate • Actions to implement for achievement of quality objectives • Responsibilities for follow-up of actions on the decisions taken in the meeting

Table A13.2 *continued*

Inputs (to be reviewed)	Outputs
Effectiveness of the actions taken to address risks and opportunities (such as SWOT or similar analysis) Opportunities for improvements of the QMS	• Management review meeting minutes to be retained as records or reports and communicated appropriately to internal and external customers and stakeholders as per NRA communication policy

M&E: monitoring and evaluation; NRA: national regulatory authority; QMS: quality management system; SWOT: strengths, weaknesses, opportunities and threats.

Management review agenda (inputs) and meeting minutes should be retained as records or reports and communicated appropriately to internal stakeholders as per NRA communication policy.

5.2.10 Improvement

There are different methods to conduct improvement, such as correcting existing nonconformities and deviations and taking actions to prevent recurrence, or conducting ongoing, small-step improvement activities based on opportunities identified either through risk analyses or breakthrough projects. These improvement activities can lead to innovation, revision and/or improvement of existing processes, or to the implementation of new processes.

NRAs should implement and document measures to record and react to nonconformances and deviations by taking actions to control and correct them, including with related plans for managing related activities, if any. In addition, NRAs should conduct a root cause analysis (RCA) and evaluate the need to act in order to avoid recurrence of the nonconformances and deviations in the affected area, as well as in any similar processes in the organization in which such nonconformances or deviations could occur. The steps involved in this process are:

- reviewing and analysing the nonconformance or deviation;
- determining, to the extent possible, the cause(s) of the nonconformance or deviation; and
- determining whether similar nonconformances exist or could potentially occur within the affected unit or function and/or other units of the NRA or functions that have similar processes.

After implementing the corrective action, NRAs should review and document the effectiveness of the corrective action taken through practical

means, including during future internal audits that look for a recurrence of the same nonconformity. The results of the RCA and the implemented corrective actions should be used to update the risk and opportunity planning, as applicable. Where corrective actions lead to changes to the process(es), NRAs should plan for similar changes to the QMS, supported by a defined change management plan. NRAs should define the communication of reports on nonconformances and corrective actions to internal and external customers, as defined in the communication policy/procedures.

For technical and administrative processes, NRAs should ensure that the handling of nonconformances, deviations and corrective actions is consistent across the entire organization. Nonconformances and deviations that are related to professional misconduct of NRA personnel should be handled in accordance with conditions of employment and service, including related national legal provisions.

Improvement can include actions to reduce process variation; increase the consistency of process outputs, products and services; and improve process capability. This should be done to enhance the NRA's performance and give benefits to its customers and stakeholders. The results from performance monitoring and evaluation and management reviews should be used to decide which continual improvement actions should be implemented and what resources and support should be provided for their implementation by top management.

6. Quality management system implementation methodology

6.1 Supporting factors for quality management system implementation

Full commitment of the head of the NRA and the heads of technical, support and administrative units (i.e. top management) is necessary for effective implementation and maintenance of the QMS in NRAs. This commitment should be supported by demonstrating leadership, management, commitment and customer focus through all stages of the implementation of the QMS. The QMS should be designed to be integrated in regulatory processes (i.e. not standalone); supported with adequate resources (human, financial, equipment and infrastructure); and created to be simple enough to remain manageable with the available resources, while being effective enough to support consistency, effectiveness and efficiency.

Potential mechanisms that can support QMS implementation include:

- establishing effective coordination and communication mechanisms;

- receiving high-level support from top management for QMS implementation;
- establishing high-level ownership and commitment by top management for QMS implementation and maintenance;
- including QMS implementation roadmaps in NRA strategic plans by top management when submitting to an oversight body (council, board, committee or ministry of health) for approval, as applicable;
- including QMS implementation by the NRA in the national health strategic plans;
- including responsibilities and authorities for contributing to the QMS in every staff job description and human resources performance appraisal;
- creating and implementing training plans for QMS personnel, based on NRA competence frameworks;
- engaging all customers and stakeholders for communication and awareness;
- implementing applicable ICT tools for internal and external implementation of QMS and communication of quality policy awareness;
- embedding assigned QMS personnel within regulatory processes, with the dual responsibilities of regulatory job functions and QMS responsibilities to support and maintain the QMS in the respective regulatory unit.

6.2 Situational analysis of quality management system implementation status in the national regulatory authority

Regardless of the size of NRA, the scope of regulatory functions and the NRA organizational model (i.e. discrete, decentralized or centralized), the recommendations in Table A13.3 for gap and situational analyses should be considered when implementing QMS and when planning for continuous improvement of a QMS that is already implemented. NRAs should first identify existing gaps and determine the level of implementation of the QMS, with the use of Appendix 2, Table A13.3 and self-benchmarking results. Table A13.3 categorizes the key aspects relevant to the different stages of the QMS, as listed next.

- **Non-existing QMS:** NRAs should focus on ensuring that processes and activities are performed consistently, regardless of the personnel or location of execution. This may be covered for certain areas with automated systems (such as laboratory information

management systems for laboratories or e-performance appraisals for human resources). NRAs should prioritize development and implementation of procedures for areas based on the related risks with respect to the products and services; the affected quality objectives; and the availability of resources for maintenance of the procedures. This means that not every area should be prioritized at the same time for QMS development and implementation (for NRAs without an implemented QMS).

- **Existing QMS without implementation:** the focus at this stage should be on ensuring that consistent procedures are developed and implemented for the QMS to support regulatory processes effectively. Careful consideration should be given at this stage to objectively addressing the activities for gap identification and validation; these steps would also be useful for NRAs that have already developed and implemented a QMS. NRAs should ensure that the person(s) identifying the gaps have the necessary competence and that top management fully supports the process. The review should be done to cover all areas in which the QMS has been implemented, and the scope should be limited to records, reports or other means of verification that procedures have been implemented and are being used to the full extent as intended. The outcome of this review should be a root cause analysis with proposed measures to implement; these measures should take into consideration the availability of resources and associated risks of delayed implementation.
- **Ineffective implementation of QMS:** addressing this stage is considered useful once the first two stages are addressed for the respective processes and activities. This stage focuses on the main objectives of the QMS, namely, to ensure that the NRA is being effective in supporting regulatory processes and activities; providing regulatory products and services; and achieving strategic objectives. Therefore, it is important that the QMS is uncomplicated/unsophisticated and manageable enough in its implementation and maintenance to avoid diverting NRA time and resources on the QMS instead of delivering regulatory products and services to the customers as provided by national legal mandates. Increasing the effectiveness and efficiency of the QMS may also involve the adoption and implementation of ICT to remove human errors while promoting consistency; reducing time for implementation and recording; and providing long-term cost reductions.

6.3 Gap analysis for developing a roadmap for quality management system implementation

The information in Table A13.3 can be used to identify gaps and define activities to be done for QMS implementation, based on the recommendations of this guideline. The planning, prioritization and implementation should be as practical as possible and be determined by the NRA, taking into consideration the availability of resources and priorities for the provision of regulatory products and services.

Table A13.3
Gap analysis

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.1 Introduction	Linking and integration of overall QMS to quality systems and (automated) software for: • registration and market authorization • laboratory inspections and licensing • vigilance • market surveillance and control • clinical trials oversight • lot release • environmental (waste) management • occupational health and safety • finance and accounting • e-procurement • planning, monitoring and evaluation • human resource performance appraisal, training and staff/talent retention • others	NRAs should perform an organization-wide review for consistency of practice by different staff using the same processes and the existing system. This review can be used identify a consistency gap for QMS intervention and document development. Once the reviews are completed and gaps established, reviews should be done to determine whether the existing systems and/or software have operational interfaces between one another when they all contribute towards achieving the same objective; these reviews can help to identify operational gaps in interfaces. The QMS should be used to link the processes and activities between systems and/or software by providing documents.	Where consistency and operational interfaces have been implemented and supported under the QMS, NRAs should conduct reviews to identify gaps in the level of implementation of the QMS documents. This should be evaluated by reviewing records and reports generated from the systems and/or software, to establish consistency and operational linkages for the same objectives. Where gaps are found to exist, NRAs should perform RCA and implement changes as appropriate to stage 1 QMS interventions.	NRAs should conduct reviews to identify gaps in the effectiveness and efficiency of the QMS interventions with respect to the achievement of the intended objectives based on evidence from stage 2 outputs. When gaps have been identified, NRAs should revise the QMS implementation documents to ensure that they are effective and efficient in contributing towards the achievement of the objectives.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.2 Scope of the QMS	Documented statement defining the scope of the regulatory functions, physical locations, processes, regulatory products and services of the NRA	To identify gaps in the scope of the QMS, NRAs should review for the existence of consistent documented scope statements, which includes all areas, locations and processes.	NRAs should review the level of implementation of the QMS across all units (including administrative) and locations, to identify gaps in the implementation of the scope.	When identifying gaps for QMS revision, NRAs should review the effectiveness and efficiency of the scope of the QMS in facilitating the provision of required products and services.
5.2.3 Organizational context of the NRA	Adequate description and mandates of NRAs in terms of: • ability to define internal and external issues and customers and stakeholders	NRAs should review and identify gaps in the consistency of how issues for planning are determined among different units of the organization. QMS documents should be developed and implemented to establish consistency.	NRAs should review the planning reports and records from different units, to identify gaps in implementation of QMS documents. Where gaps are identified, RCA should be performed to ensure that procedures are implemented.	NRAs should review the contribution of QMS documents in making the planning more effective and efficient to identify gaps. Identified gaps should be addressed by implementing changes to QMS documents.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.4 Leadership, management and organization	Adequate description and mandates of NRAs in terms of: • ability to develop and implement organizational structure • ability to develop and implement quality policy and customer-focused initiatives • ability to assign QMS responsibilities and authorities to personnel	NRAs should review the consistency of supervisory and reporting structures, consistency in developing and implementing quality objectives, and consistency of assigned QMS responsibilities and authorities across units and locations, to identify gaps in leadership, management or organization. QMS procedures should be implemented to ensure that leadership, management and organization processes are carried out consistently in implementation of the QMS	NRAs should review the level of implementation of existing QMS procedures, to ensure consistency in organizational structures, job titles, reporting lines, quality policies, QMS responsibilities and authorities across the units and locations, to identify gaps in implementation of procedures. RCA should be done to determine changes that would improve levels of implementation of QMS procedures.	NRAs should review the effectiveness and efficiency of the procedures in supporting leadership, management and organization processes to identify gaps in the existing QMS. Procedures should be revised to ensure that they are effective and efficient in supporting the NRA and all its units in having leadership, management and organization that is able to deliver on the regulatory products and services.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	**Implemented evidence (by records, reports)**	**Effectiveness and efficiency**
5.2.5 Document and data management	Documents under the QMS that are internally generated or from external origins for: • regulations • guidelines • Policies • notes and guidance • procedures (SOPs/work instructions) • lists, registers, logbooks • databases and spreadsheets • templates, forms • application documents (dossiers, files) • financial, accounting, procurement and HR records • reports, letters, emails, permits, licences, certificates, others	NRAs should identify gaps by reviewing the consistency in the development, review, approval, version and access control, distribution, storage, retrieval and disposition of documents, as applicable across all units and locations of the organization. Where gaps exist, procedures should be implemented to ensure that documents are managed consistently across all units and locations of the NRA.	NRAs should review the records in units and locations, to identify gaps in the implementation of existing procedures for management of documents. RCA should be done to determine measures to promote implementation of existing procedures.	NRAs should review the effectiveness and efficiency of the procedures in identifying gaps in the management of documents. Procedures should be revised to ensure that they are more effective and efficient in the management of NRA documents. NRAs can consider the use of IT in the management of documents, depending on the availability of resources, size of NRA and complexity of documents to be managed.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.6 Planning	Linking and integration of planning in quality systems and (automated) software for objectives in: • technical activities • support and administrative activities • M&E	NRAs should review the consistency in the planning, monitoring and evaluation of technical, administrative and support activities, with associated risk and change management plans to identify gaps across all units and locations. QMS procedures should be implemented to ensure that all planning, monitoring and evaluating of technical and support activities are done consistently and with related risk and change management plans.	NRAs should review the level of implementation of procedures for consistency in planning, monitoring and evaluating of technical and support activities. To identify gaps for QMS revision, the review should evaluate the consistency in implementation of risk and change management plans, based on existing records and reports. RCA should be done to ensure that procedures are implemented.	To identify gaps with existing procedures, NRAs should review the effectiveness and efficiency of the QMS procedures in support of planning, monitoring and evaluating of activities, risks and changes. QMS procedures should be revised or replaced with automated systems, based on the complexity and size of the NRA and its planning activities.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.7 Support and resources	Adequate and quality resources for: • personnel and competencies • organizational knowledge management • ICT • work environment • communication and awareness	NRAs should review the consistency in the allocation of personnel, training in QMS, knowledge sharing, use of ICT and communication of QMS requirements to identify gaps for QMS implementation. Procedures should be implemented to ensure consistency across all units and locations in allocation of personnel, training of staff in QMS implementation, use of intranets and other ICT tools and communication.	NRAs should review the records to identify gaps in levels of implementation of existing procedures for QMS personnel, competencies, knowledge management, ICT, work environment and communication across all units and locations. RCA should be done to ensure procedures are implemented.	To identify gaps for QMS revisions, NRAs should review the effectiveness and efficiency of the procedures in ensuring that there are adequate and quality personnel, QMS competencies, knowledge management, ICT, workspace, communication and awareness of QMS implementation. Procedures should be revised to ensure that they are effective and increase efficiency in their implementations.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.8 Operation	Process approach focused on the regulatory products and services and on NRA quality objectives	To identify gaps for QMS implementation, NRAs should review the consistency in the conduct of technical and administrative activities in providing products, services and operational interfaces or linkages among processes that contribute to the same product, service or quality objective. Where gaps exist, procedures should be implemented to ensure consistency and operational linkages of processes.	NRAs should review the records from technical and administrative units and locations, to identify gaps in the implementation of existing procedures. RCA should be performed, and measures should be put in place to ensure full implementation of procedures across all affected units and locations.	NRAs should review and identify gaps in the effectiveness and efficiency of the implemented procedures and quality systems in facilitating the provision of products and services that meet requirements and support the achievement of the objectives. Procedures and systems should be revised to ensure that they are effective and increase efficiency in the processes for providing products and services, and for supporting the achievement of NRA objectives.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.9 Performance evaluation	M&E framework with performance indicators for: • products and services requirements • quality objectives • customer complaints • QMS • resources (human, financial, ICT, equipment and infrastructure) • risk and opportunity management	NRAs should review and determine gaps in consistency in the M&E activities across all units and locations for QMS implementation. Where gaps in consistency are identified, procedures should be implemented to ensure that all M&E of performance indicators is done consistently across different units and locations of NRAs.	NRAs should review and identify gaps in the level of implementation of existing procedures and systems of the QMS for the M&E framework. RCA should be done to inform revised measures for the implementation of procedures and systems across all affected NRA units and locations.	NRAs should review and identify gaps in the effectiveness and efficiency of the implemented QMS procedures and systems used for M&E. These procedures and systems should be evaluated to ensure that their output provides evidence that is useful for planning of continuous improvements. Where gaps exist, NRAs should revise the procedures and systems to ensure that they are more effective and efficient in supporting M&E of performance indicators across all units and locations of the organizations.

Table A13.3 *continued*

Guideline section	Existing system	Stage 1 (non-existing QMS)	Stage 2 (existing QMS without implementation)	Stage 3 (ineffective implementation of QMS)
		Needed documents for consistency	Implemented evidence (by records, reports)	Effectiveness and efficiency
5.2.10 Improvement	Evidence-based improvements	NRAs should review and identify gaps in the consistency of handling and prioritization of improvements across the entire organization. Where there are inconsistencies, procedures should be implemented to ensure that all proposals for improvements are submitted with evidence and evaluated with respect to priorities and availability of resources. Procedures for improvement should define responsibilities and authorities for handling, planning and implementation of improvements.	NRAs should review and identify gaps in levels of implementation of QMS procedures for handling and implementing improvements across all units and locations of the organization. Where gaps are identified, RCA should be done with revised measures for the implementation of the procedures.	NRAs should review and identify gaps in the effectiveness and efficiency of the procedures in facilitating timely implementation of improvements. Procedures should be revised to ensure that they are more effective and efficient in facilitating timely implementation of improvements.

HR: human resources; ICT: information and communication technology; IT: information technology; M&E: monitoring and evaluation; NRA: national regulatory authority; QMS: quality management system; RCA: root cause analysis; SOP: standard operating procedure.

6.4 Quality management system development and implementation roadmap

The QMS roadmap for NRAs will depend on the respective stages of implementation. The roadmap will be used to identify activities to be done; required resources; competencies of personnel; responsibilities and authorities; timelines (time frame); and prioritization based on the needs of the NRA with respect to the regulatory products and services as mandated by national laws and regulations. Table A13.4 summarizes the steps in the development and implementation roadmap for QMS.

Table A13.4
Development of quality management system implementation roadmap

Steps	Activity	Responsible
1	Assign resources (personnel, financial, equipment and infrastructure).	Top management
2	Use Table A13.3 and results from self-benchmarking to determine the status of the QMS and submit report to top management, noting activities and areas that require actions.	Assigned staff/ consultant
3	Prioritize activities based on availability of resources (internal and external); risks of non-implementation; and regulatory products and services, as mandated by national laws and regulations.	Top management
4	Allocate responsibilities and authorities with timelines for development, review, approval, implementation, and monitoring and evaluation of prioritized QMS requirements.	Top management and assigned staff/ consultant
5	Validate the prioritization of QMS requirements, timelines, responsibilities and authorities with NRA staff, through collection of input and feedback to promote ownership of QMS implementation.	Top management and assigned staff/ consultant
6	Consolidate the feedback and input into an activity/ action plan, as a roadmap for QMS implementation for the NRA.	Assigned staff/ consultant
7	Integrate the QMS roadmap (activity/action plan) into the NRA organizational activity/action plans, the NRA strategic plans, and the ministry of health strategic plan/policy, as applicable.	Top management

NRA: national regulatory authority; QMS: quality management system.

6.5 Activity plan for quality management system implementation

Appendix 1 provides a typical action plan for the systematic development and implementation of a QMS. The plan provides a linkage between the section/subsections of this guideline and includes examples of documents and records to be established to demonstrate adequate implementation of the QMS.

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Appendix 1

References to the *WHO Global Benchmarking Tool*, revision VI

The *WHO Global Benchmarking Tool* (GBT) (*4*) is used to assess the level of implementation of a quality management system (QMS) in a national regulatory authority (NRA). The QMS indicator, RS05, consists of 14 subindicators that are used to identify the degree of QMS implementation and the existing gaps across the NRA.

Subsection in QMS guideline	GBT VI – QMS subindicators (*4*)	Related GBT VI subindicators (*4*)
5.2.1 Introduction	RS05.06	
5.2.2 Scope of the QMS	RS05.02	RS01.01, RS01.02 VL01.01 MA01.01 MC01.01 LI01.01 RI01.01 LT01.01 CT01.01 LR01.01
5.2.3 Organizational context of the NRA	RS05.06, RS05.08	RS02.04, RS03.04, RS07.04
5.2.4 Leadership, management and organization	RS05.01, RS05.02, RS05.03, RS05.04	RS02.01, RS04.01 VL02.01, VL03.02 MA02.01, MA03.02 MC02.01, MC03.02 LI02.01, LI03.02 RI02.01, RI03.02 LT02.01, LT04.02 CT02.01, CT03.02, CT04.04 LR03.02

Table *continued*

Subsection in QMS guideline	GBT VI – QMS subindicators (*4*)	Related GBT VI subindicators (*4*)
5.2.5 Document and data management	RS05.07	RS01.04, RS01.05, RS01.08, RS09.06, RS09.08 VL03.04, VL04.01, VL04.02, VL04.03 MA03.04, MA04.01, MA04.02, MA04.03, MA04.10, MA05.02, MA06.01 MC03.04, MC04.01, MC04.02, MC04.03, MC04.05, MC04.07, MC04.08, MC05.01, MC05.02 LI03.04, LI04.01, LI05.01, LI06.01 RI03.04, RI04.01, RI04.02, RI04.04, RI04.05, RI04.06, RI05.01, RI05.02 LT03.02, LT03.04, LT04.04, LT06.02, LT06.03, LT08.01 CT03.04, CT04.05, CT04.06, CT04.07, CT06.01 LR01.02, LR03.04, LR04.03
5.2.6 Planning	RS05.02	RS03.03, RS04.05 VL04.04, VL04.08 MA01.12, MA04.06, MA04.07, MA06.02 MC04.04, MC05.03 LI04.03, LI05.02 RI04.03, RI05.05 LT03.01, LT08.04 CT06.02, CT06.04 LR06.04
5.2.7 Support and resources	RS05.04, RS05.14	RS02.02, RS06.01, RS06.02, RS08.01, RS08.02, RS08.03, RS09.03, RS09.07, RS09.09 VL02.02, VL03.01, VL03.02, VL03.03, VL06.01, VL06.02, VL06.03 MA02.02, MA03.01, MA03.03, MA05.01, MA05.03, MA05.04 MC02.02, MC03.01, MC03.03, MC06.01, MC06.02, MC06.03 LI02.02, LI03.01, LI03.03, LI06.02 RI02.02, RI03.01, RI03.03, RI06.01, RI06.02, RI06.03, RI06.04 LT03.03, LT04.01, LT04.03, LT05.01, LT05.02, LT06.05, LT07.01, LT09.01, LT09.02, LT09.03 CT02.02, CT03.01, CT03.03, CT05.02 LR02.02, LR03.01, LR03.03, LR05.01, LR05.02, LR06.01

Table *continued*

Subsection in QMS guideline	GBT VI – QMS subindicators (*4*)	Related GBT VI subindicators (*4*)
5.2.8 Operation	RS05.06, RS05.09	RS02.03, RS04.02, RS04.03, RS06.03, RS06.04, RS09.05, RS09.07 VL04.05, VL04.06, VL04.07 MA01.09, MA01.10, MA01.11, MA01.13, MA04.05, MA04.08, MA04.09, MA04.10 MC01.06, MC01.07 LI01.04, LI04.02, LI04.04 RI01.04, RI05.03 LT02.02, LT06.01, LT06.04, LT10.01 CT01.09, CT01.10, CT04.01, CT04.02, CT04.03, CT05.01 LR04.01, LR04.02
5.2.9 Performance evaluation	RS05.10, RS05.11, RS05.12, RS05.13	RS01.09, RS10.01, RS10.02 VL05.02 MA04.06, MA06.02 MC04.06, MC05.03 LI05.02 RI05.04, RI05.05 LT08.02, LT08.03, LT08.04 CT06.02, CT06.04 LR06.02, LR06.04
5.2.10 Improvement	RS05.05	LR06.02

GBT: *WHO Global Benchmarking Tool* (*4*); NRA: national regulatory authority; QMS: quality management system.

Appendix 2

Activity plan for quality management system implementation

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
1.	Appointment of QMS focal person(s) or lead(s)	5.2.4.3	Official letters of appointment with defined responsibilities and authorities in the QMS	Head of the NRA
2.	QMS focal person(s) understands the QMS requirements	5.2.7.2	• Competency matrix for QMS focal person(s)/ lead(s) • Training plans for competency gaps in QMS implementation • Training records of QMS focal person(s)/lead(s) • Training/orientation records in development and implementation of QMS documents (quality manual, standard operating procedures and/or forms and templates)	Top management
3.	QMS focal person(s)/lead(s) conducts a gap analysis of the current system based on Tables A13.3 and A13.4 of the guideline and develops a QMS action plan (as part of the strategic plan)	6.1	• Documented gap or situation analysis report • Documented roadmap with resources, timelines and responsibilities (part of NRA strategic and action plans)	• Top management • QMS focal person(s)/ lead(s)

Table *continued*

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
4.	QMS focal person(s)/lead(s) conduct(s) orientation and awareness sessions for NRA employees on QMS development and implementation (with roles and responsibilities)	5.2.7.5	Accessible and available QMS orientation and awareness sessions records and materials in appropriate format	QMS focal person(s)/ lead(s)
5.	• Establishment of NRA current context (SWOT analysis), if already available • Determination of the comprehensiveness of the legal provisions (Acts and regulations) in describing interested parties relevant to the QMS • Identification of QMS processes, sequences, linkages and interdependencies • Determination of the scope of the QMS and relationships of its processes	5.2.3.1	• Documented official organizational chart covering NRA governance and top management and internal and external operational relationships • Documented description of internal and external issues, including SWOT analysis of the NRA (with defined customers and stakeholders based on legal provisions) • Documented description of internal and external customers and stakeholders, with their respective needs and expectations (if not adequately described in the national legislations) • Documented statement of scope for the QMS • Documented flowcharts, process maps and their operational linkages for all processes under the scope of the QMS, with related products and services	• Top management • QMS focal person(s)/ lead(s)

Table *continued*

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
6.	Documentation of a quality policy within the context and strategic direction of the NRA	5.2.4.2	Documented, accessible (publicly) and available quality policy understood by NRA staff	• Top management • QMS focal person(s)/ lead(s)
7.	Use information from step 5 above, as input, to determine risks and opportunities and develop risk and opportunity management plans	5.2.6.2	• Documented and controlled registry of assessed and categorized risks and opportunities (from SWOT analysis) • Risk and opportunity responsibility matrix (based on responsible, accountable, consulted and informed [RACI] principles)	• Top management • QMS focal person(s)/ lead(s)
8.	Development and documentation of SMART quality objectives, including a plan for M&E with related required resources	5.2.4.2	Documented quality objectives (and their short- and long-term targets), resources, responsibilities (ideally in NRA's strategic plan) and M&E indicators	Top management

Table *continued*

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
9.	Development of new or harmonization with existing procedures for control of measuring equipment, organizational knowledge management, personnel training and communication	5.2.7.4	Documented and implemented procedures for: • staff recruitment (based on a defined competency framework for different levels and positions), training and retraining based on established gaps as per organizational competency framework • management and maintenance of measuring equipment, as applicable in making regulatory decisions (laboratory and/or inspection equipment) • management of organizational knowledge (e.g. retirements, resignations and new knowledge acquisition) • management of internal and external communication of regulatory decisions, products, services and other engagements with customers and stakeholders • use of IT in technical and administrative processes, including management of templates used in the software or equipment or in other procedures needed to manage resources as described in the guideline	• Top management • QMS focal person(s)/ lead(s)

Table *continued*

Step	Activity	Subsection of QMS guideline	Recommendations of documents and records to be established	Responsibility within the NRA
10.	Development of new or harmonization with existing procedures for all processes in technical and administrative units of the NRA	5.2.8	Documented and implemented procedures for all applicable technical and administrative processes within the NRA and that contain the appropriate level of detail based on the complexity of the processes and associated risks. The procedures should address all activities that are involved in provision of products and services as mandated by national legislations	• Top management • QMS focal person(s)/ lead(s)
11.	Development of procedures for monitoring of customer satisfaction, internal audit, management review and complaints handling, and put them into practice	5.2.9	• Documented and implemented procedures for customer complaints and satisfaction, along with publications of guidance to the public on the procedures and communication • Documented and implemented internal audit programmes • Documented and implemented regular reviews of QMS implementation and performance by top management	• Top management • QMS focal person(s)/ lead(s)
12.	Development of procedures for corrections, corrective actions and improvements, and put them into practice	5.2.10	Documented and implemented procedures for corrective actions and change management, along with a link for updating risk and opportunity management plans	• Top management • QMS focal person(s)/ lead(s)

IT: information technology; M&E: monitoring and evaluation; NRA: national regulatory authority; QMS: quality management system; SMART: specific, measurable, attainable, realistic and time-bound; SWOT: strengths, weaknesses, opportunities and threats.

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, ninth edition.
2019 (USB keys and online)

Quality Assurance of Pharmaceuticals. WHO guidelines, good practices, related regulatory guidance and GXP-training materials
Updated, comprehensive edition, 2019 (USB keys and online)

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Fifty-third report.
WHO Technical Report Series, No. 1019, 2019 (xiv + 303 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 (including the 21st WHO Model List of Essential Medicines and the 7th WHO Model List for Children),
WHO Technical Report Series, No. 1021, 2019 (xxxviii + 639 pages)

WHO Expert Committee on Biological Standardization
Sixty-ninth 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 and provision of global regulatory tools. Standards are developed by the Expert Committee through worldwide consultation and an international consensus-building process. The following new guidelines were adopted and recommended for use:

Procedure for the elaboration, revision and omission of monographs and other texts for The International Pharmacopoeia; *International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceuticals*; *Production of water for injection by means other than distillation*; *Good chromatography practices*; *Quality management system requirements for national inspectorates*; *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance*; *Good storage and distribution practices for medical products*; *Points to consider for setting the remaining shelf-life of medical products upon delivery*; *World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices*; *World Health Organization/United Nations Population Fund technical specifications for male latex condoms*; *World Health Organization/United Nations Population Fund specifications for plain lubricants*; *WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for* WHO Model List of Essential Medicines *immediate-release, solid oral dosage forms*; and *WHO guideline on the implementation of quality management systems for national regulatory authorities*.

All of the above are included in this report and recommended for implementation.

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