WHO Technical Report Series

1033

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-fifth report

World Health Organization

The World Health Organization was established in 1948 as a specialized agency of the United Nations serving as the directing and coordinating authority for international health matters and public health. One of WHO's constitutional functions is to provide objective and reliable information and advice in the field of human health, a responsibility that it fulfils in part through its extensive programme of publications.

The Organization seeks through its publications to support national health strategies and address the most pressing public health concerns of populations around the world. To respond to the needs of Member States at all levels of development, WHO publishes practical manuals, handbooks and training material for specific categories of health workers; internationally applicable guidelines and standards; reviews and analyses of health policies, programmes and research; and state-of-the-art consensus reports that offer technical advice and recommendations for decision-makers. These books are closely tied to the Organization's priority activities, encompassing diseases prevention and control, the development of equitable health systems based on primary health care, and health promotion for individuals and communities. Progress towards better health for all also demands the global dissemination and exchange of information that draws on the knowledge and experience of all WHO's Member countries and the collaboration of world leaders in public health and the biomedical sciences. To ensure the widest possible availability of authoritative information and guidance on health matters, WHO secures the broad international distribution of its publications and encourages their translation and adaption. By helping to promote and protect health and prevent and control disease throughout the world, WHO's books contribute to achieving the Organization's principal objective – the attainment by all people of the highest possible level of health.

The *WHO Technical Report Series* makes available the findings of various international groups of experts that provide WHO with the latest scientific and technical advice on a broad range of medical and public health subjects. Members of such expert groups serve without remuneration in their personal capacities rather than as representatives of governments or other bodies; their views do not necessarily reflect the decisions or the stated policy of WHO. To purchase WHO publications, please contact: WHO Press, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel. +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int; http://www.who.int/bookorders).

WHO Technical Report Series
1033

WHO Expert Committee on Specifications for Pharmaceutical Preparations

Fifty-fifth report

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

World Health Organization

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

(WHO Technical Report Series, No. 1033)

ISBN 978-92-4-002090-0 (electronic version)
ISBN 978-92-4-002091-7 (print version)

ISSN 0512-3054

Contents

Abbreviations vi

WHO Expert Committee on Specifications for Pharmaceutical Preparations x

Declarations of interest xvi

OPEN SESSION 1

Introduction and welcome 1

I. Expert Committee on Specifications for Pharmaceutical Preparations processes and procedures 1

II. Update on new guidelines, norms and standards 2

III. Technical agenda topics of the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations 2

IV. Points of discussion 3

PRIVATE AND CLOSED SESSIONS 5

Opening 5

1. General policy 7

1.1 Process for development of WHO norms and standards 7

2. Quality assurance: collaboration initiatives 8

2.1 International Meeting of World Pharmacopoeias 8

3. Nomenclature, terminology and databases 9

3.1 International nonproprietary names for pharmaceutical substances 9

3.2 Quality assurance terminology 10

3.3 Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations 10

4. Quality control – national laboratories 11

4.1 External Quality Assurance Assessment Scheme 11

4.1.1 Final report on phase 9 11

4.1.2 Update on phase 10 12

5. Quality control – specifications and tests 13

5.1 *The International Pharmacopoeia* 13

5.2 General chapters 13

5.2.1 Dissolution test for oral dosage forms 13

5.2.2 General identification tests 14

5.2.3 Test for histamine-like substances 14

5.3 General monographs for dosage forms 15

5.3.1 Powders for inhalation 15

5.3.2 Liquid preparations for oral use 15

5.4 Specifications and draft monographs for medicines, including paediatric medicines, and candidate medicines for COVID-19 16

5.4.1 COVID-19 therapeutics 16

5.4.2 Antiviral medicines, including antiretrovirals 17
5.4.3 Medicines for tropical diseases 18
5.4.4 Medicines for maternal, newborn, child and adolescent health 19
5.4.5 Excipients 20
5.5 Update on the virtual informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines 20

6. Quality control: international reference materials 22
6.1 Update on International Chemical Reference Substances 22

7. Quality assurance: good manufacturing practice and inspection 23
7.1 Inspection guidelines and good practices with partner organizations 23
7.1.1 Revision of good manufacturing practices for sterile products 23
7.1.2 Good manufacturing practices for radiopharmaceuticals for investigational use 23
7.2 Approaches to carryover limits in cleaning validation 24
7.3 Water for pharmaceutical use 25
7.4 Guideline on data integrity 26
7.5 Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance 27
7.6 Recommendations from the virtual consultation on good practices for health products and inspection 29

8. Quality assurance: distribution and supply chain 30
8.1 Shelf life for supply and procurement of medical products 30
8.1.1 Revision to the guideline on remaining shelf life 30
8.2 Updated and new WHO guidance, procedures and operational documents for pharmaceutical procurement 31
8.2.1 World Health Organization/United Nations Population Fund prequalification guidance on condoms 31

9. Regulatory guidance and model schemes 33
9.1 Proposal to waive in vivo bioequivalence requirements for medicines on the *WHO Model List of Essential Medicines* 33
9.2 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce 36
9.3 Good practices in regulatory decision-making 38
9.3.1 Good reliance practices in the regulation of medical products 38
9.3.2 Good regulatory practices in the regulation of medical products 39
9.4 Update on WHO-listed authorities 40
9.5 Recommendations from the virtual consultation on Regulatory Guidance for Multisource Products 41

10. Miscellaneous: update on activities related to COVID-19 43
10.1 Oxygen specifications 43
10.2 Therapeutic specifications 43
10.3 Existing guidance 44
10.4 New activities 44

11. Closing remarks 45

12. Summary and recommendations 46

12.1 Guidelines and decisions adopted and recommended for use 47
12.2 Texts adopted for inclusion in *The International Pharmacopoeia* 47
12.3 Recommendations 49

Acknowledgements 52

References 71

Annex 1

Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations 75

Annex 2

Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation 93

Annex 3

Good manufacturing practices: water for pharmaceutical use 111

Annex 4

Guideline on data integrity 135

Annex 5

World Health Organization/United Nations Population Fund Recommendations for condom storage and shipping temperatures 161

Annex 6

World Health Organization/United Nations Population Fund Guidance on testing of male latex condoms 167

Annex 7

World Health Organization/United Nations Population Fund guidance on conducting post-market surveillance of condoms 189

Annex 8

WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for *WHO Model List of Essential Medicines* immediate-release, solid oral dosage forms 197

Annex 9

Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce 205

Annex 10

Good reliance practices in the regulation of medical products: high level principles and considerations 237

Annex 11

Good regulatory practices in the regulation of medical products 269

Abbreviations

ACT	Access to COVID-19 Tools
ALCOA	attributable, legible, contemporaneous, original and accurate
AMR	antimicrobial resistance
API	active pharmaceutical ingredient
AQL	acceptance quality level
AUC	area under the curve
BCS	Biopharmaceutics Classification System
BE	bioequivalence
BMDL	benchmark dose level
BPW	bulk purified water
BWFI	bulk water for injection
CAPA	corrective and preventive action
CpK	process capability (*also saved under P*)
CPP	certificate of a pharmaceutical product
DABT	Diplomate of the American Board of Toxicology
DIRA	data integrity risk assessment
EAP	WHO Expert Advisory Panel on *The International Pharmacopoeia* and Pharmaceutical Preparations
ECSPP	Expert Committee on Specifications for Pharmaceutical Preparations
EDI	electro-deionization
EDQM	European Directorate for the Quality of Medicines & HealthCare
ERT	European Registered Toxicologist
EQAAS	WHO External Quality Assurance Assessment Scheme
EMA	European Medicines Agency
EML	*WHO Model List of Essential Medicines*
EU	European Union
FAT	factory acceptance test

FEFO	first expiry-first out
FPP	finished pharmaceutical product
GBT	Global Benchmarking Tool
GCP	good clinical practice
GDP	good distribution practices
GLP	good laboratory practices
GMP	good manufacturing practices
GRP	good regulatory practices
GRelP	good reliance practices
GTDP	good trade and distribution practices
GVP	good pharmacovigilance practices
GxP	good practices
HBEL	health-based exposure limit
HPLC	high-performance liquid chromatography
HPS	Health Products Policy and Standards (WHO department)
HVAC	heating, ventilation and air-conditioning
IAEA	International Atomic Energy Agency
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICRS	International Chemical Reference Substances
IEC	International Electrotechnical Commission
IMP	investigational medical products
IMWP	International Meeting of World Pharmacopoeias
INN	International Nonproprietary Names
IQ	installation qualification
ISO	International Organization for Standardisation
LOAEL	lowest observed adverse effect level
LOEL	lowest observed effect level
MHRA	Medicines & Healthcare Products Regulatory Agency
MKT	mean kinetic temperature

MSC	maximum safe carryover
MSSR	maximum safe surface residue
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NSP	Norms and Standards for Pharmaceuticals (WHO team)
NRA	national regulatory authority
OEL	occupational exposure limit
OQ	operational qualification
PDE	permitted daily exposure
PDG	Pharmacopoeial Discussion Group
PIC/S	Pharmaceutical Inspection Co-operation Scheme
PDG	Pharmacopoeial Discussion Group
PQ	performance qualification
PQ	WHO Prequalification (WHO team)
PQCL	pharmaceutical quality control laboratory
PQTm	Prequalification of Medicines Team (WHO team)
CpK	process capability
PVDC	polyvinylidene chloride
PVDF	polyvinylidene difluoride
Q&A	question and answer
QA	quality assurance
QRM	quality risk management
QSE	quality, safety and efficacy
R&D	research and development
RO	reverse osmosis
RSS	Regulatory System Strengthening (WHO team)
SAT	site acceptance test
SOP	standard operating procedure
SRA	stringent regulatory authority
SPC	statistical process control

SPC	summary of product characteristics
TLC	thin-layer chromatography
TOC	total organic carbon
TRS	Technical Report Series
UN	United Nations
UNFPA	United Nations Population Fund
URS	user requirement specifications
VRL	visible residue limit
WFI	water for injection
WHO	World Health Organization
WLA	WHO-listed authorit
WPU	water for pharmaceutical use

WHO Expert Committee on Specifications for Pharmaceutical Preparations

The open session of the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations was coordinated from WHO headquarters, Geneva, and took place virtually on 6 October 2020

Participants[1]

Mr Baba Aye, Health and Social Sector Officer, Public Services International, Washington DC, United States of America (USA)

Ms Jane Barratt, Secretary-General, International Federation on Ageing, Toronto, Canada

Ms Janis Bernat, Director, Biotherapeutics and Scientific Affairs, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland

Ms Iris Blom, Liaison Officer to the World Trade Organization, International Federation of Medical Students' Associations, Copenhagen, Denmark

Dr Nick Cappuccino, Chair, Science Committee, International Generic and Biosimilar Medicines Association, Geneva, Switzerland

Ms Kelly Catlin, Director, Quality, Sourcing, Cost Optimization and Process Chemistry, Clinton Health Access Initiative, Boston (MA), USA

Professor Kostas Fountoulakis, World Psychiatric Association, Thessaloniki, Greece

Mr Shalini Jayasekar Zürn, Senior Advocacy Manager, Union for International Cancer Control, Geneva, Switzerland

Ms Padma Kamath, Director, Regulatory and Scientific Affairs, Global Self-care Federation, Nyon, Switzerland

Ms Marion Laumonier, Senior Advisor, Regulatory Affairs, Drugs for Neglected Diseases Initiative, Geneva, Switzerland

Dr Joanna Laurson-Doube, International Consultant, Access to Treatment, Multiple Sclerosis International Federation, London, United Kingdom of Great Britain and Northern Ireland (United Kingdom)

Dr Dong Soo Lee, President, World Federation of Nuclear Medicine and Biology, Vienna, Austria

Ms Isabel Lucas-Manzano, International Pharmacist Coordinator, Médecins Sans Frontières, Geneva, Switzerland

[1] Unable to connect: Mr Herbert Beck, Senior Advisor, Public Services International, Washington DC, USA; and Professor William Carroll, Strategy and Programme Director, World Federation of Neurology, London, (United Kingdom).

Mr Andrew Majewski, Senior Associate Director, Task Force for Global Health, Decatur (GA), USA

Mr Marco Marchetti, Health Technology Assessment International, Alberta, Canada

Dr Kevin Moore, Senior Manager, Pharmacopoeial Collaboration, US Pharmacopeia, Rockville (MD), USA

Dr Rui Nakamura, World Medical Association Inc., Ferney-Voltaire, France

Dr Lila Raj Puri, Medical Advisor – Asia, The Fred Hollows Foundation, Sydney, Australia

Dr Roxana Rustomjee, Senior Vice-President, Research and Development, Sabin Vaccine Institute, Washington DC, USA

Mr Paul L. Smock, Senior Quality, QA and CMC Oversight, Sabin Vaccine Institute, Washington DC, USA

Dr Valérie Solbes, Pharmacy Quality Advisor, Médecins du Monde, Paris, France

Ms Judy Stenmark, Director-General, Global Self-Care Federation, Nyon, Switzerland

Ms Malyika Vyas, Head of Public Policy, European Society for Medical Oncology, Lugano, Switzerland

The main session of the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations was coordinated from WHO headquarters, Geneva, and took place virtually from 12-19 October 2020

Members

Dr Habib Abboud, Damascus, Syrian Arab Republic

Dr Varley Dias Sousa, Brasília, Brazil

Dr Petra Dörr, Bern, Switzerland (*Chair*)

Professor Ines Fradi Dridi, Monastir, Tunisia

Mr Johannes Gaeseb, Windhoek, Namibia

Ms Mónica Hirschhorn, Montevideo, Uruguay

Professor Eliangiringa Amos Kaale, Dar es Salaam, United Republic of Tanzania (*Rapporteur*)

Dr Adrian Krauss, Canberra, Australia (*Co-Chair*)

Dr Min Yong Low, Singapore

Dr Justina Molzon, Bethesda (MD), USA

Mrs Lynda M. Paleshnuik, Ottawa, Canada

Dr Lembit Rägo, Tartu, Estonia

Dr Budiono Santoso, Yogyakarta, Indonesia

Dr Daisaku Sato, Tokyo, Japan

Dr G.N. Singh, Ghaziabad, India

Dr Luisa Stoppa, Rome, Italy (*Rapporteur*)

Dr Jinglin Sun, Beijing, China

Dr Adriaan J. Van Zyl, George, South Africa

Technical advisers[2]

Professor Erwin Adams, Leuven, Belgium

Professor Maria Del Val Bermejo Sanz, Valencia, Spain

Dr Rubina Bose, New Delhi, India

Dr Marius Brits, Potchefstroom, South Africa

Dr Theo G. Dekker, Potchefstroom, South Africa

Dr Dimitrios Dimas, Athens, Greece

Dr Alfredo Garcia-Arieta, Madrid, Spain

Dr Sunday Kisoma, Dar es Salaam, United Republic of Tanzania

Ms Heeyoung Park, Chungcheongbuk-do, Republic of Korea

Ms Gugu Nolwandle Mahlangu, Harare, Zimbabwe

Professor John H. McB. Miller, Ayr, United Kingdom

Dr Jochen Norwig, Bonn, Germany

Professor Giovanni M. Pauletti, Ohio, USA

Dr Celeste Aurora Sánchez González, Havana, Cuba

Professor Gerhard Scriba, Jena, Germany

Dr Mingzhe Xu, Beijing, China

Representation from intergovernmental organizations[3]

Council of Europe
represented by Dr Andrea Lodi, European Pharmacopoeia, Strasbourg, France

[2] Unable to attend: Professor Asita De Silva, Colombo, Sri Lanka; Ms Anne Hayes, Dublin, Ireland; Ms Togi Junice Hutadjulu, Jakarta, Indonesia; Dr Rodrigo Martins Bretas, Brasília, Brazil; Dr Richard Rukwata, Harare, Zimbabwe; and Dr Abdelaali Sarakha, Saint Denis, France.

[3] Unable to attend: European Commission (EC), Brussels, Belgium; European Medicines Agency (EMA), Amsterdam, Netherlands; World Bank Group, Washington DC, USA; World Intellectual Property Organization (WIPO), Geneva, Switzerland; and World Trade Organization (WTO), Geneva, Switzerland.

International Atomic Energy Agency (IAEA)
Dr Aruna Korde, Radiopharmaceutical Scientist, Vienna, Austria

United Nations Development Programme (UNDP)
Dr Jean-Michel Caudron, Head of Quality Assurance, Antwerp, Belgium

United Nations Population Fund (UNFPA)
Ms Seloi Mogatle, Technical Specialist, Procurement Services Branch, Copenhagen, Denmark; Mr David Hill, David Hill & Associates, Elsenham, United Kingdom and Mr William Potter, Stapleford Scientific Services Ltd, Cambridge, United Kingdom

United Nations Children's Fund (UNICEF)
Dr Peter Svarrer Jakobsen, Quality Assurance Specialist, Copenhagen, Denmark

United Nations Industrial Development Organization (UNIDO)
Mr Wilko von Kluechtzner, Associate Industrial Development Expert, Vienna, Austria

World Customs Organization (WCO)
Ms Jingwan Chen, Secretary Customs and Border Trade Professionals, Brussels, Belgium

State actors (pharmacopoeias)[4]

Farmacopea Argentina
Dr Melina Assalone and Dr María Celeste de Angelis, Buenos Aires, Argentina

Farmacopeia Brasileira
Dr Arthur Leonardo Lopes da Silva, Health Regulatory Agency, Brasília, Brazil

British Pharmacopoeia
Ms Helen Corns, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom

Chinese Pharmacopoeia
Dr Xiaoxu Hong, Beijing, China

European Pharmacopoeia (also representing Council of Europe)
Dr Andrea Lodi, Council of Europe, Strasbourg, France

Indonesian Pharmacopoeia
Dr Togi Junice Hutadjulu and Ms Sri Hayanti, National Agency of Drug and Food Control, Jakarta, Indonesia

Japanese Pharmacopoeia
Dr Tsuyoshi Ando, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan

[4] Unable to attend: Indian Pharmacopoeia, Ghaziabad, India; and Mexican Pharmacopoeia, Mexico City, Mexico.

Pharmacopoeia of the Republic of Korea
Dr SangAeh Park and Dr Nam-Hee Kim, Ministry of Food and Drug Safety, Chungcheongbuk-do, Republic of Korea

State Pharmacopoeia of the Russian Federation
Dr Olga Gubareva and Dr Elena Kovaleva, Federal State Budgetary Institution, Moscow, Russian Federation

Pharmacopoeia of Ukraine
Dr Maryna Dmitriieva, Ministry of Health, Kharkov, Ukraine

World Health Organization[5]

Access to Medicines and Health Products (MHP)
Dr Mariângela Simão, Assistant Director-General

Health Products Policy and Standards (HPS)
Dr Clive Ondari, Director

Norms and Standards for Pharmaceuticals (NSP)
Dr Sabine Kopp, Team Lead, NSP (and Secretary of the ECSPP)
Dr Herbert Schmidt, Technical Officer
Dr Steve Estevão Cordeiro, Consultant
Ms Sinéad Jones, Administrative Assistant
Ms Claire Vogel, Office Assistant

Contraception and Fertility Care (CFC)
Dr Petrus Steyn, Scientist

Medicines Assessment (MED)
Mr Laurence Nzumbu, Technical Officer
Mr Wondiyfraw Zeleke Worku, Technical Officer
Mrs Hua Yin, Technical Officer

Prequalification (PQT)
Mr Deus Mubangizi, Coordinator
Dr Joey Gouws, Team Lead, Inspection Services
Dr Dimitrios Catsoulacos, Technical Officer
Mr Mustapha Chafai, Technical Officer
Ms Stephanie Croft, Technical Officer
Mr Vimal Sachdeva, Technical Officer
Mrs Iveta Streipa, Technical Officer

[5] Dr Matthias Stahl, Team Lead; and Dr Andrew Chemwolo, Technical Officer, Medicines Assessment.

Regulation and Safety (REG)
Mr Hiiti Sillo, Team Lead, Regulatory Systems Strengthening
Dr Alireza Khadem Broojerdi, Scientist
Mr Mohamed Refaat, Technical Officer

Regulatory Convergence and Networks (RCN)
Dr Samvel Azatyan, Team Lead, RCN
Mrs Marie Valentin, Technical Officer

Technical Standards and Specifications (TSS)
Dr Ivana Knezevic, Team Leader, Norms, Standards and Biologicals
Dr Dianliang Lei, Scientist

Report writer
Dr Sian Lewis, London, United Kingdom

Representation from WHO Regional Offices[6]

Regional Office for the Americas, Washington DC, USA
Mr Murilo Freitas

Regional Office for the Eastern Mediterranean, Cairo, Egypt
Dr Houda Langar
Dr Adi Al-Nuseirat

Regional Office for South-East Asia, New Delhi, India
Dr Manisha Shridhar

[6] Regional Office for Africa; Regional Office for Europe; and Regional Office for the Western Pacific.

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:

Dr H. Abboud, Professor E. Adams, Professor M.D.V. Bermejo Sanz, Dr M. Brits, Professor T.G. Dekker, Dr V. Dias Sousa, Dr D. Dimas, Professor I. Fradi Dridi, Dr A. García-Arieta, Mr J. Gaeseb, Ms M. Hirschhorn, Professor E.A. Kaale, Dr A. Krauss, Dr M.Y. Low, Ms G.N. Mahlangu, Professor J.H.McB. Miller, Mr S. Kisoma, Dr J. Molzon, Dr J. Norwig, Mrs L. Paleshnuik, Ms H. Park, Dr L. Rägo, Dr C.A. Sánchez González, Dr B. Santoso, Dr D. Sato, Professor G. Scriba, Dr G.N. Singh, Dr R. Bose, Dr L. Stoppa, Dr J. Sun and Dr M. Xu reported no conflict of interest.

Dr P. Doerr reported that she provided consultancy services to the Bill and Melinda Gates Foundation in 2019 and 2020. This disclosure does not constitute a conflict of interest, as the Foundation does not manufacturer any product relevant to the topic of the meeting.

Professor G.M. Pauletti declared that he had presented collaboration with WHO and the outcome of a WHO project to the International Pharmaceutical Federation, a non-State actor in official relations with WHO. This does not present a conflict of interest for this meeting.

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

OPEN SESSION

The open session was attended by ECSPP members and 23 non-State actors.

Due to the pandemic of COVID-19, the open session of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) meeting was held virtually, prior to the private and closed sessions, on 6 October 2020.

Introduction and welcome

Dr Clive Ondari, Director, Health Products Policy and Standards (HPS), welcomed participants to the open session for stakeholders and said that ECSPP's aim was to provide information in a transparent way. He highlighted the value of in-person interactions achieved in open sessions, even if they are virtual.

Dr Ondari introduced ECSPP's standard-setting work which covers quality assurance, regulatory guidance and good practices related to medicines, the WHO model scheme and quality control specifications.

The first ECSPP was convened in 1947, and its recommendations are relevant for many parts of WHO, from country and regional offices to other expert committees and partnerships. As its decisions affect the quality of widely used medicines, the Expert Committee serves not only WHO Member States but also many programmes within WHO and other international organizations.

I. Expert Committee on Specifications for Pharmaceutical Preparations processes and procedures

Dr Sabine Kopp, Team Lead, Norms and Standards for Pharmaceuticals (NSP) and Secretary of the Expert Committee, briefly described ECSPP processes and procedures.

Like all WHO expert committees, the ECSPP is governed by strict rules and procedures which are set out in the WHO Basic Documents. Members of the ECSPP are selected from the WHO Expert Advisory Panel on *The International Pharmacopoeia* and Pharmaceutical Preparations (EAP) on the basis of their education, background and experience; and following an official nomination process.

The Expert Committee meets once a year to review NSP's ongoing work on quality assurance and control. All norms, standards and guidelines reviewed by the ECSPP are developed in consultation with the EAP and a wide range of national and international partners, including national authorities, international organizations, non-State actors, EAP members, specialists, WHO collaborating centres, pharmacopoeial authorities and regional and interregional

regulatory groups. All texts are also issued for public comment. If the Expert Committee decides that more work is required, the document returns for consultation. If it decides that a consensus has been reached, the guideline is adopted and published as an annex to the Expert Committee's meeting report where it becomes WHO technical guidance. The report is then presented by the WHO Director-General to WHO Member States for implementation.

Dr Kopp emphasized the importance of the ECSPP's work in developing robust international norms and standards to support a global approach to dossier submissions and inspections of manufacturers; standardize critical information for procurers; promote convergence and collaboration among national regulatory authorities (NRAs); and enable patients to access safe and effective medicines.

For more information on the ECSPP's role in developing WHO norms and standards, see section 1.1.

II. Update on new guidelines, norms and standards

Dr Kopp introduced the latest guidelines, norms and standards adopted by the ECSPP which were published in the Expert Committee's fifty-fourth meeting report. These include[7]:

- 13 new and revised general medicines quality assurance and regulatory guidance texts;
- 13 new and revised specifications for active substances and specific dosage forms;
- 2 new and revised general chapters in *The International Pharmacopoeia*; and
- 6 new International Chemical Reference Substances (ICRS).

III. Technical agenda topics of the Fifty-fifth Expert Committee on Specifications for Pharmaceutical Preparations

The WHO Secretariat to the ECSPP summarized the topics on the agenda of the Fifty-fifth ECSPP meeting and provided:

- a brief update on WHO's latest activities to support quality assurance, regulatory guidance and technical specifications of pharmaceuticals related to COVID-19 (section 10);
- an overview of *The International Pharmacopoeia*, which provides analytical methods and specifications for active pharmaceutical

[7] WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 5 October 2020).

ingredients (APIs), finished pharmaceutical products (FPPs), excipients and radiopharmaceuticals (section 5.1);

- a list of monographs and other pharmacopoeial texts in development (sections 5 and 6);
- a short summary of draft guidance on good manufacturing practices and inspection, including on water for pharmaceutical use, and the inclusion of health-based exposure limits in cleaning validation (section 7);
- a list of key regulatory guidance texts to be discussed by the ECSPP, including an update on the policy for, and definition of, WHO-listed authorities (WLAs) (section 9);
- an overview of the WHO Biowaiver Project, including what it does, how it works and its latest results (section 9.1); and
- a brief review of the guidance being developed in collaboration with international partners, including the European Union (EU), the European Medicines Agency (EMA) and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) (section 7.1.1), the International Atomic Energy Agency (IAEA) (section 7.1.2) and the United Nations Population Fund (UNFPA) (section 8.2).

Dr Kopp emphasized WHO's commitment in providing a coherent approach to setting norms and standards and supporting their implementation so that all Member States benefit from them. The Organization strives to ensure that all its norms and standards are globally applicable and that they address the real needs of Member States.

IV. Points of discussion

Dr Ondari invited the participants in the open session to raise queries or comments about the ECSPP's work and the proposed agenda for the Expert Committee's Fifty-fifth meeting. The three main topics of discussion are summarized below.

- **The scope and remit of ECSPP.** Asked about the role of the ECSPP in setting standards for herbal medicines, Dr Kopp confirmed that the ECSPP provides guidance on the collection and processing of plant materials used for medicines and on their production and quality control. The WHO Secretariat works with the WHO Department of Traditional, Complementary and Integrative Medicine to ensure that the guidance is relevant and welcomes suggestions for new or updated guidance as necessary (*1 – 6*).

- **The accessibility of ECSPP's work.** Participants expressed their support for the ECSPP and for the open session in raising awareness and understanding of the Expert Committee's work. They suggested, however, that the ECSPP could improve access to its work by making its working documents more visible and by indicating how users could find adopted guidance. The WHO Secretariat confirmed that work is underway to address both these concerns. A new website is in development that will enable stakeholders to sign up for email alerts when a new working document is published. An index of all adopted guidelines is also in development (section 3.3).
- **ECSPP and COVID-19 activities.** When asked how non-State actors could support the ECSPP in strengthening the Access to COVID-19 Tools (ACT) Accelerator initiative, the WHO Secretariat stressed the importance of advocacy, widespread promotion of relevant guidance and pharmacopoeial texts and feedback on further guidance required. One participant asked whether more monographs relevant to COVID-19 were planned. The WHO Secretariat answered that as soon as any new or repurposed medicine has been approved for use against COVID-19, ECSPP would prepare a monograph, if one is not publicly available in other pharmacopoeias. The WHO Secretariat also said that any information that becomes available for a COVID-19-related monograph would be shared with stakeholders through the usual channels.

This concluded the open session.

PRIVATE AND CLOSED SESSIONS

The private and closed sessions were attended by ECSPP members, technical advisers, international organizations and State actors.

The Fifty-fifth meeting of the ECSPP was held on 12–19 October 2020. Due to the COVID-19 pandemic, the meeting was held virtually by Cisco Webex. To maximize the efficiency of this online format, some agenda items were covered by correspondence prior to the online sessions.

Opening

The meeting was officially opened by Dr Mariângela Simão, Assistant Director-General, Access to Medicines and Health Products, on behalf of WHO Director-General, Dr Tedros Adhanom Ghebreyesus.

After welcoming all participants to the meeting, Dr Simão gave recognition to the enormous pressure on scientists and health professionals, as well as politicians, as they strive to bring COVID-19 under control. She described the range of activities that WHO is undertaking to support the global effort, including: establishing an independent panel to review global and national pandemic responses; collating and publishing daily data on the number of confirmed cases and deaths per country and region in an online dashboard; producing weekly epidemiological and operational updates; developing country and technical guidance; providing advice for the public; and leading numerous initiatives to accelerate research and development of diagnostics, vaccines and therapeutics, including the international Solidarity trial to collect robust data from around the world on the most effective treatments for COVID-19.

WHO is also a partner in the newly-launched Access to COVID-19 Tools (ACT) Accelerator to expedite the development, production and equitable access to COVID-19 tests, treatments and vaccines. Launched at the end of April 2020, this ground-breaking global collaboration brings together governments, scientists, businesses, civil society, philanthropists and global health organizations in an effort to speed up an end to the pandemic and to ensure high-level control of COVID-19 in the medium term. The Accelerator initiative has four pillars of work: diagnostics, treatments, vaccines and health system strengthening. For each pillar, a WHO-led Access and Allocation workstream is developing the principles, frameworks and mechanisms necessary to ensure the fair and equitable allocation of these tools. For each pillar well-conceived international norms and standards will remain paramount, as developed by the ECSPP and other expert committees.

Dr Simão emphasized the importance of norms and standards for clinical trials or to produce and test the quality of vaccines, therapeutics, medical devices and diagnostics in ensuring successful outcomes for patients, not only

of COVID-19 but of all diseases. She reminded participants that the Director-General has long identified WHO's standard-setting activities as a core function of WHO, saying that he sees the expert committees as the backbone of WHO's standard-setting process. Earlier in 2020, WHO created a new division under the Chief Scientist's Office to streamline and coordinate WHO's work in this area, including the work of the NSP Team, led by the Secretary to the ECSPP.

Election of chairpersons and rapporteurs

The ECSPP appointed Dr Petra Doerr as Chair of the meeting, Dr Adrian Krauss as Co-Chair and Dr Luisa Stoppa and Professor Eliangiringa Amos Kaale as rapporteurs.

Participation in Expert Committee on Specifications for Pharmaceutical Preparations meetings

Members of the ECSPP were reminded by correspondence of the rules governing participation in the ECSPP meeting, to which Expert Committee members and technical advisers are invited in their personal capacities. In all cases, participation is by invitation only.

Meetings of the ECSPP adhere to WHO procedures for expert committee meetings. They comprise three broad types of session:

a. **open sessions** for sharing information and updates, which are for non-State actors and members of the EAP, held this year on 6 October 2020, prior to the other ECSPP sessions;

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 agreeing to ECSPP recommendations and for finalization of the report; these are for ECSPP members only.

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

The Expert Committee noted the rules.

1. General policy

1.1 Process for development of WHO norms and standards

Dr Sabine Kopp described how the World Health Organization (WHO) norms, standards and specifications for inclusion in *The International Pharmacopoeia* (*7*) are developed and the role of the Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP). As stated by Dr Mariângela Simão, developing, establishing and promoting international standards for food and for biological, pharmaceutical and similar products are part of WHO's core mandate (Article 2, WHO Constitution). The activity involves expert committees established by the WHO World Health Assembly or the Executive Board, which are governed by set rules and procedures.

The ECSPP is responsible for WHO's guidance for the quality of medicines and regulatory standards throughout their life cycle, from development to delivery. WHO is thus responsible for more than 130 official guidance texts and guidelines. It works closely with a wide range of partners, including national and regional authorities and groupings, international organizations, professional and other associations, non-State actors, quality assurance and regulatory experts, WHO collaborating centres and pharmacopoeia authorities and secretariats. Dr Kopp emphasized the critical value of the ECSPP's work, given the importance to WHO and the broader United Nations group of ensuring patients' access to safe, quality-assured medicines. It features prominently in the UN Sustainable Development Goals, for example.

All monographs, guidance texts, good practices, model schemes 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. They are widely circulated for public comment (with at least two rounds of consultation for each document), reviewed by expert groups and discussed at annual ECSPP meetings before they are adopted by consensus. In all cases, the norms and standards developed by the ECSPP are intended to:

- be ready for adoption into national legislation;
- 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 in the WHO Technical Report Series (*8*).

The Expert Committee noted the process.

2. Quality assurance: collaboration initiatives

2.1 International Meeting of World Pharmacopoeias

Members of the ECSPP were updated by correspondence on the latest International Meeting of World Pharmacopoeias (IMWP). Each pharmacopoeia addresses a different country or region but all work to protect public health by creating and making available public standards to ensure the quality of medicines. They meet each year to share experience and expertise and find ways to synchronize their work.

The Eleventh IMWP, in February 2020, was hosted by WHO and the European Directorate for the Quality of Medicines & HealthCare (EDQM) in Strasbourg, France. National and regional pharmacopoeial authorities at the meeting strengthened their cooperation by agreeing on a new framework for exchanging information within the Pharmacopoeial Discussion Group (PDG). The framework, which will be trialled for a year, lays out new modalities for cooperation and is expected to improve information exchange within the Group.

Participants of the IMWP also adopted a white paper on the added value of pharmacopoeial standards for public health which will be published by WHO on the world pharmacopoeias' behalf. Other results of the meeting were:

- an exchange of information on the pharmacopoeias' responses to the *N*-nitrosamine contamination of medicines;
- the issuance of a global pharmacopoeial alert to ensure rapid discussion and collaboration among pharmacopoeias in response to the COVID-19 pandemic (section 10.2.2);
- the launching of a WHO-hosted website and file-sharing platform for world pharmacopoeias to exchange knowledge and work together more effectively; and
- an agreement to meet more frequently.

The next IMWP meeting was to be hosted by the Mexican Pharmacopoeia in Mexico City, Mexico, in February 2021 but will now be held virtually, in view of the COVID-19 pandemic. More information is available at: https://www.who.int/teams/health-product-and-policy-standards/pharmacopoeia/world-pharmacopoeias.

The Expert Committee thanked the EDQM for hosting the Eleventh IMWP, expressed its support for the IMWPs and encouraged WHO to continue serving as the secretariat for those events. It noted, in particular, the value of the global pharmacopoeial alert and its work to address questions on the quality of therapeutics in response to COVID-19. The Expert Committee also encouraged WHO and its pharmacopoeial partners to publish articles about both the alert and the broader IMWP in open-access peer-reviewed journals.

3. Nomenclature, terminology and databases

3.1 International nonproprietary names for pharmaceutical substances

Members of the ECSPP were updated by correspondence on WHO's latest work on international nonproprietary names (INNs) which serve to identify pharmaceutical substances or APIs. WHO collaborates with INN experts and national nomenclature committees in choosing a single name that is acceptable worldwide for each active substance to be marketed as a pharmaceutical. Since the turn of the century, increasing globalization and rapid scientific and technical development have fuelled a rapid rise in the number of new biological products that are developed and approved for use. This trend, which is expected to continue, is reflected in the growing number of INN requests received each year, which rose from around 150 in 2000 to nearly 350 in 2020.

Four activities were highlighted:

- **INN consultations**. Every year, a global INN consultation is convened to discuss proposals for new INNs and any objections to existing ones. This year, an additional ad hoc meeting was held to consider INNs for medical substances pertinent to the COVID-19 pandemic. Of 30 INN requests submitted, 23 were for biological substances (including 13 monoclonal antibodies) and seven for chemical substances. One request was withdrawn; INNs were selected for the other 29.
- **Improving INNs for cell therapy**. The INN cell therapy application form has been revised to elicit more information on the substance, for substances claimed to be stem cells and for those claimed to be stromal cells. In recognition of the importance of harmonizing cell definitions, a white paper covering regulatory issues for advanced therapies is being drafted, to be shared with all regulators.
- **School of INN (SoINN)**. This virtual school, available at https://extranet.who.int/soinn, promotes INNs as a central theme in teaching and learning for all health professionals. The school offers online webinars and courses in the science of nomenclature of pharmaceutical substances and also publications to raise awareness about the INN programme in the scientific and educational community. Since its launch in October 2019, the website has been visited by nearly 3,000 unique visitors. Work is underway to translate courses into Chinese, French and Spanish.
- **"Stem in a pill"**. The aim of this School of INN project is to review all stem cells and to categorize them into pharmacological classes.

It is progressing slowly, with only 14 classes completed so far. The project would benefit from more input from experts in clinical pharmacology.

More information is available at: https://www.who.int/medicines/services/inn

The Expert Committee noted the update.

3.2 Quality assurance terminology

Members of the ECSPP were reminded by correspondence that all the terms and definitions used in ECSPP norms, standards, guidelines and reports are published in the Quality Assurance of Medicines Terminology Database (*9*). This database, which is updated every year, is intended to harmonize the terminology and prevent any misunderstanding that may arise from different interpretations of terms. More information is available at: https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database.

The Expert Committee noted the latest update of the database and encouraged the WHO Secretariat to continue updating the database annually.

3.3 Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations

Members of the ECSPP were updated by correspondence on WHO's work to consolidate all the guidelines and guidance texts adopted by the ECSPP. Until now, each adopted guideline has been published as an annex to the relevant annual ECSPP report. They are also available as a collection of norms and standards on the WHO website (*10*), where they are categorized into six broad topics: development, distribution, inspections, regulatory standards, production, quality control and prequalification. More than 130 ECSPP-endorsed guidelines, standards and good practices are also reproduced in the e-publication, *Quality assurance of pharmaceuticals 2019* (*11*). Both the website and the e-publication are being transferred to new systems and formats.

In 2020, following a request from WHO partners and donors, a full updated list of current ECSPP-adopted guidelines, standards and good practices was drawn up under the six categories used on the WHO website. The list is intended to encourage broader implementation of WHO norms and standards.

Members of the ECSPP agreed, by correspondence, that the new list could be useful but expressed some reservations about whether it was ready for publication. They made several suggestions for improvements.

The Expert Committee noted the update and agreed that the new list should be integrated into the ECSPP report (Annex 1).

4. Quality control – national laboratories

4.1 External Quality Assurance Assessment Scheme

Members of the ECSPP were updated by correspondence on activities in the External Quality Assurance Assessment Scheme (EQAAS) which offers a platform for pharmaceutical quality control laboratories (PQCLs) to measure their performance in a confidential system of blind testing.

Organized by WHO with assistance from EDQM, EQAAS has been evaluating the technical performance of PQCLs since 2000. This proficiency testing scheme serves to: demonstrate the reliability of laboratory analytical results objectively, independently verify a laboratory's competence, establish mutual confidence with collaborating networks and support continuous improvement in performance.

EQAAS is run according to international standards for proficiency testing set by the International Organization for Standardization (ISO) and the International Electrotechnical Commission (IEC). Since the Scheme started, laboratories in all six WHO regions have participated in more than 1,100 studies, with 33 tests.

4.1.1 Final report on phase 9

The 43 participants in phase 9 of the EQAAS (from all WHO regions) were asked to complete three procedures, with chewable mebendazole tablets as the common test sample. Most of the laboratories passed the tests, which were well designed, and the results obtained were subject to sound statistical evaluation.

- Test 1: laboratories were asked to determine in triplicate the percentage content of mebendazole using liquid chromatography. Three laboratories reported unacceptable results.
- In test 2, they were asked to confirm the polymorphic form of mebendazole by infrared absorption spectrophotometry. Five laboratories reported a wrong result and nine did not report a result.
- Test 3 comprised conducting the dissolution test and determining the percentage of mebendazole released after 60 minutes. Seven laboratories reported unsatisfactory results and five did not report a result.

Laboratories that provided acceptable results were encouraged to use the EQAAS as a stimulus for continuous improvement. Laboratories that failed a test were asked to investigate the root cause and to use the results to inform targeted action plans and training as necessary. They were invited to take part in a post-EQAAS phase 9 assistance programme to support laboratories

in identifying and investigating problems of quality and to take corrective or preventive action to prevent their recurrence. Four laboratories chose to participate. More information on phase 9 of the EQAAS and the assistance programme is to be published in the journal WHO Drug Information.

The Expert Committee noted the update and encouraged WHO to continue the EQAAS in support of national and regional PQCLs, including continuing the post-assessment assistance programme.

4.1.2 Update on phase 10

Three procedures have been confirmed for the EQAAS phase 10:

- Test 1 is to assay by means of a complexometric titration, using zinc sulfate dispersible tablets.
- Test 2 is to perform a disintegration test on zinc sulfate dispersible tablets.
- Test 3 is to conduct counter-ion identification testing using two blinded zinc salt samples to identify which sample is zinc sulfate.

The Expert Committee noted the update.

5. Quality control – specifications and tests

5.1 *The International Pharmacopoeia*

Dr Herbert Schmidt, Technical Officer, NSP, presented an overview of *The International Pharmacopoeia* (*1*) which is a collection of quality specifications for pharmaceutical substances and dosage forms, together with supporting general methods of analysis. The collection, which is free to use, serves as source material for reference or adaptation by any WHO Member State that wishes to establish pharmaceutical requirements. It provides the means for national quality control laboratories, procurers and public pharmacies to independently check the quality of a medicine at any time during its shelf life.

The International Pharmacopoeia provides standards for essential medicines for meeting global public health priorities. It therefore includes mainly medicines that are on the *WHO Model List of Essential Medicines*, are the subject of invitations to submit an expression of interest for prequalification, or are recommended by WHO and United Nations programmes on specific diseases. *The International Pharmacopoeia* is developed in collaboration with laboratories and expert groups and in consultation with stakeholders. The process for preparing monographs, which is governed by publicly available rules and procedures, is designed to ensure complete transparency and to enable the participation of all interested parties. Before its inclusion in the collection, each monograph must be formally adopted by the ECSPP.

First published in the 1950s, *The International Pharmacopoeia* will be available in its 10th edition in 2020 as a digital publication on the WHO website and on USB memory sticks. The 10th edition will contain five new texts, 10 revised texts and one corrected text, as agreed by the Fifty-fourth ECSPP in 2019. They include two monographs on sofosbuvir and sofosbuvir tablets, which are the first public standards to be made available for these medicines. Two texts have been removed. The 10th edition was prepared with strong support from ECSPP experts, EDQM, WHO collaborating centres, collaborating laboratories and organizations, the ICRS Board and many WHO colleagues.

The 10th edition of *The International Pharmacopoeia* contains 373 monographs on pharmaceutical substances, 150 monographs on specific dosage forms, 8 monographs on general dosage forms and 71 methods of analysis.

The Expert Committee noted the update.

5.2 General chapters

5.2.1 Dissolution test for oral dosage forms

The ECSPP was asked to consider revisions to the general chapter on a dissolution test for solid oral dosage forms (chapter 5.5) in *The International Pharmacopoeia* to include a section on analysis of suspensions and powders for suspension.

The existing chapter is based on the corresponding internationally harmonized text by the PDG; the proposed amendment is specific to *The International Pharmacopoeia* and is not part of the PDG text.

The proposed revision was discussed in May 2020 at an informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines and was sent for public consultation in July–August 2020.

The ECSPP discussed the revised chapter, noting that the current draft of the monograph covers only oral suspensions and powders for oral suspension. It commented that it should be extended to include granules for oral suspension.

The Expert Committee adopted the revised chapter, subject to the changes discussed.

5.2.2 General identification tests

The ECSPP was asked to consider revisions to the chapter on general identification tests (chapter 2.1) in *The International Pharmacopoeia* to avoid the use of harmful reagents. The revisions follow a recommendation made at the informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines in May 2020. They build on previous work to avoid harmful reagents in methods of analysis in *The International Pharmacopoeia*, including revisions to replace mercury salts in non-aqueous titration (chapter 2.6) and to replace chromium (VI) salts in the colour of liquids (chapter 1.11).

The Expert Committee discussed the revision, including comments received during the public consultation, and adopted the revised chapter.

5.2.3 Test for histamine-like substances

The ECSPP considered a proposal to remove the test for histamine-like substances (vasodepressor substances, chapter 3.6) from *The International Pharmacopoeia*, and all references to the test in individual monographs. Thus, references to the test would be deleted in monographs on bleomycin sulfate and spectinomycin hydrochloride, and references to the test in the monograph on streptomycin sulfate would be replaced by the statement: "streptomycin sulfate is produced by methods of manufacture designed to eliminate or minimize substances lowering blood pressure".

This proposal follows a recommendation made at the informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines in May 2020 and is in line with the ECSPP's overall strategy to phase out animal testing where possible and justified (the test for vasodepressor substances is performed on cats).

The proposed revisions to *The International Pharmacopoeia* were sent out for public consultation in August–September 2020.

The ECSPP reviewed the revisions and discussed whether, in monographs on aminoglycosides, the test should be replaced by a statement that the described substance should be produced by methods of manufacture designed to eliminate or minimize substances that lower blood pressure.

The Expert Committee agreed to omit chapter 3.6 from *The International Pharmacopoeia* and all references to the test for histamine-like substances (vasodepressor substances) in specific monographs. It further agreed that a small group of experts should provide advice on the statement for manufacturers.

5.3 General monographs for dosage forms

5.3.1 Powders for inhalation

The ECSPP was asked to consider a new general chapter on powders for inhalation for inclusion in *The International Pharmacopoeia*. The chapter, which was drafted in early 2020, is based on the chapters on preparations for inhalation in the European and Japanese pharmacopoeias which were harmonized bilaterally.

The first draft was discussed at the informal consultation of experts on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines in May 2020 and sent for public consultation in July–August 2020. The draft has been revised to address all the comments made.

The Expert Committee adopted the monograph.

5.3.2 Liquid preparations for oral use

The ECSPP was asked to consider a revision to the general monograph on liquid preparations for oral use in *The International Pharmacopoeia* to comply with the new section on suspension and powders for suspension in the dissolution test for oral dosage forms (chapter 5.5).

As the revision was required as a consequence of the adopted revisions to the dissolution test for oral dosage forms, it was not sent for public consultation.

The ECSPP discussed the revision, noting that it should include a requirement for compliance with the dissolution test for oral dosage forms for powders and granules for oral suspension.

The Expert Committee adopted the revised monograph, subject to the changes discussed.

5.4 Specifications and draft monographs for medicines, including paediatric medicines, and candidate medicines for COVID-19

5.4.1 COVID-19 therapeutics

Many medicines currently being investigated for the treatment of COVID-19 are repurposed. While investigations continue, in order for any medicine to be safe and efficacious, it must be of assured quality for its intended use. Pharmacopoeial monographs support objective assessment of the quality of medicines by providing methods, acceptance criteria and supporting information.

Dexamethasone sodium phosphate

Dexamethasone phosphate injection

The ECSPP was asked to consider a revision to the monographs on dexamethasone sodium phosphate and dexamethasone phosphate injection, to change prescription of dexamethasone sodium phosphate ICRS to prescription of dexamethasone phosphate ICRS. Dexamethasone phosphate is considered to be less hygroscopic and should therefore be a more suitable quantitative reference substance.

The change was proposed during discussions with the custodial centre for ICRS, the EDQM and has been agreed by the ICRS Board. It was further discussed at the informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines in May 2020, where participants agreed to the revision and recommended its submission to the ECSPP without public consultation.

The ECSPP discussed both monographs and agreed to correct an error in the name of the new reference substance in the text of one of the monographs.

The Expert Committee adopted the revised monographs, subject to the change discussed.

Remdesivir

Remdesivir intravenous infusion

The ECSPP was asked to consider the inclusion of two new monographs, on remdesivir and remdesivir intravenous infusion, in *The International Pharmacopoeia*. The proposed monographs would be the first public specifications for remdesivir API and FPP and, as such, are expected to play an important role in ensuring access to safe, effective and quality-assured medicines in the treatment of COVID-19.[8] Based on information submitted by manufacturers, the proposed monographs were drafted in September 2020.

[8] Subsequent to the Fifty-fifth ECSPP meeting, the WHO issued a conditional recommendation on 20 November 2020 against the use of remdesivir in COVID-19 patients: https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients, accessed 29 January 2021.

Laboratory investigations are due to start soon; and both monographs are scheduled to be sent for public consultation at the end of 2020 or beginning of 2021. After the public consultation, the draft monographs and the comments received will be discussed in May 2021 at the informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines before it is finalized.

The ECSPP discussed various aspects of the monographs, including potential alternative methods to verify the identity of remdesivir and to determine its purity and content. The Expert Committee suggested the need to consider recommended storage conditions. It also encouraged the WHO Secretariat to develop a public standard on remdesivir sterile concentrate.

The Expert Committee adopted the monographs, subject to finalization by a group of experts in line with the proposed next steps.

5.4.2 Antiviral medicines, including antiretrovirals

Dolutegravir sodium

Dolutegravir tablets

In 2018, the ECSPP was asked to consider inclusion of new monographs on dolutegravir sodium and dolutegravir tablets in *The International Pharmacopoeia*. The proposed monographs would be the first public standards for dolutegravir and would therefore be expected to be important in ensuring access to safe, effective, quality-assured antiretrovirals.

In 2019, the ECSPP discussed the proposed texts for both monographs which had already been through a round of informal consultation with experts and public consultation. Since that meeting, the monographs on dolutegravir sodium and dolutegravir tablets have been refined further, following laboratory investigations and discussion at the informal consultation of experts on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines in May 2020. Further laboratory investigations are underway for both. Once these are completed, both monographs will be subject to a second public consultation.

The Expert Committee agreed with the next steps and adopted both monographs, subject to finalization by experts after an additional round of public consultation. Should major comments be received during the consultation, the monograph should be resubmitted to the ECSPP at its meeting in 2021.

Zanamivir

Zanamivir powder for inhalation, pre-metered

Draft monographs on zanamivir and zanamivir powder for inhalation, pre-metered, were proposed for inclusion in *The International Pharmacopoeia*. Both monographs are based on submissions from a manufacturer and on laboratory investigations. In order to align the tests and specifications with those of other pharmacopoeias as closely as possible, the monograph on zanamivir powder for inhalation, pre-metered, was prepared in partnership with The British Pharmacopoeia, while the monograph on zanamivir drew on information in existing monographs.

The two draft monographs were discussed at the informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines in May 2020 and sent for public consultation in July–September 2020. Laboratory investigations are underway for both, and the results and any further revisions will be discussed at the informal consultation in May 2021.

The ECSPP discussed various aspects of the draft monographs, including the methods prescribed to determine the water content of zanamivir.

The Expert Committee adopted the monographs, subject to finalization by experts, in line with the proposed next steps. Should major comments be received during the consultation, the monograph should be resubmitted to the ECSPP at its meeting in 2021.

5.4.3 Medicines for tropical diseases

Albendazole chewable tablets

A revision to the monograph on albendazole chewable tablets was proposed in response to information received from a manufacturer. In particular, the proposal is to revise the test for dissolution by recommending use of different dissolution media for different dosage strengths.

The proposed revision was discussed at the July 2020 meeting of the Working Group on albendazole for *The International Pharmacopoeia* and verified by laboratory testing. It was then drafted and sent for public consultation in July–August 2020. After further laboratory investigations conducted in August–October 2020, additional modifications to the test for dissolution were proposed.

The monograph on albendazole will be revised in line with recommendations from the Fifty-fourth ECSPP in 2019, and the new monograph on albendazole tablets is being prepared.

The Expert Committee adopted the revised monograph on albendazole chewable tablets, subject to finalization by experts after an additional round of public consultation. Should major comments be received during consultation, the monograph should be resubmitted to the ECSPP at its meeting in 2021.

Ivermectin tablets

ECSPP members were asked to consider a revision to the monograph on ivermectin tablets to align quantitative determination of the finished product monograph with the provisions in the API monograph.

The proposed change emerged from discussions with the custodial centre for ICRS, the EDQM, and has been agreed by the ICRS Board. It was further discussed at the informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines in May 2020, where participants agreed to the revision and recommended that it be submitted to the ECSPP without public consultation.

The Expert Committee adopted the revised monograph.

5.4.4 Medicines for maternal, newborn, child and adolescent health

Norethisterone enantate

Norethisterone enantate injection

The ECSPP was asked to consider a revision of the monograph on norethisterone enantate and to adopt a new monograph on norethisterone enantate injection on the basis of a submission from a manufacturer and laboratory investigations.

The draft revisions and new text were first proposed in June 2017 by a collaborating laboratory. Since then, they have been sent for public consultation (July–September 2017), presented at three ECSPP meetings (2017, 2018 and 2019), further revised and discussed at three informal consultations on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines (2018, 2019 and 2020). A fourth draft of revisions includes the results of the latest rounds of discussion and laboratory investigations.

The ECSPP provided feedback on the current versions of both monographs and noted that laboratory investigations are still underway.

The Expert Committee noted the progress made and requested that both monographs be resubmitted for possible adoption at the ECSPP meeting in 2021.

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 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 ECSPP meeting in 2018. It was subsequently discussed by the ECSPP in October 2019 and at two informal consultations on Screening Technologies and

Pharmacopoeial Specifications for Medicines in 2019 and 2020. After laboratory investigations, the monograph will be sent for public consultation.

The Expert Committee noted the progress made and requested that the monograph be resubmitted for possible adoption at its meeting in 2021.

5.4.5 Excipients

Sodium starch glycolate

Sodium laurilsulfate

Hydroxypropylcellulose, low-substituted

Three draft monographs for excipients were presented at the ECSPP for possible inclusion in *The International Pharmacopoeia*: on sodium starch glycolate, sodium laurilsulfate and hydroxypropylcellulose, low-substituted. All three texts are based on monographs developed by the PDG, with editorial modifications to bring them in line with the house style of *The International Pharmacopoeia*.

The monographs were sent for public consultation in August–October 2020 and the comments received are due to be discussed at the next informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines, in 2021.

The proposal to include the excipient monographs is part of ongoing efforts to benefit from PDG's offer to publish general chapters and monographs in The International Pharmacopoeia (with due recognition of the source) and so promote broader use of global quality standards. *The International Pharmacopoeia* has already accepted several chapters, including on the dissolution test for oral dosage forms.

The Expert Committee adopted all three monographs, subject to their finalization by experts. It asked the WHO Secretariat with developing a concept for future work on excipient monographs in *The International Pharmacopoeia*, considering the need for such monographs from a public health perspective and addressing known deficiencies in quality. The concept note should include ways to harmonize specifications on excipients with those in other pharmacopoeias.

5.5 Update on the virtual informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines

ECSPP members were updated by correspondence on the annual informal consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines which took place in May 2020. This year, due to the COVID-19 pandemic, the consultation was held as a series of virtual meetings. At the consultation, 17 international experts were updated on the

44 monographs and general texts under development for *The International Pharmacopoeia*. The experts discussed draft proposals and reports of laboratory investigations; and provided guidance on future work.

The Expert Committee noted the update.

6. Quality control: international reference materials

6.1 Update on International Chemical Reference Substances

The ECSPP subgroup on ICRS updated members of the Expert Committee on ICRS activities by correspondence.

ICRS are used to identify and determine the purity or assay of pharmaceutical substances and preparations or to verify the performance of test methods. The EDQM has been the custodial centre for ICRS since 2010 and is responsible for establishing, storing and distributing ICRS.

Since the latest meeting of the ECSPP, in October 2019, the ICRS Board has released the following chemical reference substances, established by the EDQM for use according to the provisions of *The International Pharmacopoeia*:

- estradiol valerate ICRS, batch 1; and
- moxifloxacin hydrochloride ICRS, batch 1.

Some of EDQM's achievements in relation to ICRS in 2019 include completing four ICRS establishment reports for WHO (three of which were adopted) and monitoring 22 standards for continuous fitness for purpose (with no significant findings on quality).

The WHO Secretariat thanked 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 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 estradiol valerate ICRS, batch 1 and moxifloxacin hydrochloride ICRS, batch 1.

7. Quality assurance: good manufacturing practice and inspection

7.1 Inspection guidelines and good practices with partner organizations

7.1.1 Revision of good manufacturing practices for sterile products

Members of the ECSPP were updated by correspondence on the progress in revising the *WHO good manufacturing practices for sterile pharmaceutical products* (*12*), which has continued since 2017. The work is performed in collaboration with the EU, the EMA, PIC/S and WHO to align standards across the world. The establishment of a common language is expected to benefit authorities and manufacturers, save resources and, ultimately, improve patients' access to good quality medicines.

The revised guidance has new sections on scope, utilities, 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, it was revised internally and sent for public consultation between December 2017 and March 2018. The public consultation resulted in 6,200 comments from more than 140 companies and organizations which were used to make further revisions to the guidance, approved by the Inspection Working Group at the EMA in November 2019.

At its Fifty-fourth meeting, the ECSPP commended the work to harmonize guidance on sterile products but, given the extent of the changes made to the document in 2019, called for a second public consultation before consideration of the guidance for adoption by WHO. In February 2020, WHO sent the latest version of the guidance for consultation in parallel with a targeted consultation led by the EU. The 318 comments received were reviewed by a WHO-convened international working group and recommendations for action were shared with the PIC/S-EMA drafting group. The EU consultation closed in July 2020 and the comments received are still being reviewed by the EU and EMA. The suggested actions by both the WHO- and the EU-led processes will be considered to finalize the guidance.

The Expert Committee noted the progress report and expressed its support for continued collaboration with the EU, EMA and PIC/S to harmonize guidance on sterile products. It asked for a revised guideline to be presented, if feasible, for possible adoption at its next meeting in 2021.

7.1.2 Good manufacturing practices for radiopharmaceuticals for investigational use

Members of the ECSPP were updated by correspondence on the development of good manufacturing practices (GMP) guidelines for radiopharmaceuticals by

the IAEA and WHO. In late 2019, the ECSPP adopted the *International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceuticals* (*13*), subject to finalization by a small group of experts. The final version was shared with ECSPP members before its inclusion in the fifty-fourth ECSPP meeting report.

The newly adopted guideline covers compounding and dispensing of radiopharmaceuticals, representing one part of IAEA and WHO work to update broader guidance on GMP for radiopharmaceuticals, as recommended by IAEA experts in early 2018. The other two areas are investigational radiopharmaceuticals and cold kits used in industrial radiopharmaceutical production.

In June 2020, at a virtual meeting of experts, IAEA and WHO decided to focus first on a guideline on GMP for radiopharmaceuticals for investigational use. A working group has been formed to agree on a structure for the guideline and to start drafting the text. The group is scheduled to meet, virtually or face-to-face as appropriate, at the end of October 2020.

The Expert Committee noted the update.

7.2 Approaches to carryover limits in cleaning validation

ECSPP member, Dr Adriaan J. Van Zyl, presented a new draft of points to consider when including health-based exposure limits (HBELs) in cleaning validation, as recommended by the Fifty-fourth ECSPP in 2019.

Updating of the WHO guidance on validation and its seven appendices started in 2013. The main text and six appendices have now been revised and adopted by the ECSPP. The appendices are those on validation of heating, ventilation and air-conditioning systems (*14*); validation of water systems for pharmaceutical use (*15*); validation of analytical procedures (*16*); validation of computerized systems (*17*); guidelines on qualification (*18*); and validation of non-sterile processes (*19*). Updating of the appendix on cleaning validation (*20*) was discussed during the informal consultation on Good Practices for the Manufacture and Inspection of Health Products in July 2019 and presented at the ECSPP meeting in October 2019. Much of the discussion at both meetings was on the methods for establishing limits for carryover in safe cleaning as these limits are important for assessing the risk of whether a dedicated facility is required and also to prevent cross-contamination in shared facilities.

The Fifty-fourth ECSPP agreed that guidelines for inspectorates and manufacturers should be harmonized and considered whether HBELs should be included in WHO guidelines where appropriate. After a discussion, the Expert Committee recommended that, first, a text be written to introduce the topic and its complexities and to establish common understanding in this area before potentially including the concept as a requirement in international guidelines.

During the past year, the WHO Secretariat has coordinated preparation of a document presenting the main points to be considered in reviewing the current status of and approaches to cleaning validation in multi-product facilities and a science-based approach to establishing safe carryover limits. The document covers documentation, equipment, cleaning agents, sampling, cleanability studies, risk management, guidance for setting HBELs, acceptance criteria, analytical procedures, data integrity, cleaning verification, visual inspection, cleaning capability, personnel, quality metrics and life cycle.

The draft document was sent for public consultation in May–June 2020 and the draft, and the more than 450 comments received, were discussed by an expert group of inspectors during the virtual meetings that replaced the planned consultation on Good Practices for the Manufacture and Inspection of Health Products in August 2020. The expert group recommended that consideration and application of HBELs should extend beyond cleaning validation and urged the ECSPP to consider extending the inclusion of HBELs and their implementation to relevant GMP guidelines.

A second public consultation generated approximately 200 comments which were reviewed by an expert working group and used to further refine the draft document. The main comments addressed definitions of terms (including point of departure and verification), established cleaning limits, selection of cleaning agents, sampling, HBEL setting, quantification of visually clean criteria and calculation of cleaning capability. There were several requests for editorial changes and a request to remove the section on quality metrics and key performance indicators.

The ECSPP noted the work that had been involved in finalizing the document in view of its anticipated large impact on pharmaceutical manufacturers and inspectors. It reviewed the latest draft document and suggested use of the term "qualified expert" rather than "qualified person" in the guidance for setting HBELs. The Expert Committee also suggested that a list of abbreviations be added.

The Expert Committee adopted *Points to consider when including health-based exposure limits in cleaning validation* (Annex 2), subject to the changes discussed. It recommended that the existing cleaning validation guideline be opened for review and updated in accordance with the latest good practices.

7.3 Water for pharmaceutical use

Dr Adriaan J. Van Zyl and Dr Sabine Kopp reported on the revision of *WHO good manufacturing practices: water for pharmaceutical use* (*21*), as recommended by the ECSPP in 2020, to integrate the WHO guideline on Production of water for injection by means other than distillation (*22*).

Recently, after extensive consultation with stakeholders, several pharmacopoeias have adopted revised monographs on water for injection that include production by non-distillation techniques, such as reverse osmosis. In 2017, the ECSPP recommended that the WHO Secretariat collect feedback on whether the WHO specifications and GMP on water for injection should be revised and how. After discussion in several consultations, the ECSPP agreed that the monograph on water for injection in *The International Pharmacopoeia* and the WHO guideline on water for pharmaceutical use both be revised to include technologies other than distillation for the production of water for injection.

A guideline on the production of water for injection by means other than distillation was drafted in early 2019 and, after two rounds of expert and public consultations and revision, was adopted by the ECSPP in October 2019. In early 2020, a proposal was drafted for revising the *WHO good manufacturing practices: water for pharmaceutical use* to incorporate the newly adopted guideline. The proposed revision was sent to stakeholders, including the EAP, and sent for public consultation in May 2020. The text and more than 360 comments received were discussed at a virtual meeting of inspectors in August 2020, in lieu of the annual consultation on Good Practices for Health Products Manufacture and Inspection. The text was then revised and sent out again for feedback, including to the EAP and the public. This consultation generated approximately 140 comments which were reviewed by an expert working group. The comments received included requests to expand the section on stages of qualification; address minimizing contamination rather than preventing it; delete water quality specifications for other grades of water; clarify operational considerations under the three-phased approach to validation; and make several editorial changes. The text was revised accordingly and presented to the ECSPP.

The ECSPP acknowledged the importance of the document and thanked all those involved in reviewing and revising it. It discussed the latest changes and made suggestions for minor revisions.

The Expert Committee adopted the revised *WHO good manufacturing practices: water for pharmaceutical use* (Annex 3).

7.4 Guideline on data integrity

Dr Adriaan J. Van Zyl informed ECSPP members on the development of a new guideline on data integrity intended to replace the WHO *Guidance on good data and record management practices* (*23*) which is considered to be too lengthy, especially in comparison with the texts of many other agencies that have been adjusted recently to better reflect current expectations and focus on necessary information. The new guideline, which was recommended by the Fifty-fourth ECSPP in 2019, covers 10 main areas: data governance, quality risk management, management review, outsourcing, training, data, data

integrity, good documentation practices, computerized systems, and corrective and preventive actions. It includes an annex with 10 examples of data integrity management, from quality risk management to data entry, changes and controls.

A first draft of the new guideline was sent to stakeholders, including the EAP, and sent for public consultation between November 2019 and January 2020. The text, and more than 440 comments received, were discussed at a virtual meeting of inspectors in June 2020 which replaced the annual consultation on Good Practices for Health Products Manufacture and Inspection. The text was then revised and sent out again for feedback, including to the EAP and the public. The WHO Secretariat received approximately 650 comments during this second consultation. The suggestions were to reorganize the introduction; add information on data governance, data transfer and computerized systems; extend the section on controls in quality risk management; clarify management review systems and action in case of noncompliance; add a new section on data review and approval; refine some of the examples; and make several editorial changes. The text was revised accordingly for presentation to the ECSPP. Some new definitions were added to the glossary and others were revised.

The ECSPP reviewed the latest changes and discussed issues including compliance with data protection legislation and best practices, timeframes for retaining data and requirements on data transfer. It also discussed the scope of the document, such as the value of including vector control products and data on safety and efficacy generated in clinical research under good clinical practice. ECSPP members therefore proposed new wording for the scope and suggested adding the term "medical products" to the glossary. Overall, the Expert Committee expressed strong support for the new guideline on data integrity, commenting that it is comprehensive and much improved. ECSPP members agreed that the new guideline will be of great value to industry and inspectors and thanked all those involved in collating, reviewing and integrating the hundreds of comments received.

The Expert Committee adopted the *Guideline on data integrity* (Annex 4), subject to the changes discussed.

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

Members of the ECSPP were updated by correspondence on activities for the prevention of antimicrobial resistance (AMR) in manufacturing and inspection. Against a backdrop of rising global concern about AMR, the ECSPP, at its meeting in October 2019, adopted a document outlining points for manufacturers and inspectors to consider in preventing AMR (*24*). It recommended that WHO conduct a survey of pharmaceutical manufacturers that are engaged in synthesis

and/or production of antimicrobials to collect information on current waste and wastewater management practices and to verify correct implementation of the recommendations in the newly adopted document (*18*). WHO developed a survey and sent it to 39 manufacturers of APIs that are part of the WHO Prequalification (PQ) Programme. A total of 29 manufacturers completed the survey and the NSP and PQ teams collated and analysed their responses.

ECSPP members were given an overview of the findings, as follows:

- 89% of respondents showed a basic understanding of WHO requirements on waste management and AMR by agreeing that antimicrobials should not be released into water streams or, if they are, only at concentrations within established limits.
- 62% of respondents reported that they used incineration to dispose of waste, 31% that they recycled their waste and 14% that they used zero-liquid discharge to reduce environmental contamination with antimicrobials.
- 7% of respondents send aqueous waste to a municipal plant without treating it.
- Only one respondent submitted detailed information on their risk management approach; most could not provide a clear rationale for their decontamination procedures.
- 31% of respondents did not adhere to any discharge targets; 55% claimed to follow national requirements, although it was unclear that they are designed to control antimicrobial residues at levels that are adequate to prevent AMR.
- 55% of respondents rated their compliance with the points in the ECSPP document (*24*) as high, and 41% rated their compliance as medium.
- All respondents estimated that they would require 0–2 years to implement adequate waste management programmes to prevent contamination of the environment with antimicrobials.

The Expert Committee noted the report on the manufacturers' survey and encouraged the WHO Secretariat to publish the results in a regulatory journal. It encouraged national inspectorates to include aspects of waste management during GMP inspections in collaboration with and in accordance with the legal authority of environmental agencies. The Expert Committee also urged the WHO Secretariat to assist national inspectorates and manufacturers in implementing the recommendations in *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of AMR* (*24*).

7.6 Recommendations from the virtual consultation on good practices for health products and inspection

ECSPP members were updated by correspondence on the annual consultation on Good Practices for Health Products and Inspection which took place in July 2020 as a series of virtual meetings due to the COVID-19 pandemic. During the meetings, groups of experts discussed GMPs for sterile products and radiopharmaceuticals (sections 7.1.1 and 7.1.2), points to consider when including HBELs in cleaning validation (section 7.2), GMP for water for pharmaceutical use (section 7.3) and guidelines for data integrity (section 7.4).

The group made a series of proposals for future activities:

- ***Update WHO guideline on Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans*** (*25*). This document, which was published in 1996, should be updated urgently, especially in view of inspections for COVID-19 therapeutics.
- ***Determine whether WHO guidelines on transfer of technology in pharmaceutical manufacturing*** (*26*) should also be updated. This document was published in 2011 and, like that cited above, may require updating, not least to support inspections for COVID-19 therapeutics.
- ***Explore the preparation of a GMP guideline on required practices during research and development of medical products.*** Tackling the COVID-19 pandemic requires rapid development of therapies, which in turn urgently requires preparation of a guideline on the manufacture of developmental and pilot batches and the sequential data on stability that are submitted in product applications for marketing authorization and prequalification. Data obtained from these batches have an effect on a product's stability, process validation, analytical method development and validation; however, there are currently no regulatory guidelines.

The Expert Committee noted the update and agreed to update the WHO guideline on *Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans*. It asked the WHO Secretariat to explore whether the *WHO guidelines on transfer of technology in pharmaceutical manufacturing* should also be updated and whether a guideline on good practices in the research and development of medical products should be prepared.

8. Quality assurance: distribution and supply chain

8.1 Shelf life for supply and procurement of medical products

The ECSPP was updated by correspondence on the progress in implementing the *Points to consider for setting the remaining shelf life of medical products upon delivery* guideline (*27*) adopted by the Expert Committee in 2019. The purpose of the guideline is to facilitate the 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 nearly out-of-date medical products. In adopting it, the ECSPP acknowledged the value of a new guideline for guiding procurement agencies, regulators and other stakeholders; harmonizing policies in this area; and addressing the problem of short remaining shelf lives of donated medicines during emergencies.

During the past year, the WHO Secretariat was contacted by and met various colleagues involved in procurement to consider how best to help implement the new guideline. WHO colleagues plan to draft an advocacy note to showcase WHO guidance on importation, good storage and distribution and acceptable remaining shelf life and to ask WHO Country Offices to advocate for use of the guidance by national regulatory and customs authorities and by quality control laboratories. WHO colleagues have committed themselves to cover the topic of acceptable remaining shelf life at the (virtual) Suppliers Summit in October 2020 to increase awareness in countries of the new WHO guideline and to better manage stocks by conducting forecasting exercises.

The Expert Committee noted the update and recommended proceeding with the next steps implementing the WHO guidance texts (on importation, acceptable remaining shelf life and good storage and distribution) through WHO procurement channels and networks.

8.1.1 Revision to the guideline on remaining shelf life

Members of the ECSPP were also asked to consider amending the guideline on remaining shelf life to include the example of emergency health kits. The topic of inclusion of health kits for use in emergencies in the guideline was raised during the 2019 public consultation on the guideline; however, the 2019 ECSPP decided to focus first on individual medical products. These kits are distributed by a group of agencies and humanitarian organizations - including the International Committee of the Red Cross, Médecins Sans Frontières, Save the Children, United Nations Children's Fund, United Nations Population Fund and WHO. Since publication of the guideline, however, members of these agencies and organizations have submitted a draft proposal for an amendment.

The Expert Committee recommended circulation for public consultation of the proposed amendment to consider emergency health kits

for use in humanitarian emergency response as an additional example to the *Points to consider for setting the remaining shelf life of medical products upon delivery* guideline.

8.2 Updated and new WHO guidance, procedures and operational documents for pharmaceutical procurement

8.2.1 World Health Organization/United Nations Population Fund prequalification guidance on condoms

Ms Seloi Mogatle, Mr David Hill and Mr William Potter, United Nations Population Fund (UNFPA), and Dr Sabine Kopp, WHO, summarized the updating of the existing prequalification guidance texts for contraceptive devices and condoms, published in 2008, which no longer reflect understanding and evidence in the field. As agreed by the ECSPP in October 2018, UNFPA and WHO separated aspects of the current procedures for contraceptive devices and condoms into seven documents:

- Prequalification programme guidance for contraceptive devices: male latex condoms, female condoms and intra-uterine devices;
- technical specifications for male latex condoms;
- specifications for plain lubricants;
- guidance on testing of male latex condoms;
- recommendations for condom storage and shipping temperatures;
- guidance on conducting post-market surveillance of condoms; and
- condom quality assurance.

The first three documents were sent for expert and public consultation, subsequently revised and adopted by the ECSPP in 2019.

The documents on testing male latex condoms, storage and shipping recommendations and post-market surveillance were presented to the ECSPP for adoption. All three were restructured and revised in the first half of 2019, sent to the EAP and then sent for public consultation in July 2019. The comments received were reviewed by a group of specialists in October 2019 and new drafts were prepared for expert and public consultation in May 2020. The comments received were reviewed and revised versions were presented to the ECSPP. The ECSPP reviewed the three documents, noting that many of the comments received were requests for minor editorial changes. It further noted that all the comments received had been considered and addressed and that all three documents were supported by the regulatory agencies that submitted comments.

The Expert Committee adopted the following guidelines: *Recommendations for condom storage and shipping temperatures* (Annex 5), *Guidance on testing of male latex condoms* (Annex 6) and *Guidance on conducting post-market surveillance of condoms* (Annex 7).

9. Regulatory guidance and model schemes

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

Professor Maria del Val Bermejo Sanz and Professor Giovanni Pauletti described the WHO Biowaiver Project and presented its work during the past year. As part of its 2006 guidance on waiving bioequivalence requirements for immediate-release oral solid dosage forms on the *WHO Model List of Essential Medicines*, 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 the *Biowaiver List* based on experimental laboratory data.

The Biowaiver Project, started in 2018, is based on sound methods developed and optimized for the Project and detailed in the WHO protocol for equilibrium solubility tests to classify APIs for biowaiver according to the Biopharmaceutics Classification System framework. In 2018, during the pilot phase of the project (cycle I), a first set of three APIs was classified for a revised WHO list. A second set of 15 APIs was prioritized in collaboration with the WHO PQ Team and sent for public consultation before being classified in 2019 as part of cycle II. The results of cycles I and II were collated in a living document, the WHO *Biowaiver List*, which was published as an annex to the report of the Fifty-fourth ECSPP (*28*). The results were also published in the peer-reviewed, open-access journal *ADMET & DMMPK* (*29*).

In 2020, a set of 11 APIs was prioritized and classified in cycle III; the data were presented to this year's ECSPP and will be integrated into an updated version of the *Biowaiver List* (Annex 8).

A fourth set of 10 APIs has been prioritized and the list was presented to the ECSPP as the proposed focus of cycle IV of the Biowaiver Project in 2021 (Table 1).

Table 1
Prioritized APIs proposed for study in cycle IV of the Biowaiver Project.

API in *WHO Model List of Essential Medicines*[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]
abacavir	Antiretrovirals	Treatment and prevention of HIV infection	600 mg

Table 1 *continued*

API in *WHO Model List of Essential Medicines*[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]
Dexamethasone *	(1) Gastrointestinal medicines (2) Immunomodulators and antineoplastics (3) Medicines for pain and palliative care	(1) Antiemetic medicines (2) Acute lymphoblastic leukaemia (2) Multiple myeloma (3) Medicines for other common symptoms in palliative care	(1) (3) 0.75–9 mg a day, depending on the disease being treated (2) 40 mg
Doxycycline	(1) Antiprotozoals (2) Antibacterials	(1) Antimalarial medicines (2) Antibiotics (access group)	(1) and (2) 100 mg (as hyclate)
Ethambutol	Antibacterials	Antituberculosis medicines	2 g
Isoniazid	Antibacterials	Antituberculosis medicines	300 mg
hydroxychloroquine	Medicines for diseases of joints	Disease-modifying agents used in rheumatoid disorders	400–600 mg
Lamivudine	Antiretrovirals	Treatment and prevention of HIV	300 mg
levonorgestrel	Medicines for reproductive health and perinatal care	Oral hormonal contraceptives	1.5 mg
Nifurtimox	Antiprotozoal medicines	African trypanosomiasis and American trypanosomiasis	10.0 mg/kg

Table 1 *continued*

API in *WHO Model List of Essential Medicines*[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]
Proguanil	Antiprotozoals	Antimalarial medicines	100 mg (as hydrochloride)

* dexamethasone has been characterized in an expedited fashion to address the current global public health emergency. Results are presented in Annex 8.

[a] 21st *WHO Model List of Essential Medicines* (2019) (*30*).

[b] According to *Summary of product characteristics* from WHO Prequalification or national/regional regulatory authority.

The list of proposed APIs includes two medicines that are in clinical trials for use in the COVID-19 pandemic in early 2020: dexamethasone and hydroxychloroquine. In June 2020, at the informal consultation on Regulatory Guidance for Multisource Products, participants urged an expedited characterization of the solubility of dexamethasone tablets at 6 mg per day (the dosage used in the COVID-19 Recovery Trial). The WHO Secretariat therefore expedited the characterization of dexamethasone and the results have been integrated into the latest *Biowaiver List* and shared with the ECSPP.

Professor Bermejo Sanz also presented two proposals for extending the Biowaiver Project, as recommended by the group of experts at the informal consultation on Regulatory Guidance for Multisource Products:

- A short-term exploratory study, potentially during cycle IV, to consider API stability under pH conditions representative of the stomach and small intestine, in order to support regulatory decisions. This would involve measuring API stability for a period equivalent to the estimated in-vivo contact of the substance in gastric fluid (e.g. 1 h at pH 1.2, 37 °C) and small intestinal fluid (e.g. 3–6 h at pH 6.8, 37 °C) and quantifying the parent drug molecule with the validated analytical method.
- A medium- to long-term study to define the suitability of the system for performing in-vitro permeability experiments that would generate meaningful results for classification according to the Biopharmaceutics Classification System. The study would involve comparison of the experimental design of acceptable in-vitro cell culture models (e.g. Caco-2, MDCK), including recommended model substances and limited validation requirements. The time frame for this study would be defined after the COVID-19 pandemic.

The ECSPP thanked all those involved in enabling the Biowaiver Project to characterize the solubility profiles of prioritized APIs through experimental laboratory data, including the network of laboratories involved in expediting characterization of dexamethasone for public health during the current pandemic. The Expert Committee discussed various aspects of the Project and made several suggestions for improvement. The topics of discussion included: the consistency of results from different laboratories, inclusion of polymorphic forms in the Project's studies and consideration of API stability and potential quantification of degradation.

The Expert Committee agreed to integrate the results of cycle III into the *Biowaiver List* (Annex 8). It further suggested promotion of the results of the Biowaiver Project by presentation at scientific conferences, publication in peer-reviewed and open-access journals and by advocacy, engagement and partnership. The Expert Committee accepted the prioritized APIs proposed for study in cycle IV and supported the planning of two exploratory projects on stability and permeability.

9.2 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

Dr Celeste Aurora Sánchez González and Dr Sabine Kopp gave an update on the revision 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 a voluntary international agreement designed to assure participating countries of the quality of the pharmaceutical products they import and export. In operation since 1969, the Scheme was amended four times between 1975 and 1997. It currently works by issuing three types of certificate for quality assurance: a certificate of a pharmaceutical product (CPP), a statement of the marketing authorization status of a pharmaceutical product and a batch certificate.

New worldwide trends pose a number of challenges to the operation of the Scheme since 2007 and the ECSPP recommended that the Scheme be revised at its Forty-third meeting in 2008. An interim solution, a question-and-answer document on the Scheme's function, was developed in 2010 (and revised in 2015), but the Scheme itself remains unchanged.

In 2017, the ECSPP again called for the Scheme to be revised and a series of revisions was proposed by the WHO Secretariat and sent for public consultation in 2018. These were discussed by the ECSPP in 2018.

A second round of consultation in 2019 raised some 180 comments. A group of 14 regulatory authorities interested in collaborating with WHO on revising the Scheme were brought together in a series of virtual meetings in August 2020 that were held in lieu of this year's informal consultation on

Regulatory Tools for Medicines. Participants reviewed all the comments received and shared practical experiences and challenges in operating the Scheme. After the meeting, the Scheme was further revised, based on the feedback of the participants, before being presented to the Expert Committee. The latest draft includes revisions to:

- allow participation of regional and multi-State organizations;
- maintain an updated list of current participants;
- ensure that certificate-issuing countries include a firm declaration that the competent regional or national authority meets the Scheme's requirements for notification to the Director-General of WHO;
- include the concept of reliance among participating authorities and promotion of its use to ensure timely access to medicines;
- improve the transparency of information on manufacturing (in a revised model template);
- discourage legalization procedures that unduly delay certificates;
- establish standard time frames for decision-making (20–30 working days); and
- reflect current procurement practices (by removing statements on marketing authorization from the Scheme and clarifying that batch (lot) release certificates are not part of the Scheme).

Minor editorial changes were also incorporated into the latest proposed revision.

The ECSPP thanked all those involved in revising the Scheme and thoroughly reviewed the provisions of the amended Scheme, discussing points, including membership renewals, the definition of regional authorities and what constitutes an efficient surveillance system. ECSPP members requested a number of further revisions, in particular to: acknowledge different types and pathways for marketing authorizations; introduce provision for links to product marketing authorization webpages, if available; make ensuring GMP compliance regardless of location an option rather than an obligation; and removing the reference to GMP for assuring the quality of APIs.

The Expert Committee emphasized that options should be explored for promoting a shift to use of electronic systems and certificates by authorities implementing the Scheme. It also recommended that certifying authorities be encouraged to ensure that they have the competence and capacity to implement the Scheme by citing the WHO Global Benchmarking Tool in the Scheme's preamble and adding it to the list of references.

The Expert Committee noted that, once the revised Scheme guidelines are adopted, a number of implementation and operating issues might have

to be addressed; for example, by incorporating an additional set of questions and answers.

The Expert Committee adopted the revised *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* (Annex 9), subject to the changes discussed. It requested WHO to ensure speedy implementation of the revised Scheme and encouraged the WHO Secretariat to work with interested parties to facilitate implementation of the Scheme through electronic systems, including e-CCPs (certificates of pharmaceutical products).

9.3 Good practices in regulatory decision-making

9.3.1 Good reliance practices in the regulation of medical products

Dr Samvel Azatyan and Mrs Marie Valentin, WHO Regulatory Convergence and Networks, updated the ECSPP on the development of the proposed good reliance practices (GRelP) in the regulation of medical products. The aim of this high-level document, which was prepared in parallel to the concise good regulatory practice (GRP) guidance, is to provide a more efficient approach to regulatory oversight, thereby promoting access to quality-assured, effective, safe medical products.

In September 2019, a consultation on GRelP concluded that the concept note of the Pan American Health Organization and the Pan American Network for Drug Regulatory Harmonization on regulatory reliance principles (*31*) be used as the basis for a high-level WHO document on good reliance practices. Results and suggestions from a WHO survey conducted on behalf of the International Pharmaceutical Regulators Programme on reliance in June 2019 (*32*) were also considered in preparing the document. The document, drafted in early 2020, covers: basic definitions and key concepts in reliance; the six principles of reliance (universality, sovereignty of decision-making, transparency, respect for a national and regional legal basis, consistency and competence); general considerations; potential barriers; and enablers. Examples of GReIP are annexed.

The document was then considered in a targeted consultation with stakeholders in April–May 2020 and in two public consultations, in June–July 2020 and August–September 2020. The main comments from the public consultations were to: simplify the title and align it with the guideline for GRP; reinforce the importance of "sameness of product" and local capacity; ensure that reliance timelines allow for local assessment; and emphasize safeguarding and strengthening local competence and capacity. Examples of using reliance were added to the annex, including examples on unilateral recognition, reliance in pharmacovigilance and reliance in public health emergencies. After each consultation, all the comments were collated, reviewed and addressed through revisions.

The ECSPP reviewed the high-level document, discussed the terms used in the title ("regulation" rather than "regulatory oversight" or "regulatory assessment"), definition of terms and key concepts, deletion of stringent regulatory authorities in Annex 1 and the concept of "reliance on reliance". It suggested that additional explanation be provided of "reliance on reliance" with, for example, practical examples or questions and answers.

The Expert Committee recognized the importance of the new guideline, noting that it will shape the strategies for many of WHO's regulatory activities in Member States and that its implementation may have implications for other documents and guidelines.

The Expert Committee adopted *Good reliance practices in the regulation of medical products: high-level principles and considerations* (Annex 10).

9.3.2 Good regulatory practices in the regulation of medical products

Dr Samvel Azatyan and Mrs Marie Valentin updated the ECSPP on the development of *Good regulatory practices for regulation of medical products*. Originally drafted in 2016, the document is a response to requests from national authorities responsible for regulatory oversight of medical products for guidance in addressing common gaps in regulatory practices identified during benchmarking exercises.

The draft document was revised several times at stakeholder consultations in 2016 and 2017. In September 2019, an international consultation of experts discussed the text again and agreed to redraft it as a short, concise document focusing on scope, intended use, purpose, principles, enablers and examples for policy-makers and regulators. They agreed that the concise guidance should be complemented by a series of guidance texts providing practical tools and tactics for implementing GRP, such as case studies or practice guides.

The concise guidance was drafted in the first half of 2020; it identifies nine principles of good regulatory practices: legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency and transparency. The document was sent for public consultation in August–September 2020, resulting in 410 comments from 19 parties. Most of the comments were for revisions to: reinforce the role of industry and stakeholders in ensuring good regulatory practices through, for example, public consultation and user feedback mechanisms; include the performance of medical devices; emphasize flexibility and responsiveness in the regulatory framework; ensure consistency in risk-based regulatory oversight across all products and entities; and add some terms to the glossary.

All the comments were reviewed and, as appropriate, incorporated into a revised version before presentation to the ECSPP.

The ECSPP thanked all those involved in preparing the document, reviewed the newly drafted guidance and made several suggestions for improvements. Topic of discussion included: shared responsibilities of regulating and regulated parties in achieving efficient regulatory environments; the role of patients as increasingly active stakeholders; the importance of inter- and intra-organizational coordination and collaboration; and the appropriateness of the guideline title ("regulation" rather than "regulatory oversight").

The Expert Committee adopted *Good regulatory practices in the regulation of medical products* (Annex 11).

9.4 Update on WHO-listed authorities

Mr Hiiti Sillo, Team Lead, Regulatory Systems Strengthening, updated ECSPP members on the development of a policy for evaluating and publicly designating regulatory authorities as "WHO-listed authorities" (WLAs). The policy aims to ensure a transparent and evidence-based pathway for global recognition of regulatory authorities that meet and apply WHO and other internationally recognized standards and guidelines, as well as good regulatory practices. The WLA designation is intended to replace the concept of a "stringent regulatory authority".

The first draft of the policy was based on a concept note published in May 2019 and on the 493 comments received on the note after it was sent for public comment. It was subsequently discussed at two consultations with Member States and interested stakeholders (first in September 2019 and again in June–July 2020) and in two public consultations (December 2019–February 2020 and August–September 2020). After each consultation, the comments received were collated, reviewed and used to revise the draft document. Participants in the meetings and consultations voiced their overall support for the draft WLA policy and for the roadmap for developing operational guidance for implementation, including the performance evaluation framework. The latest draft policy includes the context, purpose, scope and operating principles of evaluating and publicly listing WLAs and also a definition of a WLA.

The new policy is intended to promote trust among regulatory authorities, increase the pool of authorities that contribute to the WHO PQ programme and increase investment in and improvement of regulatory systems.

Members of the ECSPP discussed the WLA definition, noting that regulatory authorities may apply for a WLA listing for specific regulatory functions, for product streams and for all regulatory functions, as defined in the WHO Global Benchmarking Tool. They suggested a minor clarification of the definition.

The Expert Committee also discussed aspects of the draft WLA policy including the interim list of NRAs as a proxy for WLAs and the necessity for

transitional arrangements for existing reference authorities (such as stringent regulatory authorities), to be addressed in the WLA operational guidance.

The ECSPP noted that, once the new definition is accepted, it should be integrated into all relevant documents that currently refer to stringent regulatory authorities. It further noted that the WLA definition and draft policy will also be presented to the Expert Committee on Biological Standardization in October 2020 and is expected to be approved and published by WHO by the end of 2020. It will be tested during 2021 and become fully operational in early 2022.

The Expert Committee adopted the definition of a WLA as *"a regulatory authority or a regional regulatory system which has been documented to comply with all the relevant indicators and requirements specified by WHO for the requested scope of listing based on an established benchmarking and performance evaluation process"*, in which "regulatory authority" is understood to cover all the institutions, working together in an integrated and effective manner, that are responsible for the regulatory oversight of medical products in a given country or region. The Expert Committee asked the WHO Secretariat to prepare a situation analysis and to propose ways to replace references to "stringent regulatory authorities" by "WLAs" in relevant WHO documents and guidance texts.

9.5 Recommendations from the virtual consultation on Regulatory Guidance for Multisource Products

ECSPP members were updated by correspondence on the annual consultation on Regulatory Guidance for Multisource Products between the NSP Team and the PQ Team - Assessment Group. This year, due to the COVID-19 pandemic, the consultation was held as a series of virtual meetings.

The annual meeting provides a regular platform for the two teams to exchange information on their current activities and to discuss potential future activities in the areas of bioequivalence and biowaiver, assisted by specialists in the field. Participants were updated on activities for supporting PQ applicants in designing bioequivalence studies for prequalification.

- **Product-specific guidance texts.** After discussion, the group of experts suggested consideration of whether product-specific guidance texts from the PQ Team on the design of bioequivalence studies could be presented to the ECSPP with a view to making it more generally available to regulators.
- **WHO *List of International Comparator Products*.** The experts emphasized the importance of the WHO List of International Comparator Products (*33*) in guiding the development of multisource pharmaceutical products as a critical tool for both

manufacturers and regulators. The group suggested pro-active triggering of an update, also to align it with the latest *WHO Model List of Essential Medicines*.

- **WHO guidance on registration requirements to establish interchangeability for generics.** The experts recommended consideration of whether the WHO guidance on biowaivers (*34*) should be revised in view of the text recently published by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (*35*). In addition, they suggested consideration of the Council's progress with regard to the new guidance on bioequivalence for immediate-release solid oral dosage forms (*36*) to update the section on highly variable drugs, with provisions on average scaled criteria for the extent of absorption (area under the curve {AUC}).
- **WHO Biowaiver Project cycle IV (2021).** The experts agreed on a potential set of APIs for cycle IV for presentation to the ECSPP and proposed two further exploratory studies (see section 9.1).

The Expert Committee noted the update and asked the WHO Secretariat to explore the feasibility of receiving product-specific guidance texts from the PQ Team on the design of bioequivalence studies with a view to making them more generally available to regulators. It further urged the WHO Secretariat to continue updating the WHO *List of International Comparator Products* (*33*) and to evaluate possible revision of Annex 6 to *Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*37*).

10. Miscellaneous: update on activities related to COVID-19

Dr Sabine Kopp updated ECSPP members on the range of activities undertaken in response to the COVID-19 pandemic, which include developing and sharing specifications, leveraging existing guidelines and supporting new activities.

10.1 Oxygen specifications

The NSP Team worked with the Medical Devices and Diagnostics Team to provide specifications for oxygen for medical use. Drawing on information in *The International Pharmacopoeia*, they prepared a document outlining the requirements for the pharmaceutical quality of oxygen for medical use. This document will form part of a compilation of advice on oxygen use for Member States.

10.2 Therapeutic specifications

Work is also underway to improve and include monographs in *The International Pharmacopoeia* that could have a direct bearing on treatment of COVID-19. This includes revising the monograph on dexamethasone phosphate injection to improve the test for related substances and preparing new monographs on remdesivir and remdesivir intravenous infusion (section 5.4.1).

In February 2020, the IMWP triggered action through the global pharmacopoeial alert system for COVID-19. Pharmacopoeial alerts enable rapid discussions among pharmacopoeias in order to respond to urgent public health needs. The pharmacopoeial alert system brings pharmacopoeias together to support the global response to COVID-19, including by providing guidance and information to manufacturers, regulators and stakeholders on critical medicines (both new and repurposed) being used or investigated to treat the disease. For example, world pharmacopoeias have collaborated to map the availability in world pharmacopoeias of monographs on medicines that are being investigated for COVID-19 and to publish the map online (*38*). Many pharmacopoeias have improved the accessibility of supportive pharmacopoeial texts by making them freely available online.

In addition to issuing a global pharmacopoeial alert, the IMWP established a subgroup of interested pharmacopoeias to explore the development of IMWP monographs for two therapeutic products being tested for use in COVID-19, for which there are no public specifications: remdesivir and favipiravir. While the originator of remdesivir was not interested in participating in the project, the manufacturer of favipiravir is working with the subgroup on a collaborative IMWP specification.

10.3 Existing guidance

In April 2020, the NSP Team collated the most relevant ECSPP-adopted guidance on pharmaceutical quality assurance and regulation of medicines and published it online (*39*). The list is structured to mirror the different phases of a product's life cycle. It draws on existing guidance texts to support the development, production, evaluation, distribution and quality control of medicines that might be or are already being used to treat COVID-19.

The NSP Team also contributed to a question-and-answer document prepared by the PQ Inspections Team to address queries about regulatory flexibility during the COVID-19 pandemic (*40*). The aim of the document, which will be updated periodically, is to help manufacturers understand potential differences in regulatory expectations during the pandemic.

10.4 New activities

Dr Kopp summarized three new activities related to COVID-19:

- **proposals for new or updated guidelines** by the PQ Inspection and Local Production and Assistance teams, considered to be particularly useful in the global response to COVID-19 (section 7.6);
- **expedited biowaiver studies**, in particular on solubility characterization of dexamethasone tablets, which has been completed (section 9.1); and
- **practical considerations for PQCLs during COVID-19**, which were summarized by the director of the PQCL and the WHO Collaborating Centre in South Africa in an article in *The Journal of Medical Laboratory Science & Technology South Africa* in September 2020 (*41*). The aim of the article is to inform PQCL managers and support them in ensuring safe working environments for analytical and administrative staff and continued service throughout the pandemic.

Members of the ECSPP also mentioned the initiative of the Pan American Health Organization to list essential medicines for managing patients admitted to intensive care units with suspected or confirmed COVID-19 (*42*) as an additional activity related to COVID-19.

The Expert Committee noted the update and acknowledged the value, and encouraged the use, of existing guidance texts in the context of the COVID-19 pandemic.

11. Closing remarks

The Expert Committee thanked the Chair and the WHO Secretariat for their exceptional work in ensuring such a smooth virtual meeting under the challenging circumstances of COVID-19.

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 supporting the Expert Committee and all ECSPP members for their active participation. Dr Sabine Kopp thanked participants 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 making the meeting efficient.

The Chair closed the meeting.

12. Summary and recommendations

The WHO ECSPP advises the Director-General of WHO in the area of medicines quality assurance. It oversees maintenance of *The International Pharmacopoeia* and provides guidance for use by relevant WHO units and regulatory authorities in WHO Member States, to ensure that medicines meet unified standards of quality, safety and efficacy. The ECSPP's guidance texts are developed through a broad consensus-building process, including iterative public consultations. Representatives of 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-fifth meeting, held virtually from 12 to 19 October 2020, the ECSPP received updates on cross-cutting issues from other WHO bodies, including the Prequalification Team, the Regulatory Systems Strengthening Unit and the INN Team. Updates were also provided by partner organizations, including the IMWP, the IAEA and UNFPA, on collaborative projects. The ECSPP was further updated on the latest work to ensure that manufacturers and inspectors address AMR.

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

The ECSPP reviewed new and revised specifications and general texts for the quality control testing of medicines for inclusion in *The International Pharmacopoeia*. The Expert Committee adopted 17 pharmacopoeial texts (4 general chapters, 11 new and revised monographs, including 10 that are subject to a final review by a subgroup and 2 corrections), and confirmed the release of 2 new ICRS established by the custodial centre for use in connection with *The International Pharmacopoeia*.

The ECSPP reviewed proposals for new and updated quality assurance and regulatory guidance and adopted 10 new guidance texts. In line with last year's recommendations, the ECSPP updated the WHO *Biowaiver List* as an annex to its report. Moreover, it agreed to annex a consolidated list of all current guidelines and guidance texts adopted by the ECSPP. After an update from the Regulatory Systems Strengthening unit and further discussion, the Expert Committee adopted a definition of "WHO-listed authorities" (WLAs).

The sections that follow summarize the specific decisions and recommendations made by the ECSPP during its Fifty-fifth meeting in 2020.

12.1 Guidelines and decisions adopted and recommended for use

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

- *Points to consider when including health-based exposure limits in cleaning validation* (Annex 2)
- *Good manufacturing practices: water for pharmaceutical use* (Annex 3)
- *Guideline on data integrity* (Annex 4)
- *World Health Organization/United Nations Population Fund recommendations for condom storage and shipping temperatures* (Annex 5)
- *World Health Organization/United Nations Population Fund guidance on testing of male latex condoms* (Annex 6)
- *World Health Organization/United Nations Population Fund guidance on conducting post-market surveillance of condoms* (Annex 7)
- *WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (Annex 8)
- *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* (Annex 9)
- *Good reliance practices in the regulation of medical products: high-level principles and considerations* (Annex 10)
- *Good regulatory practices in the regulation of medical products* (Annex 11)

12.2 Texts adopted for inclusion in *The International Pharmacopoeia*

The ECSPP adopted the texts, chapters and monograph listed below.

12.2.1 General chapters

- Dissolution test for solid oral dosage forms (revision)
- General identification tests (revision)

12.2.2 Monographs

General monographs for dosage forms

- Powders for inhalation (new)
- Liquid preparations for oral use (revision)

COVID-19 therapeutics

- dexamethasone sodium phosphate (correction)
- dexamethasone phosphate injection (correction)
- remdesivir (new)*
- remdesivir intravenous infusion (new)*

Antiviral medicines, including antiretrovirals

- dolutegravir sodium (new)*
- dolutegravir tablets (new)*
- zanamivir (new)*
- zanamivir powder for inhalation, pre-metered (new)*

Medicines for tropical diseases

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

Excipients

- sodium starch glycolate (new)*
- sodium laurilsulfate (new)*
- hydroxypropylcellulose, low-substituted (new)*

12.2.3 Omissions

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

- test for histamine-like substances (vasodepressor substances), including the whole of Chapter 3.6 and all reference to vasodepressor substances in the monographs on bleomycin sulfate, spectinomycin hydrochloride and streptomycin sulfate.

12.2.4 ICRS

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

- estradiol valerate ICRS, batch 1; and
- moxifloxacin hydrochloride ICRS, batch 1.

12.3 Recommendations

The ECSPP made recommendations on norms and standards for pharmaceuticals, listed below. Progress in completing the suggested actions will be reported to the ECSPP at its Fifty-sixth meeting in October 2021.

The Expert Committee recommended that the WHO Secretariat, in collaboration with experts as appropriate, take the actions listed below.

12.3.1 *The International Pharmacopoeia*

- Continue preparation of monographs, general methods, texts and general supplementary information, including two IAEA/WHO specifications for radiopharmaceuticals, in accordance with the 2020–2021 workplan and as decided at the meeting.
- Develop a concept for future work on monographs on excipients in *The International Pharmacopoeia*, including consideration of whether such monographs are necessary from a public health perspective, known quality deficiencies and ways to harmonize specifications with those in other pharmacopoeias.

12.3.2 Quality control – national laboratories

- Continue the EQAAS to support national and regional PQCLs, including continuation of the post-assessment assistance programme.

12.3.3 Good manufacturing practices and related areas

- Continue collaboration with the EU, EMA and PIC/S to harmonize guidance on sterile products and, if feasible, present such guidance for possible adoption at the next ECSPP meeting, in 2021.
- Continue preparation of a new IAEA/WHO text on GMP for radiopharmaceuticals for investigational use.
- Open the WHO guideline on cleaning validation to review, and update it in accordance with the latest good practices, including the newly adopted *Points to consider when including health-based exposure limits in cleaning validation*.
- Publish the results of the survey of pharmaceutical manufacturers that engage in synthesis and/or production of antimicrobials on their waste and wastewater management practices in a regulatory journal.

- Assist national inspectorates and manufacturers in implementing recommendations made in the *Points to consider for manufacturers and inspectors: environmental aspects of manufacturing practices for the prevention of AMR*.
- Update the WHO guidance on *Good manufacturing practices: supplemental guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans*.
- Determine whether the *WHO guidelines on transfer of technology in pharmaceutical manufacturing* should be updated.
- Explore whether a new guideline is required on good practices during the research and development of medicinal products.

12.3.4 Distribution and supply chain

- Encourage WHO colleagues involved in procurement to support implementation of *Points to consider for setting the remaining shelf life of medical products upon delivery*.
- Circulate for public consultation the proposed amendment to include emergency health kits for use in humanitarian emergency response as an additional example to the *Points to consider for setting the remaining shelf life of medical products upon delivery* guideline.

12.3.5 Regulatory mechanisms

- Start the next phase of the WHO Biowaiver Project (cycle IV), to continue the Biopharmaceutics Classification System-based classification of further APIs: abacavir, doxycycline, ethambutol, isoniazid, hydroxychloroquine, isoniazid, lamivudine, levonorgestrel and proguanil.
- Undertake a pilot expansion study in cycle IV of the WHO Biowaiver Project to consider API stability under pH conditions representative of the stomach and small intestine.
- Promote the results of the WHO Biowaiver Project in publications, advocacy, engagement and partnerships.
- Explore the feasibility of presenting product-specific guidance texts of the PQ Team on the design of bioequivalence studies to the ECSPP with a view to making them more generally available to regulators.
- Continue updating the *WHO List of International Comparator Products*.

- Evaluate a possible revision of *WHO multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability* (*30*).
- Ensure speedy implementation by WHO of the revised *WHO certification scheme on the quality of pharmaceutical products moving in international commerce*.
- Work with interested parties to facilitate implementation of the WHO Certification Scheme with electronic systems, including the use of e-CCPs.
- Prepare a situation analysis and propose a way to replace references to stringent regulatory authorities (SRAs) with WLAs in relevant WHO documents and guidance.

12.3.6 Other

- Continue to serve as the WHO Secretariat for IMWPs and to publish articles about the IMWP, especially the pharmacopoeial global alert on COVID-19, in open-access peer-reviewed journals.
- Continue annual updating of the Quality Assurance of Medicines Terminology Database.
- Promote the use of existing guidelines and guidance in the context of the COVID-19 pandemic.

Acknowledgements

The Expert Committee acknowledges the following contributors at WHO: Dr A. Al-Nuseirat, WHO Regional Office for the Eastern Mediterranean; Dr S. Azatyan, Group Lead, Regulatory Convergence and Networks; Professor H.H. Balkhy, Assistant Director-General, Antimicrobial Resistance; Dr R. Ballocco, Unit Head, International Nonproprietary Names and Classification of Medical Products; Ms B. Cappello, Essential Medicines; Dr D. Catsoulacos, Inspection Services; Mr M. Chafai, Inspection Services; Ms H.L. Choi, Medicines Assessment; Mr M. Conrad, Inspection Services; Ms E. Cooke, Director, Regulation and Prequalification Department; Ms S. Croft, Inspection Services; Dr N. Dellepiane, Consultant, Regulatory System Strengthening; Dr J. Dong, Local Production and Assistance; Dr S. Estevão Cordeiro, Norms and Standards for Pharmaceuticals; Mr M. Freitas Dias, WHO Regional Office for the Americas; Dr V. Gigante, Norms and Standards for Pharmaceuticals; Dr J. Gouws, Team Lead, Inspection Services; Dr L. Gwaza, Facilitated Product Introduction; Ms S. Jones, Norms and Standards for Pharmaceuticals; Dr A. Khadem Broojerdi, Regulation and Safety; Dr I. Knezevic, Team Lead, Norms and Standards for Biological Products; Dr S. Kopp, Team Lead, Norms and Standards for Pharmaceuticals; Dr H. Langar, WHO Regional Office for the Eastern Mediterranean; Ms S. Laroche, Global Supply Policies; Dr S. Lewis, Consultant, Norms and Standards for Pharmaceuticals; Dr D. Lei, Norms and Standards for Biological Products; Mr D. Mubangizi, Unit Lead, Prequalification; Mr M. Musonda, Prequalification; Mr L. Nzumbu, Medicines Assessment; Dr C. Ondari, Director, Health Product Policy and Standards; Dr R. Ostad Ali Dehaghi, Regulation and Safety; Mr M. Refaat, Regulation and Safety; Dr M. Roldao Santos, Regulatory System Strengthening; Mr V. Sachdeva, Inspection Services; Ms A. Sands, Incidents and Substandard/Falsified Medical Products; Dr H. Schmidt, Norms and Standards for Pharmaceuticals; Dr M. Shridhar, WHO Regional Office for South-East Asia; Mr H. Sillo, Team Lead, Regulation and Safety; Dr M. Simão, Assistant Director-General, Access to Medicines and Health Products; Dr M. Stahl, Team Lead, Medicines Assessment; Dr P. Steyn, Contraception and Fertility Care; Mrs I. Streipa, Inspection Services; Mrs M. Valentin,Regulatory Convergence and Networks; Ms C. Vogel, Norms and Standards for Pharmaceuticals; Mr W.Z. Worku, Medicines Assessment; and Mrs H. Yin, Medicines Assessment.

Technical guidance included in this report was prepared with the financial assistance of the Bill & Melinda Gates Foundation, the German Federal Ministry of Health, The Global Fund to Fight AIDS, Tuberculosis and Malaria and the United Nations Development Programme.

The Expert Committee also acknowledges with thanks the valuable contributions made to its work by the following agencies, institutions,

organizations, pharmacopoeias, WHO collaborating centres, WHO programmes (especially the Regulatory and Prequalification Teams) and individuals:

Brazilian Health Surveillance Agency, Brasília DF, Brazil; Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring (MD), USA; Comisión Federal para la Protección contra Riesgos Sanitaríos, and Administration and Finance, Secretaria de Salud, Mexico City, Mexico; European Commission, Brussels, Belgium; European Directorate for the Quality of Medicines & HealthCare, Council of Europe, Strasbourg, France; European Healthcare Distribution Association, Brussels, Belgium; European Medicines Agency, Amsterdam, Netherlands; Global Self-Care Federation (formerly World Self Medication Industry), Nyon, Switzerland; International Atomic Energy Agency, Vienna, Austria; International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; International Generic and Biosimilar Medicines Association, Brussels, Belgium; International Pharmaceutical Excipients Council Federation ASBL, Brussels, Belgium; International Pharmaceutical Federation, The Hague, Netherlands; International Society for Pharmaceutical Engineering, Tampa (FL), USA; Medicines for Europe, Brussels, Belgium; Medicines and Healthcare Products Regulatory Agency, Inspection, Enforcement and Standards Division, London, United Kingdom; National Agency of Drug and Food Control, Jakarta Pusat, Indonesia; National Food and Drug Authority, Kampala, Uganda; Parenteral Drug Association, Bethesda (MD), USA; Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Swissmedic, Swiss Agency for Therapeutic Products, Bern, Switzerland; The Global Fund to Fight AIDS, Tuberculosis and Malaria, Geneva, Switzerland; The Stop TB Partnership, Geneva, Switzerland; Therapeutic Goods Administration, Woden, ACT, Australia; Turkish Medicines and Medical Devices Agency, Ankara, Turkey; United Nations Children's Fund, Supply Division, Copenhagen, Denmark; United Nations Development Programme, Châtelaine, Switzerland; United Nations Industrial Development Organization, Geneva, Switzerland; United Nations Population Fund, Copenhagen, Denmark.

Laboratoire National de Contrôle des Produits Pharmaceutiques, Dély Ibrahim, Algeria; Instituto Nacional de Medicamentos, Buenos Aires, Argentina; Expert Analytic Laboratory, Centre of Drug and Medical Technology Expertise, Yerevan, Armenia; University of Liège, Liège, Belgium; Laboratoire National de Contrôle de Qualité des Médicaments et Consommables Médicaux, Cotonou, Benin; Agency for Medicinal Products and Medical Devices, Control Laboratory, Sarajevo, Bosnia and Herzegovina; Instituto Nacional de Controle de Qualidade em Saúde, Rio de Janeiro, Brazil; Laboratoire National de Santé Publique, Ouagadougou, Burkina Faso; National Product Quality Control Centre, Ministry of Health, Phnom Penh, Cambodia; Laboratoire National de Contrôle de Qualité des Médicaments et d'Expertise, Yaoundé, Cameroon; Departamento de Control

Nacional, Unidad de Control de Calidad de Medicamentos Comercializados, Institutu de Salud Pública, Santiago de Chile, Chile; Changzhou Center for Food and Drug Control, Changzhou, China; Chengdu Institute for Food and Drug Control, Sichuan, China; Chongqing Institute for Food and Drug Control, Chongqing City, China; Dalian Drug Quality Control Institute, Dalian City, China; Guangzhou Municipal Institute for Drug Control, Guangzhou, China; Hubei Institute For Drug Control, Wuhan, China; Jiangsu Institute for Food and Drug Control, Nanjing, China; Guangdong Institute for Drug Control, Guangdong, China; National Institutes for Food and Drug Control, Beijing, China; Shandong Institute for Food and Drug Control, Shandong, China; Shenzhen Institute for Drug Control Jiangsu Province, Shenzhen, China; Sichuan Institute for Food and Drug Control, Sichuan, China; Suzhou Institute for Drug Control, Jiangsu, China; Tianjin Institute for Drug Control, Tianjin, China; Wuxi Institute For Drug Control, Jiangsu, China; Xiamen Institute for Food and Drug Control, Xiamen, China; Zhejiang Institute for Drug and Food Control, Zhejiang, China; Medicamentos y Productos Biológicos, Instituto Nacional de Vigilancia de Medicamentos y Alimentos, Bogotá, Colombia; Laboratorio de Análisis y Asesoría Farmacéutica, Facultad de Farmacia, Universidad de Costa Rica, San José, Costa Rica; Laboratorio de Normas y Calidad de Medicamentos, Caja Costarricense de Seguro Social, Universidad de Costa Rica, Alajuela, Costa Rica; Laboratoire National de la Santé Publique, Abidjan, Côte d'Ivoire; Agency for Medicinal Products and Medical Devices of Croatia, Official Medicines Control Laboratory Division, Zagreb, Croatia; Oficina Sanitaria Panamericana, WHO on behalf of Centro para el Control Estatal de Medicamentos, Havana, Cuba; National Organization for Drug Control and Research, Cairo, Egypt; Food, Medicine and Healthcare Administration and Control Authority of Ethiopia, Addis Ababa, Ethiopia; Jimma University Laboratory of Drug Quality, Jimma, Ethiopia; Centrale Humanitaire des Métiers de la Pharmacie, Clermont Ferrand, France; Center for Pharmaceutical Advancement and Training, Accra, Ghana; Food and Drugs Board, Quality Control Laboratory, Accra, Ghana; Laboratoire National de Contrôle de Qualité des Medicaments, Conakry, Guinea; Laboratory for Quality Evaluation and Control, National Institute of Pharmacy, Budapest, Hungary; National Quality Control Laboratory of Drug and Food, National Agency for Food and Drug Control, Yogyakarta, Indonesia; Food and Drugs Control Laboratories, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran; Caribbean Public Health Agency Drug Testing Laboratory, Kingston, Jamaica; Mission for Essential Drugs and Supplies, Nairobi, Kenya; National Quality Control Laboratory for Drugs and Medical Devices, Nairobi, Kenya; Central Analytical Laboratory, Bishkek City, Kyrgyzstan; Arwan Pharmaceutical Industries Lebanon s.a.l., Jadra, Lebanon; Food and Drug Quality Control Centre, Ministry of Health, Vientiane, Lao People's Democratic Republic; Ministry of Health, Maseru, Lesotho; Laboratoire

de Contrôle de Qualité des Médicaments, Agence du Médicament de Madagascar, Antananarivo, Madagascar; Centre for Quality Control, National Pharmaceutical Control Bureau, Petaling Jaya, Selangor, Malaysia; Laboratoire National de la Santé du Mali, Bamako, Mali; Laboratoire National de Contrôle de Qualité des Médicaments, Nouakchott, Mauritania; Laboratoire National de Contrôle des Médicaments, Rabat, Morocco; National Laboratory for Medicine Quality Testing Ministry of Health, Maputo, Mozambique; Quality Surveillance Laboratory, Windhoek, Namibia; National Medicines Laboratory, Department of Drug Administration, Kathmandu, Nepal; Laboratoire National de Santé Publique et d'Expertise, Niamey, Niger; National Agency for Food and Drug Administration and Control, Abuja, Nigeria; Central Quality Control Laboratory, Directorate General of Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Drug Control and Traditional Medicine Division, National Institute of Health, Islamabad, Pakistan; Getz Pharma (Pvt.) Ltd, Karachi, Pakistan; Instituto Especializado de Análisis, Universidad de Panamá, Panama; Centro Nacional de Control de Calidad, Instituto Nacional de Salud, Lima, Peru; Bureau of Food and Drugs, Department of Health, Muntinlupa City, Philippines; Laboratory for Quality Control of Medicines, Medicines Agency, Ministry of Health, Chisinau, Republic of Moldova; Saudi Food and Drug Authority, Section Head of Operations Performance Measurement, Riyadh, Saudi Arabia; Laboratoire National de Contrôle des Médicaments, Dakar Etoile, Senegal; Drug Quality Control Laboratory, Ministry of Health, Victoria, Seychelles; National Pharmaceutical Quality Control Laboratory, Registrar Pharmacy Board of Sierra Leone, Freetown, Sierra Leone; WHO Collaborating Centre for Drug Quality Assurance, Pharmaceutical Division, Applied Sciences Group, Singapore; Adcock Ingram Healthcare, Bryanston, South Africa; Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; National Drug Quality Assurance Laboratory, Ministry of Health, Colombo, Sri Lanka; National Drug Quality Control Laboratory, Directorate General of Pharmacy, Federal Ministry of Health, Khartoum, Sudan; Pharmaceutical Analysis Laboratory, R&D, Tanzania Food and Drug Authority, Dar es Salaam, United Republic of Tanzania; School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand; Laboratoire National de Contrôle des Médicaments, Tunis, Tunisia; National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; Central Laboratory for Quality Control of Medicines, Ministry of Health, Kiev, Ukraine; Laboratory of Pharmaceutical Analysis, State Pharmacological Centre, Ministry of Health, Kiev, Ukraine; Laboratorio Control de Productos Ministerio de Salud Pública, Comisión Para El Control de Calidad de Medicamentos, Montevideo, Uruguay; Instituto Nacional de Higiene "Rafael Rangel", Caracas, Venezuela; National Institute of Drug Quality Control, Hanoi, Viet Nam; Zambia

Medicines Regulatory Authority, Lusaka, Zambia; Medicines Control Authority of Zimbabwe, Harare, Zimbabwe.

African Pharmacopoeia, Abuja, Nigeria; Farmacopea Argentina, Buenos Aires, Argentina; Austrian Pharmacopoeia, Vienna, Austria; State Pharmacopoeia of the Republic of Belarus, Minsk, Belarus; Belgian Pharmacopoeia Commission, Brussels, Belgium; Agency for Medicinal Products and Medical Devices, Sarajevo, Bosnia and Herzegovina; Farmacopeia Brasileíra, Brasília DF, Brazil; Bulgarian Drug Agency, Sofia, Bulgaria; *Farmacopea Chilena, Valparaíso, Chile*; Chinese Pharmacopoeia Commission, Beijing, China; Agency for Medicinal Products and Medical Devices, Zagreb, Croatia; Pharmaceutical Services, Nicosia, Cyprus; Czech Pharmacopoeia Commission, Prague, Czechia; Danish Pharmacopoeia Commission, Copenhagen, Denmark; Permanent Commission of the Egyptian Pharmacopoeia, Cairo, Egypt; State Agency of Medicines, Tartu, Estonia; Pharmacopoeial Committee of the Eurasian Economic Union, Moscow, Russian Federation; European Pharmacopoeia, European Directorate for the Quality of Medicines and HealthCare, Council of Europe, Strasbourg, France; Finnish Medicines Agency Pharmacopoeia Committee, Finnish Medicines Agency, Helsinki, Finland; Pharmacopée française, Agence Nationale de Sécurité du Médicament et des Produits de Santé, Saint-Denis, France; German Pharmacopoeia Commission, Bonn, Germany; Greek Pharmacopoeia Commission, Holargos Attikis, Greece; Hungarian Pharmacopoeia Commission, Budapest, Hungary; Icelandic Medicines Agency, Reykjavik, Iceland; Indian Pharmacopoeia Commission, Ghaziabad, India; Indonesian Pharmacopoeia Commission, Jakarta Pusat, Indonesia; The International Pharmacopoeia, World Health Organization, Geneva, Switzerland; Iranian Pharmacopoeia, Tehran, Islamic Republic of Iran; Italian Pharmacopoeia Commission, Rome, Italy; Committee of the Japanese Pharmacopoeia, Pharmaceutical Affairs Food Sanitation Council, Tokyo, Japan; The State Pharmacopoeia of the Republic of Kazakhstan, Almaty, Kazakhstan; Lithuanian Pharmacopoeia Commission, Vilnius, Lithuania; Malta Medicines Authority, San Gwann, Malta; Mexican Pharmacopoeia, México DF, Mexico; Norwegian Pharmacopoeia Authority, Oslo, Norway; Pakistan Pharmacopoeia Commission, Islamabad, Pakistan; Philippines Pharmacopoeia, Manila, Philippines; Polish Pharmacopoeia Commission, Warsaw, Poland; Portuguese Pharmacopoeia, Porto, Portugal; Pharmacopoeia of the Republic of Korea, Chuncheongbuk-do, Republic of Korea; Romanian Pharmacopoeia Commission, Bucharest, Romania; State Pharmacopoeia Council of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; Serbian Pharmacopoeia, Belgrade, Serbia; Slovak Pharmacopoeia Commission, Bratislava, Slovakia; Slovenian Pharmacopoeia Commission, Ljubljana, Slovenia; Spanish Pharmacopoeia, Madrid, Spain; Swedish Pharmacopoeia Commission, Uppsala, Sweden; Swiss Pharmacopoeia, Bern, Switzerland; Thai Pharmacopoeia Commission, Nonthaburi, Thailand;

Turkish Medicines and Medical Devices Agency, Department of Analysis and Control Laboratories, Vice Presidency of Economic Assessments and Laboratory Services, Ankara, Turkey; Pharmacopoeia of Ukraine, Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines, Kharkov, Ukraine; British Pharmacopoeia Commission, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; United States Pharmacopeia, Rockville (MD), USA; Vietnamese Pharmacopoeia Commission, Hanoi, Viet Nam.

WHO Centre Collaborateur pour la Conformité des Médicaments, Laboratoire National de Contrôle des Produits Pharmaceutiques, Algiers, Algeria; WHO Collaborating Centre for Drug Quality Assurance, Therapeutic Goods Administration Laboratories, Woden, ACT, Australia; WHO Collaborating Centre for Drug Quality Assurance, National Institutes for Food and Drug Control, Beijing, China; WHO Collaborating Centre for Drug Quality Assurance, Pharmaceutical Laboratory, Centre for Analytical Science, Health Sciences Authority, Singapore; WHO Collaborating Centre for Quality Assurance of Drugs, North-West University, Potchefstroom, South Africa; WHO Collaborating Centre for Quality Assurance of Essential Drugs, Bureau of Drug and Narcotic, Department of Medical Sciences, Ministry of Public Health, Nonthaburi, Thailand.

Antimicrobial Resistance Division, WHO, Geneva, Switzerland; Regulation and Prequalification, WHO, Geneva, Switzerland; Global Malaria Programme, Universal Health Coverage/Communicable and Noncommunicable Diseases, WHO, Geneva, Switzerland; Global Tuberculosis Programme, WHO, Geneva, Switzerland; HIV/AIDS, WHO, Geneva, Switzerland; International Nonproprietary Names and Classification of Medical Products, WHO, Geneva, Switzerland; Office of the Legal Counsel, WHO, Geneva, Switzerland; Prequalification, WHO, Geneva, Switzerland; Prevention and Control of Noncommunicable Diseases, WHO, Geneva, Switzerland; Regulation of Medicines and other Health Technologies, WHO, Geneva, Switzerland; Technologies Standards and Norms, WHO, Geneva, Switzerland.

WHO Regional Office for Africa, Brazzaville, Congo; WHO Regional Office for the Americas, Washington DC, USA; WHO Regional Office for the Eastern Mediterranean, Cairo, Egypt; WHO Regional Office for Europe, Copenhagen, Denmark; WHO Regional Office for South-East Asia, New Delhi, India; WHO Regional Office for the Western Pacific, Manila, Philippines.

Dr H. Abboud, National Drug Quality Assurance and Research Laboratories, Damascus, Syrian Arab Republic; ACS Dobfar S.p.A., Italy; Dr S. Adam, Senior Manager for Regulatory and Scientific Affairs, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; Professor E. Adams, Pharmaceutical Analysis, K.U. Leuven, Leuven, Belgium; Dr A. Adisa, Principal Evaluator, Therapeutic Goods Administration, Woden, Australia; Dr F. Aguilar-Parrilla, Bayer AG, Berlin, Germany; Mr Y.

Al-Nujaym, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Professor V.R. Alamà, Universidad Cardenal, Valencia, Spain; Dr I. Aljuffali, Executive Vice-President, Drug Sector, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Dr J. Albanese, Director, Analytical Strategy and Compliance, Janssen Research and Development, USA; Mr I. Alstrup, Medicines Inspector, Danish Medicines Agency, Copenhagen, Denmark; Dr M. Ali Alqubati, Pharmacist, Sana'a, Yemen; Mr D. Anderson, Global Business Unit Quality Director, Solvay, Brussels, Belgium; Dr T. Ando, Division of Pharmacopoeia and Standards for Drugs, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; Mr K. Andrei, Federal State Budgetary Institution, Scientific Centre for Expert Evaluation of Medicinal Products of the Ministry of Health of the Russian Federation, Moscow, Russian Federation; Dr M.H. Al Rubaie, Director General, Ministry of Health, Muscat, Oman; Ms Y. Anastasio, National Administration of Drugs, Food and Medical Devices, Buenos Aires, Argentina; Dr B. Appiasam-Dadson, Food and Drugs Authority, Accra, Ghana; Mr R. Arcuri, Executive President, FarmaBrasil Group, Brasilia, Brazil; Dr A. Arias, Senior Advisor, Health Canada, Ottawa, Canada; Ms S. Arsac-Janvier, International Committee of the Red Cross, Geneva, Switzerland; Dr M. Assalone, Technical Secretary of Argentinian Pharmacopoeia, Medicines National Institute, Buenos Aires, Argentina; Aurobindo Pharma Limited, Hyderabad, India; Ms S. Ayral, World Trade Organization, Geneva, Switzerland; Dr O. Badary, National Organization for Drug Control and Research, Cairo, Egypt; Ms H. Baião, Infarmed, Lisbon, Portugal; Mr N. Banerjee, Microbiology Head, Aurobindo Pharma, East Windsor (NJ), USA; Mr A. Bansal, Drugs Inspector, Central Drugs Standard Control Organisation, New Delhi, India; Mr A. Barojas, Technical Adviser, Product Quality and Compliance, Durham (NC), USA; Mr I. Basade, Mylan Laboratories Ltd, Hyderabad, India; Professor S.A.O. Bawazir, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; Professor M. Beksinska, Deputy Executive Director, MatCH Research Unit, Durban, South Africa; Dr M. Belayneh, Pharmacist, United States Agency for International Development, Washington DC, USA; Professor M. Bermejo-Sanz, Department of Pharmaceutical Technology and Pharmaceutics, Universidad Miguel Hernández de Elche, Alicante, Spain; Mr L. Blankenfeldt, trans-o-flex Express GmbH, Weinheim, Germany; Dr A. Blommaert, Faculty of Pharmacy, Paris, France; Ms R.F. Boadu, Food and Drugs Authority, Accra, Ghana; Mr S. Bodemeier, Ritex GmbH, Bielefeld, Germany; Mr B. Boedecker, Hanover, Germany; Mr M. Boisen, Quality Intelligence Manager, Novo Nordisk A/S, Bagsværd, Denmark; Mr K. Bokaba, Medicines Control Council, South Africa; Ms A. Bonneure, Active Pharmaceutical Ingredients Committee, European Chemical Industry Council, Brussels, Belgium; Ms V. Bonilla, Comisión para el Control de Calidad de Medicamentos, Montevideo, Uruguay; Professor R. Boudet-Dalbin, Paris, France; Mr R.M. Bretas, Good Manufacturing Practice Inspector, Health Regulatory Agency, Brasília, Brazil; Dr M. Brits, Operations

Manager, Research Institute for Industrial Pharmacy Inc., Centre for Quality Assurance of Drugs, North-West University, Potchefstroom, South Africa; Dr R. Bose, Deputy Drugs Controller, Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, New Delhi, India; Ms Y. Bowman, Netherlands; Mr D. Brunner, Pharmaceutical Inspection Co-operation Scheme, Geneva, Switzerland; Dr T. Brusselmans, Directorate General Inspection, Industry Division, Medicines, Federal Agency for Medicines and Health Products, Brussels, Belgium; Ms K. Bugge Skou, Scientific Officer, Lægemiddelstyrelsen, Danish Medicines Agency, Denmark; Dr N. Bunnuan, Director, Manufacturing Quality Assurance, LifeStyles, Bangkok, Thailand; Mr M. Bursian, Head Archive Operations, Grünenthal GmbH, Aachen, Germany; Mr Y. Cai, Process Support Specialist, Fresenius Kabi SSPC, Wuxi, China; Dr M. Camelia, Radiologist, Federal Institute for Drugs and Medical Devices, Bonn, Germany; Ms S. Camplisson, Director of Pharmaceutical Technology, Allergan Pharmaceuticals Ireland, Westport, Ireland; Dr A.M. Cancel, Product Quality and Compliance, FHI 360, Durham, NA, USA; Mr Y. Cao, Deputy Director of the 4th Divison Inspections, Centre for Food and Drug Inspection of National Medical Products Administration, Beijing, China; Dr N. Cappuccino, Chair, Science Committee, International Generic and Biosimilar Medicines Association, Geneva, Switzerland; Mr G. Carroll, General Manager Development Programme, Operations Manager and Senior Inspector, Inspections Enforcement and Standardization, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Ms M. Casais, Senior Advisor, Bill & Melinda Gates Foundation, London, United Kingdom; Dr J.M. Caudron, United Nations Development Programme, Châtelaine, Switzerland; Mr S. Cavalheiro Filho, Assistant Manager, Regulatory Affairs, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; Mr S. Champaneri, Certification Manager/Product Technical Specialist, British Standards Institution, London, United Kingdom; Dr T. Chanprapaph, Thailand Food and Drug Administration, Nonthaburi, Thailand; Ms P. Chauhan, Global Regulatory eCommerce & Intelligence, Reckitt Benckiser Healthcare, Hull, United Kingdom; Ms J. Chen, World Customs Organization, Brussels, Belgium; Mr M.R. Chowdhury, Novartis (Bangladesh) Ltd, Site Data Integrity Lead, Dhaka, Bangladesh; Dr Lakshman Chunduru, Laurus Labs, India; Dr W.K. Chui, Department of Pharmacy, Faculty of Science, National University of Singapore, Singapore; Ms A. Clark, Senior External Engagement Manager, United States Pharmacopeia, Rockville (MD), USA; Ms A. Cockrell, Executive Director, Society of Quality Assurance, Charlottesville (VA), USA; Dr R. Conocchia, European Medicines Agency, Amsterdam, Netherlands; Ms A.G. Cord'homme, Product Safety Manager, Health, Environmental and Regulatory Services, Puteaux, France; Dr A.R. Cornelio Geyer, Agência Nacional de Vigilância Sanitária (Anvisa), Brasilía, Brazil; Dr H. Corns, Principal Pharmacopoeial Scientist,

Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Dr R. Cumberbatch, Director, International and Regulatory Affairs, Animal Health Institute, Washington DC, USA; Ms V. Dagois, Director, CAPE-Expert, Cannet, France; Mr H. Dahmani, Pharmacist Quality Assessor, National Control Laboratory of Tunisia, Tunis, Tunisia; Mr D.I. Dalal, Executive Quality Assurance, Zim Laboratories Ltd, Nagpur, India; Mrs H.H. Dam, Officer, Drug Business Administration Division, Drug Administration of Viet Nam, Hanoi, Viet Nam; Ms Daryani, Indonesian Pharmacopoeia Commission, National Agency of Drug and Food Control, Jakarta Pusat, Indonesia; Mr D.X. Da Silva, Technical Regulatory and Innovation Analyst, Sindusfarma, São Paulo, Brazil; Ms C. Daugherty, Specialist, Quality Regulatory Intelligence, GlaxoSmithKline plc, Montrose, United Kingdom; Dr M.C. De Angelis, Technical Secretary, Argentinian Pharmacopoeia, Buenos Aires, Argentina; Professor T. Dekker, Research Institute for Industrial Pharmacy, North-West University, Potchefstroom, South Africa; Dr V. Dias Sousa, Directorate Advisor, Brazilian Health Surveillance Agency, Brasilía, Brazil; Dr M. Dmitriieva, Scientifc Secretary, Ukrainian Scientific Pharmacopoeial Center for Quality of Medicines, State Service of Ukraine on Medicinal Products, Ministry of Health, Kharkov, Ukraine; Professor E. Doelker, Geneva, Switzerland; Dr D. Dimas, Good Manufacturing Practice Inspector, National Organization for Medicines, Attiki, Greece; Mr J. Dobaria, Hetero Labs Ltd, Hyderabad, India; Dr P. Doerr, Bern, Switzerland; Dr O. Douglas; Mrs S. Dube-Mwedzi, South Africa Development Community, Medicines Regulatory Harmonization Project Coordinator, Zazibona Inspectorate, Medicines Control Authority of Zimbabwe, Harare, Zimbabwe; Mr W. Drummond, Senior Director, Charles River, Laboratories, Horsham (PA), USA; Professor G. Dutta, Quality Manager, A.N. Pharmacia Laboratories Pvt Ltd., West Bangal, India; Egis Pharmaceuticals Plc., Budapest, Hungary; Mr A. Evans, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Executive Direction of International Operation, Comision Federal para la Proteccion contra Riesgos Sanitarios, Mexico City, Mexico; Mr M. Falcon, Regulations and Standards Surveillance Manager, LFB S.A., Courtaboeuf Cedex, France; Dr A.M. Fallas, Technical Director, Gutis Ltda, San José, Costa Rica; Professor R. Fernandopulle, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka; Ms G.F. Ferreiro, Centro para el Control Estatal de Medicamento, Equipos y Dispositivos Médicos, Havana, Cuba; Ms M.P. Filliot, Global Quality Management APIs & Strategic Raw Materials, Bayer Consumer Care A.G., Basel, Switzerland; Dr G. Fischer, Head of Quality Regulatory Intelligence, Boehringer Ingelheim Corporate Center GmbH, Rhein, Germany; Mr M. Fleischer, Director, Quality, Transport, World Courier, Berlin, Germany; Dr A. Flueckiger, former Head of Occupational Health and Toxicology, Roche, PattenIn, Germany; Dr R. Forsyth, Senior Consultant, Forsyth Pharmaceutical Consulting, Royersford (PA), USA; Professor I. Fradi Dridi, Service Pharmacie,

Centre National de Greffe de Moelle Osseuse, Faculté de Pharmacie de Monastir, Monastir, Tunisia; Mr G.M. Francis, Pharmacy and Poisons Board, Nairobi, Kenya; Mr M. Friis, Epista Life Science, Hørsholm, Denmark; Ms K. Froidbise, Head of Division Industry, Directorate General Inspection, Federal Agency for Medicines and Health Products, Brussels, Belgium; Ms R. Gadde, Vice President, Global Health, Becton Dickinson, Franklin Lakes (NJ), USA; Mr J. Gaeseb, Namibia Medicines Regulatory Council, Ministry of Health and Social Services, Windhoek, Namibia; Mr A. Garcia-Aríeta, Head of Service on Pharmacokinetics and Generic Medicines, Division of Pharmacology and Clinical Evaluation, Department of Human Use Medicines, Spanish Agency of Medicines and Medical Devices, Madrid, Spain; Mr O. Garg, Chairman and Managing Director, Cupid Ltd, Nashik, India; Mr J. Gaeseb, Windhoek, Namibia; Dr K. Gao, National Institutes for Food and Drug Control, Beijing, China; Professor A. Genazzani, Novara, Italy; Dr M. Gencoglu, Regulatory Affairs Manager, International Federation of Pharmaceutical Manufacturers and Associations, Geneva, Switzerland; Mr J. Gerofi, Managing Director, Enersol, Sydney, Australia; Ms A.L. Ghilini, Quality Control Director, Minakem SAS, Dunkerque, France; Dr G. Gildeeva, Federal State Budgetary Institution, Scientific Centre for Expert Evaluation of Medicinal Products, Ministry of Health, Moscow, Russian Federation; Mrs E. Gladkaya, Head, Quality Assurance Division, Federal State Budgetary Institution, Scientific Centre for Expert Evaluation of Medicinal Products, Ministry of Health, Moscow, Russian Federation; Ms B. Goede, Senior International Product Manager, Virology, Roche, San Francisco (CA), USA; Mr C. B. Goldsmith Químico Farmacéutico, Santiago, Chile; Dr J. Gordon, Wolfville, Nova Scotia, Canada; Mr D. Greney, Quality Assurance Director, Recipharm, Kaysersberg, France; Mr P. Goyal, Senior Manager Quality, Lupin Ltd, Mumbai, India; Ms O. Gubareva, Head, International Cooperation Department, Federal State Budgetary Institution, Scientific Centre for Expert Evaluation of Medicinal Products, Ministry of Health, Moscow, Russian Federation; Ms I. Guerra, Associate Manager, Regeneron UK, Tarrytown (NY), USA; Ms N.M. Guerrero Rivas, Radiofarmacia de Centroamérica, S.A., Panamá, Panama; Ms M. Guest, Associate Principal Scientist, AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom; Ms R.C. Guimarães, Quality Deputy Director, Bio-Manguinhos-Fiocruz, Rio de Janeiro, Brazil; Mr C.S. Gumpally, Senior Executive, Neopharma LLC, Abu Dhabi, United Arab Emirates; Professor Z.P. Guo, Chinese Pharmacopoeia Commission, Beijing, China; Guilin Pharmaceutical Company Ltd, Guilin, China; Ms P. Hauschildt de Oliveira Mendes, Regulatory Expert, Health Regulatory Agency, Brasília, Brazil; Mr O. Hawari, Quality Assurance Manager, External Collaborations, Hoffman La Roche, Mississauga, ON, Canada; Ms Sri Hayanti, National Agency of Drug and Food Control, Jakarta, Indonesia; Mr W. Heimes, Administration Manager, European Compliance Academy Foundation, Heidelberg, Germany; Dr R. Hernández

Medina, Mexican Pharmacopoeia, Mexico City, Mexico; Dr M. Heuermann, Official Medicines Control Laboratory, Münster, Germany; Mr D. Hill, David Hill & Associates, International Latex Consultancy, Elsenham, United Kingdom; Ms M. Hirschhorn, Head, Quality and Chemistry Sector, Comisión para el Control de Calidad de Medicamentos, Montevideo, Uruguay; Mr J. Hodgson, Pharmaceutical Inspection Co-operation Scheme Secretariat, Geneva, Switzerland; Mr P. van der Hoeven, European Chemical Industry Council, Managing Director, Association for Professionals in Infection Control and Epidemiology, Brussels, Belgium; Dr P. Holland, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Mr M. Holmes, Management Committee Member, Pharmaceutical and Healthcare Sciences Society, Swindon, United Kingdom; Ms B. Holst, Danish Medicines Agency, Copenhagen, Denmark; Mr G. Holzem, Senior Manager, Grünenthal GmbH, Aachen, Germany; Dr X. Hong, Pharmacopoeia of the People's Republic of China, Beijing, China; Professor J. Hoogmartens, Catholic University of Leuven, Leuven, Belgium; Ms S. Hoogmoed, Regulatory Affairs and Assurance Manager, ACIC Pharmaceuticals Inc., Coral Springs (FL), USA; Mr I. Hussain, Information Technology Good Practice Validation Manager, Zealand Pharma IT, Soeborg, Denmark; Dr N. Hussain, Associate Director, Gilead Sciences, London, United Kingdom; Ms T.J. Hutadjulu, National Agency of Drug and Food Control, Jakarta, Indonesia; Dr K.E. Iddir, Director, Direction de la pharmacie et du médicament de Tunisie, Tunis, Tunisia; Indian Pharmaceutical Congress, Chennai, India; Mr S. Indoe, Associate Director, Merck Manufacturing Division, Pharmaceutical technical Operations Logistics and Distribution Technology, Merck & Co., Kenilworth (NJ), USA; Indus Medicare, Hyderabad, India; Ipca Laboratories Ltd., Maharashtra, India; Dr G.P.S. Jadaun, Senior Scientific Officer, Indian Pharmacopoeia Commission, Ghaziabad, India; Mr J. Jadav, Senior Executive, Assurance, Concord Biotech Ltd., Ahmedabad, India; Dr S.A. Jaffar, Director General, Pharmaceutical Affairs and Drug Control, Ministry of Health, Muscat, Oman; Dr P. Jakšić, Principal Advisor for Pharmacopoeia, Official Medicines Control Laboratory Division, Agency for Medicinal Products and Medical Devices, Zagreb, Croatia; Professor S. Jin, Chief Expert for Pharmaceutical Products, National Institutes for Food and Drug Control, Beijing, China; Mr D. John, Senior Technical Manager, Animal Health Europe, Brussels, Belgium; Mr J.L. Jouve, A3P association, eCompliance SIG Chairman, Lyon, France; Dr U. Juárez-Sevilla, Mexican Pharmacopoeia, Mexico City, Mexico; Ms A. Julsing, Medicines Control Council, Pretoria, South Africa; Professor E.A. Kaale, School of Pharmacy, Muhimbili University of Health and Allied Sciences, Dar es Salaam, United Republic of Tanzania; Mr B. Kalaivani, Manager Assurance and Risk Assessment, TTK Healthcare Ltd, Protective Devices Division, Chennai, India; Ms J. Kalina, Corporate Affairs Manager, European Healthcare Distribution Association, Brussels, Belgium; Dr S. Kamakshinatha, Pharmedices Technical

Services, Chennai, India; Mr S. Kare Nielsen, Chairman, Novo Nordisk Focus Group on Supply Chain, Novo Nordisk A/S, Bagsværd, Denmark; Karex, Selangor, Malaysia; Mr A. Kayongo, Consultant, UBOPACT Africa Ltd, Mukono, Uganda; Dr S. Keitel, Director, European Directorate for the Quality of Medicines and Health Care, Council of Europe, Strasbourg, France; Mr A. Kessete, Acting Head, Product Evaluation and Registration, National Medicines and Food Administration, Ministry of Health, Asmara, Eritrea; Mr D. Kharote, Assistant General Manager, Serum Institute of India Pvt. Ltd, Pune, India; Dr S. Khoja, Deputy General Manager, Quality Assurance, Skant Healthcare Ltd, Vapi, India; Mr S. Kigera, Mission for Essential Drugs and Supplies, Nairobi, Kenya; Mrs K. Kikule, Arlington (VA), USA; Dr N.H. Kim, Pharmaceutical Standardization Research and Drug Research Division, National Institute of Food and Drug Safety Evaluation, Chungcheongbuk-do, Republic of Korea; Mr S. Kisoma, Tanzania Medicines and Medical Devices Authority, Dar-es-Salaam, United Republic of Tanzania; Dr N.N.K. Kkrumah, Medicines Evaluation and Registration Department, Food and Drug Administration, Cantonment-Accra, Ghana; Mr S. Klidzia, Assurance Lead, Fujifilm Diosynth Biotechnologies, Bryan (TX), USA; Dr E Klenke, Head Preclinical Review, Bern, Switzerland; Mrs W. Kongsuk, Bureau of Drug and Narcotic, Department of Medical Sciences, Nonthaburi, Thailand; Dr A. Korde, Technical Officer, Radioisotope Products and Radiation Technology Section, Division of Physical and Chemical Sciences, International Atomic Energy Agency, Vienna, Austria; Dr E. Kovaleva, Deputy Director of the Centre for Evaluation and Control of Medicinal Products, Moscow, Russian Federation; Dr A. Krauss, Woden, Australia; Mr P. Kumar, Senior Manager, Institutions, International Business Division, HLL Lifecare Ltd, Trivandrum, India; Dr A. Kupferman, Industy Pharmacist, Bangkok, Thailand; Dr Z. Kusynova, Lead for Policy, Practice and Compliance, International Pharmaceutical Federation, The Hague, Netherlands; Dr W. Kwiringira, National Drug Quality Control Laboratory, National Drug Authority, Kampala, Uganda; Ms I. Laccisaglia, Global Quality Specialist, Kuehne+Nagel, Contern, Luxemburg; Professor J. Ladutko Mikhailovna, Department of Technology of Dosage Forms, Federal State Budgetary Educational Institution of Higher Education, St Petersburg State Chemical Pharmaceutical University, Ministry of Health, Moscow, Russian Federation; Mr K. Laenen, Quality and Regulatory Affairs Manager, Medicines for Europe, Brussels, Belgium; Laurus Labs Limited, Visakhapatnam, Italy; Ms L. Lavergne. Technical Coordinator, Pharmacist, Quality Medicine for All, Paris, France; Professor B.J. Lee, College of Pharmacy, Ajou University, Suwon, Republic of Korea; Ms Y. Lee, Ministry of Food and Drug Safety, Seoul, Republic of Korea; Professor M.P. Lefranc, International ImMuno Information Genetics System, Laboratoire d'Immunogénétique Moléculaire, Toulouse, France; Dr K.C. Leong, Health Science Authority, Singapore; Ms F. Lessa, Programme Specialist, Health Systems and Services,

Medicines and Health Technologies Unit, Pan American Health Organization, Washington DC, USA; Dr B. Li, Director General, National Institutes for Food and Drug Control, Ministry of Public Health, Beijing, China; Dr J. Lidner, Parallel Distribution and Certificates, Committees and Inspections Department, European Medicines Agency, Amsterdam, Netherlands; Dr M. Limoli, Senior International Health Advisor, Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring (MD), USA; Dr R. Lino de Brito and Agência Nacional de Vigilancia Sanitaría, Brasília, Brazil; Mr L. Locks, World Trade Organization, Geneva, Switzerland; Dr A. Lodi, Head of Laboratory, European Directorate for the Quality of Medicines and Health Care, Council of Europe, Strasbourg, France; Dr S. Logez, Procurement and Supply Management Specialist, United Nations Development Programme, Geneva, Switzerland; Ms S. Lohani, General Manager, Beximco Pharmaceuticals Ltd, Gazipur, Bangladesh; Ms H. Longden, Senior Marketing Manager, Informatics and Regulatory Compliance, Waters Corporation, Milford (MA), USA; Dr A.L. Lopes da Silva, Health Regulation Specialist, Brazilian Pharmacopoeia Coordination, Brazilian Health Regulatory Agency, Brasilía, Brazil; Ms A. López de la Rica Manjavacas, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; Ms M.Y. Low, Director, Pharmaceutical Division, Applied Sciences Group, Health Sciences Authority, Singapore; Ms B. Lugosi-Czangár, Validation Manager, Gedeon Richter Plc, Budapest, Hungary; Lupin Ltd, Mumbai, India; Dr C. Macé, Senior Health Procurement and Supply Chain Advisor, Global Fund/Health Implementation Support Team, United Nations Development Programme, Geneva, Switzerland; Mr D. Madan, Quality Control Specialist, Mylan Dublin Respiratory, Dublin, Ireland; Mr T. Madigan, Good Distribution Practice Inspector, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; Mr P. Magyari, Plant Manager, Gedeon Richter Plc, Budapest, Hungary; Ms G.N. Mahlangu, Director, Technical Services, Medicines Control Authority, Harare, Zimbabwe; Professor S.F. Malan, Director of School of Pharmacy, University of the Western Cape, Bellville, South Africa; Dr J.D. Mallet, Paris, France; Dr K.P. Mang, Head of Segment Management Process Analytics, Mettler-Toledo GmbH, Giessen, Germany; Mangalam Drugs and Organics Limited, Mumbai, India; Ms L. Margaryants, Scientific Centre of Drug and Medical Technology Expertise, Yerevan, Armenia; Mrs D. Marin, Director, Drug Inspectorate Unit, Ministry of Health, Belize; Dr C. Masinga, Lab Supervisor, Virbac Veterinary, Johannesburg, South Africa; Dr J.Y. Martey, Accra, Ghana; Mr W. Mathiya, Pharmacy Medicines and Poisons Board of Malawi, Lilongwe, Malawi; Mrs R. Matos Gonçalves, Brazilian Health Regulatory Agency, Brasília, Brazil; Dr J.L. Mazert, Paris, France; Dr A. Matias, Quality Control First Line Leader, GlaxoSmithKline Plc, Grand Rapids (MI), USA; Mr D. McCartney, Head of SRHR Connect, International Planned Parenthood Federation, London, United Kingdom; Dr R.D. McDowall, Director, RD McDowall Ltd, Bromley,

United Kingdom; Professor M. McIntosh, Monash Institute of Pharmaceutical Sciences, Monash University, Parkville, Australia; Dr F. Meadows, Senior Technical Advisor, US Pharmacopeial Convention, Rockville (MD), USA; Mr M. Meakin, Vice-President, Global Quality Regulatory and Compliance, DHL Supply Chair, Leicester, United Kingdom; Professor B. Meddah, Laboratoire National de Contrôle de Médicaments, Direction du Médicament et de la Pharmacie, Rabat, Morocco; Ms C. Mendy, Director, Scientific and Regulatory Affairs, Global Self-Care Federation, Nyon, Switzerland; Professor V. Merino Sanjuán, Facultad de Farmacia, Valencia, Spain; Dr S. Mielcarek, Good Manufacturing Practice Inspector, Chief Pharmaceutical Inspectorate, Warsaw, Poland; Dr G. Mignot, Saint Paul, France; Ms R.K. Miller, Director of Regulatory Affairs, Parenteral Drug Association, Bethesda (MD), USA; Mr J. Miller, Assistant-Director Scientific Affairs, Parenteral Drug Association, Bethesda (MD), USA; Dr J.H.McB. Miller, Ayr, Scotland; Mr K. Miura, Membrane Sales Department, Daicen Membrane Systems Ltd, Tokyo, Japan; Ms G. Mkomagi, Tanzania Food and Drug Authority, Dar-es-Salaam, United Republic of Tanzania; Mr K. Mochizuki, Chief Executive Officer, Xpro Associates LLC, Yokohama, Japan; Dr N. Modutlwa, Gaborone, Botswana; Dr S. Mogatle, United Nations Population Fund, UN City, Copenhagen, Denmark; Mr B.R. Mohanty, Indus Medicare Ltd, Hyderabad, India; Mr D. Moholkar, Head, Assurance, Natco Pharma Ltd, Dehradun, India; Dr J.A. Molzon, Bethesda (MD), USA; Mr S. Mooney, Senior Regulatory Affairs Specialist, Charles River Laboratories, Wilmington (MA); Dr K. Moore, Manager, Pharmacopeial Harmonization, US Pharmacopeia, Rockville (MD), USA; Ms T. Moore, Medicines and Healthcare Products Regulatory Agency, Good Manufacturing Practice inspector, London, United Kingdom; Mr R. Moorthy, Quascenta Pte Ltd, Singapore; Ms M. Morales Sánchez, Medical Devices and Other Technologies Direction, Instituto Nacional de Vigilancia de Medicamentos y Alimentos, Bogotá, Colombia; Ms S. P. Morales, Quality Control Director, PiSA Pharmaceutical Co, Guadalajara, Mexico; Dr C. de la Morena Criado, Head of Service, Quality Evaluation, Department of Chemistry and Pharmaceutical Technology, Spanish Agency of Medicines and Medical Devices, Madrid, Spain; Mr M. Multhauf, Consultant Pharmaceutical Engineering, European Compliance Academy Foundation, European Compliance Academy, Heidelberg, Germany; Mr M. Muñoz, Good Manufacturing Practice Coordinator, Grünenthal Chile, Santiago, Chile; Ms M. Muñozcano Quintanar, Comisión Federal para la Protección contra Riesgos Sanitarios, Mexico City, Mexico; Ms C. Munyimba-Yeta, Director Operations (Plant), NRB Pharma Zambia Ltd, Lusaka, Zambia; Mylan Laboratories Ltd, Hyderabad, India; Ms C. Mvurume, Regulatory Officer, Medicines Control Authority, Harare, Zimbabwe; Mr A. Mwipi, Dublin, Ireland; Professor H. Nakagawa, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; Dr B. Naik, General Manager Technical Services, Mangalam Drugs & Organics Ltd, Vapi,

India; Mr K. Nakano, Senior Consultant, Bunzen Co. Ltd, Sagamihara, Japan; Dr N. Nakashima, Senior Director for International Programmes, Associate Centre Director for Asia Training Centre, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; Dr P. Nandi, Vice President Global Regulatory Affairs, Laurus Labs, India; Dr C. Nanga, Ministry of Health, Ouagadougou, Burkina Faso; Dr S. Narendran, Assistant Drug Controller, Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, New Delhi, India; Professor G. Navas, Professor of Pharmaceutical Analysis, School of Pharmacy, University of Panama, Panamá City, Panama; Ms S. Nazzaro, Senior Program Officer, Product Introduction, Market Dynamics and Access, Bill & Melinda Gates Foundation, Seattle (WA), USA; Ms J. Netterville, Associate Director, AstraZeneca plc, Gaithersburg (MD), USA; Professor A. Nicolas, Paris, France; Dr B. Ning, National Institutes for Food and Drug Control, Beijing, China; Dr J. Norwig, Federal Institute for Drugs and Medical Devices, Bonn, Germany; Mr D. Nti, Food and Drugs Authority, Accra, Ghana; Mr S. Nyamryenchin, Third Secretary, Embassy of Mongolia, Geneva, Switzerland; Dr A. Nyika, Senior Regulatory Officer/Good Manufacturing Practice Inspector, Zazibona Inspections Coordinator, Medicines Control Authority, Harare, Zimbabwe; Dr C. Ogeto, Mission for Essential Medicines and Supplies, Nairobi, Kenya; Mr T. Oi, Deputy Director, Office of the Committee on Oversight of Pharmaceuticals and Medical Devices Safety Regulation, Health Science Division, Minister's Secretariat, Ministry of Health, Labour and Welfare, Tokyo, Japan; Ms L. P. Ojeda, Head of International Affair Office, Centro para el Control Estatal de Medicamentos, Equipos y Dispositivos Médicos, Cuba; Mrs A. Ojoo, Technical Specialist, Paediatric Formulations, UNICEF Supply Division, Nordhavn, Copenhagen, Denmark; M.T. Okuwoga, National Agency for Food and Drug Administration and Control, Ajuba, Nigeria; Professor D.W. Oliver, North-West University, Potchefstroom, South Africa; Dr H. Okuda, Deputy Director-General, National Institute of Health Sciences, Tokyo, Japan; Ms A. Olivares, Comisión Federal para la Protección contra Riesgos Sanitarios, Mexico City, Mexico; Dr C. Ondo, Ministry of Health, Bata, Equatorial Guinea; Mr J. Opit, Assistant Assurance Manager, Abacus Parenteral Drugs Ltd, Kampala, Uganda; Mr P. Osatapirat, Thailand Food and Drug Administration, Nonthaburi, Thailand; Mr J.V. Oudtshoorn, South African Health Products Regulatory Authority, South Africa; Ms A. Paavola, Senior Researcher, Finnish Medicines Agency, Helsinki, Finland; Dr N.B. Patel, Assistant Manager, Assurance, Mepro Pharmaceuticals Pvt. Ltd, Surendranagar, India; Mr A. Padua, Assurance, Allergan Sales LLC, Irvine (CA), USA; Mrs L.M. Paleshnuik, LP Inc., Ottawa, Canada; Ms H. Park, Ministry of Drug and Food Safety, Chungcheongbuk-do, Republic of Korea; Dr S. Park, Ministry of Drug and Food Safety, Chungcheongbuk-do, Republic of Korea; Dr S. Parkash, Assistant Vice-President, Regulatory Affairs, Laurus Labs Ltd, Hyderabad, India; Dr S. Parra, Manager, Generic Drugs Quality Division 1,

Bureau of Pharmaceutical Sciences, Therapeutic Products Directorate, Health Canada, Ottawa, Canada; Mr Y Patel, Information Technology Validation Consultant, GC Biotherapeutics Inc., Quebec, Canada; Dr S.R. Srinivas Patnala, Faculty of Pharmacy, Rhodes University, Grahamstown, South Africa; Professor G.M. Pauletti, Associate Dean for Graduate Studies, Gustavus & Henry Pfeiffer Chair, Department of Pharmaceutical and Administrative Sciences, University of Health Sciences & Pharmacy, St Louis College of Pharmacy, St Louis (MI), USA; Mr S.T. Pedersen, Senior Director, External Affairs, Quality Intelligence and Inspection, Novo Nordisk A/S, Bagsværd, Denmark; Dr G. Penzlin, Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany; Dr L. Perez Albela Vera, Pfizer Inc., New York City (NY), USA; Ms C. Planchon, Inspection, Federal Agency for Medicines and Health Products, Brussels, Belgium; Ms T. Poh Suan, Senior Manager, Assurance, Karex, Selangor, Malaysia; Ms S. Polovic, Head of Inspectorate, Agency for Medicinal Products and Medical Devices, Zagreb, Croatia; Dr A. Porrás, Unit Chief, Medicines and Health Technologies, WHO Regional Office for the Americas, Washington DC, USA; Ms K. Porras, Instituto Nacional de Vigilancia de Medicamentos y Alimentos, Bogota, Colombia; Dr W. Potter, Stapleford Scientific Services Ltd, Cambridge, United Kingdom; Mr S. Prasad, General Manager Corporation, Quality Control, Akums Drugs and Pharmaceuticals Ltd, New Delhi, India; Dr S. Pretorius, Research Institute for Industrial Pharmacy Inc., Centre for Quality Assurance of Drugs, Potchefstroom, South Africa; Ms S. Pulido, PiSA Farmacéutica, Guadalajara, Mexico; Ms H. Qorani, Jordan Food and Drug Administration, Amman, Jordan; Ms Z. Raditladi, Manager, Quality Management, Botswana Medicines Regulatory Authority, Gaborone, Botswana; Mrs P. Rafidison, University of Paris, Paris, France; Dr L. Rägo, Secretary-General, Council of International Organizations of Medical Sciences, Geneva, Switzerland; Professor M.A.U. Rahman, Controller (Engineering), AGP Limited, Karachi, Pakistan; Mr C. Ranga, Deputy Drugs Controller (I), Central Drugs Standard Control Organization, New Delhi, India; Ms G. Rao, Aurobindo Pharma Ltd, India; Ms E. Ratkowska, Good Manufacturing Practice Inspector, Chief Pharmaceutical Inspectorate, Warsaw, Poland; Mr K. Rehemtulla, Drug Registration Officer, Tanzania Food and Drugs Authority, United Republic of Tanzania; Mr R. dos Reis, Health Regulatory Agency, Brasília, Brazil; Dr H.K. Remmelt Van Der Werf, European Directorate for the Quality of Medicines and Health Care, Council of Europe, Strasbourg, France; Professor M. Rizzi, University of Piemonte Orientale, Novara, Italy; Dr J.L. Robert, Luxembourg; Mr N. Robert, Chief Executive Officer, Robert Neri Consulting, France; Dr J. Robertson, Hertfordshire, United Kingdom; Professor K. Rocha Rezende, Universidade Federal de Goiás, Faculdade de Farmácia BioPk, Laboratório de Biofarmácia e Farmacocinética, Goiás, Brazil; Ms I. Rodríguez, Comisión para el Control de Calidad de Medicamentos, Montevideo, Uruguay; Dr J. Isasi Rosas, Inspection Services, Centro Nacional de Control de Calidad,

Lima, Peru; Mr T. Rücker, General Manager, Letzner Pharmawasseraufbereitung GmbH, Hückeswagen, Germany; Mr R.T. Rukwata, Head of Licensing and Inspection, Medicines Control Authority, Harare, Zimababwe; Dr J. Sabartova, Prague, Czechia; Dr E.I. Sakanyan, Director, Centre of the Pharmacopoeia and International Collaboration, Federal State Budgetary Institution, Scientific Centre for Expert Evaluation of Medicinal Products, Moscow, Russian Federation; Mr H. Sakurai, Specialist for Inspection, Office of Manufacturing/Quality and Compliance, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; Ms K. Salin, Environmental Strategist, Scientific Expertise, Swedish Medical Products Agency, Uppsala, Sweden; Dr A. Salinas Rivera, Institute of Public Health, Santiago, Chile; Dr P. Salo, Head of Pharmaco-Chemical Section, Finnish Medicines Agency, Helsinki, Finland; Sandoz, Mumbai, India; Mr Y. Samson, Director, Kereon AG, Basel, Switzerland; Dr C.A. Sánchez González, Adviser, Centre para el Control de Medicamentos, Equipos y Dispositivos Médicos, Havana, Cuba; Sanofi, Gentilly, France; Sanofi Pasteur, Marcy-l'Étoile, France; Dr B. Santoso, Yogyakarta, Indonesia, Yogyakarta, Indonesia; Ms A. Saragih, Indonesian Pharmacopoeia Commission, National Agency of Drug and Food Control, Yogyakarta, Indonesia; Dr D. Sato, Chief Management Officer, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan; Mr N. Schaaf, Programme Manager, Swedish Water House, Stockholm International Water Institute, Stockholm, Sweden; Dr P.E. Schaeffer, Regulatory Affairs, Regulatory Science and Policy Associate, European Union Region/Asia, Middle East and European Region, Sanofi-Aventis R&D, Chilly-Mazarin, France; Dr S. Schäfermann, Research Associate, Medi-Quality Security Institute, Kanazawa University, Kanazawa, Japan; Dr J. Schläpfer, Head, Sector Management Services and International Affairs, Swissmedic, Bern, Switzerland; Mr J. Screbo, JS International Auditing & Consulting, Stockholm, Sweden; Professor G.K.E. Scriba, Professor, Pharmaceutical Chemistry, Friedrich-Schiller University, Jena, Germany; Mrs P. Serpa, Coordinator, National Sanitary Surveillance Agency, Brasiliía, Brazil; Serum Institute of India, Pune, India; Shanghai Desano Chemical Pharmaceutical Co. Ltd, Shanghai, China; Ms H. Sharma, Manager, Rusan Pharma, Mumbai, India; Professor G. Shashkova, Moscow, Russian Federation; Shenyang Antibiotic, Shenyang, China; J. Shin, Medical Officer, World Health Organization, Geneva, Switzerland; Mrs V. Shridhankar, Cipla Ltd, Mumbai, India; Dr S.C. Shubat, Director, United States Accepted Names Program, American Medical Association, Chicago (IL), USA; Mr S. Shull, Manufacturing Process Engineer IV, Abbvie, Cincinnati (OH), USA; Dr M. Sibutha, Quality Control Manager, Datlabs, Belmont, Zimbabwe; Mr D. Silva, Sindusfarma, Sindicato da Indústria de Produtos Farmacêuticos, São Paulo, Brazil; Dr W.C. Simon, Associate Director, Bureau of Pharmaceutical Sciences, Ottawa, Canada; Dr G.N. Singh, Ghaziabad, India; Dr G.P. Singh, Senior Scientific Officer, Indian Pharmacopoeia Commission, Ministry of Health and Family Welfare,

Ghaziabad, India; Ms I. Šipić, Public Relations Office, Croatian Agency for Medicinal Products and Medical Devices, Zagreb, Croatia; Ms M. Skiba, Good Manufacturing Practice Inspector, Chief Pharmaceutical Inspectorate, Warsaw, Poland; Ms J. Skutnik-Wilkinson, Associate Director, Quality Intelligence, Biogen, Research Triangle Park (NC), USA; Dr L. Smallshaw, Co-Chair, European Compliance Academy Foundation Board, European Compliance Academy, Heidelberg, Germany; Mr D. Smith, Principal Scientist, SSI Schaefer Systems SA, Pretoria, South Africa; Dr D.J. Snodin, Principal, Xiphora Biopharma Consulting, Bristol, United Kingdom; Mrs M. Soares, Brasília, Brazil; Mr T. Spooner, Director, Engineering, Amgen Inc., West Greenwich (RI), USA; Dr Sornakumar, Senior Manager Qulaity Assurance, Sequent Research Ltd, Hyderabad, India; Mr E. Sousa Silva, Health Regulatory Agency, Brasília, Brazil; Dr A. Ssenkindu, National Drug Authority, Kampala, Uganda; Dr L. Stoppa, Inspections and Certifications Department, Manufacturing Authorisation Office, Italian Medicines Agency, Rome, Italy; Dr C. Strnadova, Senior Scientific Advisor, Therapeutic Products Directorate of Health Canada, Ottawa, Canada; Ms Y. Suarez, Health Regulatory Agency, Brasília, Brazil; Dr J. Sun, Deputy Director General Department of Drug and Cosmetics Supervision, China Food and Drug Administration, Beijing, China; Dr D. Sun Cuilian, Deputy Laboratory Director, Pharmaceutical Laboratory, Pharmaceutical Division, Health Sciences Authority, Singapore; Dr P. Svarrer Jakobsen, United Nations Children's Fund, Supply Division, Copenhagen, Denmark; Ms E. Tack, Directorate General Inspection, Distribution Division, Distribution and Publicity Medicines Entity, Federal Agency for Medicines and Health Products, Brussels, Belgium; Dr A. Terhechte, Bezirksregierung Münster, Bonn, Germany; Ms A. Tiley, Head, Global Sustainable Antibiotics Program, Centrient Pharmaceuticals, Rotterdam, Netherlands; Dr R. Torano, Pharmacopoeial Technical Expert, GlaxoSmithKline, Barnard Castle, United Kingdom; Dr J.M. Trapsida, Niamey, Niger; Mr S. Tripathi, Assurance Head, Rusoma Laboratories Pvt. Ltd, Indore, India; Mr F. Trucco, Ministerio de Salud Pública, Montevideo, Uruguay; TTK Healthcare Ltd, Chennai, India; Mr N. Twitchen, Executive Director, Global Quality Assurance, The Female Health Company (UK), London, United Kingdom; Mr C. Twumasi-Danquah, Food and Drugs Authority, Accra, Ghana; Professor N. Udupa, Research Director, Health Sciences, Manipal Academy of Higher Education, Manipal, India; Dr A.J. Van Zyl, George, South Africa; Dr K. Vashi, Vice-President, Technical Operations, Mangalam Drugs & Organics Ltd, Valsad, India; Dr C.C.F. Vidotti, Ministry of Health, Brasília, Brazil; Dr O. del Rosario Villalva Rojas, Executive Director, Quality Control Laboratories, National Quality Control Center, National Institute of Health, Lima, Peru; Mr W. Von Kluechtzner, United Nations Industrial Development Organization, Vienna, Austria; Mr A. Walsh, President, Center for Pharmaceutical Cleaning Innovation, Hillsborough (NJ), USA; Ms M. Wanyama, Mission for Essential Drugs and Supplies, Nairobi, Kenya; Mr W. Watson, Senior

Director, Gilead Sciences, Cambridge, United Kingdom; Dr P. Weiglmeier, Validation Management and Technical Transfer, Fareva, Feucht, Germany; Dr K. Weisser, Senior Assessor, Paul-Ehrlich-Institut, Langen, Germany; Mr J. Welink, Medicines Evaluation Board, Utrecht, Netherlands; Ms K. Wessberg, Senior Director, Regulatory Affairs, Abbott Park (IL), USA; Professor A. Wessels, North West University, Potchefstroom, South Africa; Dr M. Wiggens, Merck & Co. Inc., Kenilworth (NJ), USA; Mr K. Wilberforce, Directorate of Laboratory Services, National Drug Authority, Kampala, Uganda; Ms C. Winfield, Senior Director, Regulatory Operations, International Society for Pharmacopepidemiology, Bethesda (MD), USA; Dr C. Wirthumer-Hoche, Head, Austrian Medicines and Medical Devices Agency, Vienna, Austria; Ms K. van Wonderen, Health and Youth Care Inspectorate, Ministry of Health, Welfare and Sport, DA Heerlen, The Netherlands; Mr W. Wulandari, Good Manufacturing Practice Inspector, Indonesian Food and Drug Authority, Jakarta Pusat, Indonesia; Dr M. Xu, Deputy Director, Instituite for Chemical Drug Control, China National Institutes for Food and Drug Control, China; Dr T. Yi, National Medical Products Administration, Beijing, China; Dr L.M. Yong, Health Science Authority, Singapore; Dr J. Zhang, Guangzhou Institute for Drug Control, Guangzhou, China; Zhejiang Jiangbei Pharmaceutical Co. Ltd, Zhejiang, China.

References

1. WHO guidelines on good manufacturing practices for the manufacture of herbal medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 2 (WHO Technical Report Series, No. 1010; https://www.who.int/traditional-complementary-integrative-medicine/publications/trs1010_annex2.pdf?ua=1, accessed 6 February 2021).
2. WHO guidelines on good herbal processing practices for herbal medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 1 (WHO Technical Report Series, No. 1010; https://www.who.int/traditional-complementary-integrative-medicine/publications/trs1010_annex1.pdf?ua=1, accessed 6 February 2021).
3. Good pharmacopoeial practices: chapter on monographs on herbal medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 7 (WHO Technical Report Series, No. 1010; https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex7.pdf, accessed 6 February 2021).
4. Quality control methods for medicinal plant materials. Geneva: World Health Organization; 1998 (https://apps.who.int/iris/handle/10665/41986, accessed 6 February 2021).
5. WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 1 (WHO Technical Report Series, No. 1003; https://www.who.int/traditional-complementary-integrative-medicine/publications/trs1003_annex1.pdf, accessed 6 February 2021).
6. WHO guidelines on good agricultural and collection practices (GACP) for medicinal plants. Geneva: World Health Organization; 2003 (https://apps.who.int/iris/bitstream/handle/10665/42783/9241546271.pdf?sequence=1, accessed 6 February 2021).
7. *The International Pharmacopoeia*, 10th edition. Geneva: World Health Organization; 2021 (in press).
8. Specifications for pharmaceutical preparations. In: Essential medicines and health products. Geneva: World Health Organization; 2020 (https://www.who.int/medicines/publications/pharmprep/en/, accessed 24 September 2020).
9. Quality assurance of medicines terminology database. Geneva: World Health Organization; 2019 (https://www.who.int/publications/m/item/quality-assurance-of-medicines-terminology-database, accessed 22 September 2020).
10. Norms and standards: guidelines. Geneva: World Health Organization; 2020 (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/norms-and-standards-for-pharmaceuticals/guidelines, accessed 21 September 2020).
11. Quality assurance of pharmaceuticals 2019. Geneva: World Health Organization; 2019 (http://digicollection.org/whoqapharm/p/about/, accessed 21 September 2020).
12. WHO good manufacturing practices for sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 6 (WHO Technical Report Series, No. 961; https://apps.who.int/iris/bitstream/handle/10665/44079/WHO_TRS_961_eng.pdf?sequence=1, accessed 30 October 2020).

13. International Atomic Energy Agency and World Health Organization guideline on good manufacturing practices for radiopharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; í2020: Annex 2 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 30 October 2020).

14. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019:Annex 2 (WHO Technical Report Series, No. 1019; https://apps.who.int/iris/handle/10665/312316, accessed 25 September 2020).

15. Supplementary guidelines on good manufacturing practices: validation. Appendix 2. Validation of water systems for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006:Annex 4 (WHO Technical Report Series, No. 937; https://apps.who.int/iris/handle/10665/43443, accessed 25 September 2020).

16. Good manufacturing practices: guidelines on validation. Appendix 4. Analytical procedure validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://apps.who.int/iris/handle/10665/312316, accessed 25 September 2020).

17. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019:Annex 3 (WHO Technical Report Series, No. 1019; https://apps.who.int/iris/handle/10665/312316, accessed 25 September 2020).

18. Good manufacturing practices: guidelines on validation. Appendix 6. Guidelines on qualification. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://apps.who.int/iris/handle/10665/312316, accessed 25 September 2020).

19. WHO guidelines on good manufacturing practices: validation. Appendix 7: Non sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://apps.who.int/iris/handle/10665/176954, accessed 25 September 2020).

20. Good manufacturing practices: guidelines on validation. Appendix 3. Cleaning validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 23 September 2020).

21. WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 960; https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en, accessed 29 September 2020).

22. Production of water by means other than distillation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 3 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 23 September 2020).

23. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2012: Annex 5 (WHO Technical Report Series, No. 996; https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf, accessed 29 September 2020).

24. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fifth report. Geneva: World Health Organization; 2020: Annex 6 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 30 October 2020).

25. Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fourth report. Geneva: World Health Organization; 1996, Annex 7, Geneva: World Health Organization; (WHO Technical Report Series, No. 863; https://www.who.int/medicines/areas/quality_safety/quality_assurance/InvestigationalPharmaceuticalProductsClinicalTrialsHumansTRS863Annex7.pdf?ua=1, accessed 30 October 2020).

26. WHO guidelines on transfer of technology in pharmaceutical manufacturing. Geneva: World Health Organization; In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 7 (WHO Technical Report Series, No. 961; https://www.who.int/medicines/areas/quality_safety/quality_assurance/TransferTechnologyPharmaceuticalManufacturingTRS961Annex7.pdf?ua=1, accessed 30 October 2020).

27. Points to consider for setting the remaining shelf life of medical products upon delivery. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 8 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 23 September 2020).

28. WHO "*Biowaiver List*": 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: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 12 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 23 September 2020).

29. Gigante V, Pauletti GM, Kopp S, Xu M, Gonzalez-Alvarez I, et al. Global testing of a consensus solubility assessment to enhance robustness of the WHO biopharmaceutical classification system. ADMET DMPK. 2020:doi:10.5599/admet.850.

30. World Health Organization Model List of Essential Medicines, 21st list. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf, accessed 6 February, 2021).

31. Pan American Health Organization, Pan American Network for Drug Regulatory Harmonization. Regulatory reliance principles: concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization, San Salvador, 2018. Washington DC: Pan American Health Organization; 2018 (https://iris.paho.org/handle/10665.2/51549, accessed 29 September 2020).

32. Outcome of WHO survey on reliance [website]. International Pharmaceutical Regulators Programme; 2019 (http://www.iprp.global/news/outcome-who-survey-reliance, accessed 30 September 2020).

33. List of international comparator products. Geneva: World Health Organization; 2016 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/list_int_comparator_prods_after_public_consult30.9.xlsx, accessed 3 August 2020).

34. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; https://www.who.int/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf?ua=1, accessed 22 July 2020).

35. ICH harmonised tripartite guideline. Biopharmaceutics Classification System-based biowaivers M9. Brussels: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2019 (https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf, accessed 3 August 2020).

36. Final concept paper. M13: Bioequivalence for immediate-release solid oral dosage forms. Brussels: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; 2019 (https://database.ich.org/sites/default/files/ICH_M13_Concept_Paper_2020_0710.pdf, accessed 30 October 2020).

37. Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics Classification System, as an appendix to the WHO guidelines on multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_1003_full-version.pdf?ua=1, accessed 30 October 2020).

38. Monograph availability of COVID-19 investigated drugs in world pharmacopoeias. Geneva: International Meeting of World Pharmacopoeias; 2020 (https://public.tableau.com/profile/emma.huang6254#!/vizhome/IMWPMonographMapping/Dashboard, accessed 5 October 2020).

39. Relevant WHO guidance for SARS-CoV2 COVID-19 treatment: medicines. Geneva: World Health Organization; 2020 (https://www.who.int/publications/m/item/relevant_WHO_documents_for_SARS_CoV_2_from_ECSPP, accessed 5 October 2020).

40. Frequently asked questions by the manufacturing, trial and testing organizations in connection with some of their constraints faced during the COVID-19 outbreak. Geneva: World Health Organization; 2020 (https://extranet.who.int/prequal/sites/default/files/documents/Covid-19_Q-A_2020.pdf, accessed 5 October 2020).

41. Brits M. Practical considerations for the pharmaceutical quality control laboratory during the COVID-19 pandemic. J Med Lab Sci Technol South Africa. 2020;2(2):1–12.

42. Essential medicines list for management of patients admitted to intensive care units with suspected or confirmed COVID-19 diagnosis. Washington DC: Pan American Health Organization; 2020 (https://iris.paho.org/handle/10665.2/52191, accessed 16 October 2020).

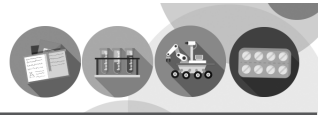
Annex 1

Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations

As recommended by World Health Organization (WHO) partners and donor organizations, a full and updated list of WHO norms and standards for medicines, quality assurance and regulatory guidance texts adopted by the Expert Committee and published in the WHO Technical Report Series has been drawn up as follows.

LIST OF NORMS AND STANDARDS FOR PHARMACEUTICALS GUIDELINES

Norms and Standards for Pharmaceuticals (NSP)
Health Products Policy and Standards (HPS)



Category	Guideline	TRS	Annex	Year	comments
All guidelines	Procedure for the development of World Health Organization medicines quality assurance guidelines	1019	Annex 1	2019	
Development	Development of paediatric medicines: points to consider in formulation	970	Annex 5	2012	
Development	Pharmaceutical development of multisource (generic) finished pharmaceutical products: points to consider	970	Annex 3	2012	
Distribution	**Pharmacy services**				
Distribution	FIP - WHO good pharmacy practices: standards for quality of pharmacy services	961	Annex 8	2011	
Distribution	**Starting materials**				
Distribution	Control and safe trade of starting materials for pharmaceutical products	https://www.who.int/medicines/publications/qa_starter/en/			
Distribution/ Quality assurance	WHO good trade and distribution practices for pharmaceutical starting materials	966	Annex 6	2016	
Distribution	**Compounding**				
Distribution	FIP - WHO technical guidelines: Points to consider in the provision by health-care professionals of children-specific preparations that are not available as authorized products	966	Annex 2	2016	

Category	Guideline	TRS	Annex	Year	comments
Distribution	**Monitoring**				
Distribution/ Quality assurance	WHO guidelines on the conduct of surveys of the quality of medicines	966	Annex 7	2016	
Distribution	**Finished Products**				
Distribution/ Regulatory standards	WHO certification scheme on the quality of pharmaceutical products moving in international commerce	https://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/			
Distribution/ Regulatory standards	WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation	917	Annex 3	2003	
Distribution/ Regulatory standards	WHO guidelines on import procedures for medical products	1019	Annex 5	2019	
Distribution	**Procurement**				
Distribution/ Quality assurance	WHO model quality assurance system for procurement agencies	986	Annex 3	2014	EN
Distribution/ Quality assurance	Système modèle d'assurance de la qualité de l'OMS pour les agences d'approvisionnement	986	Annex 3	2014	FR
Distribution/ Quality assurance	WHO model quality assurance system for procurement agencies: Interagency finished pharmaceutical product questionnaire	986	Appendix 6	2014	
Distribution/ Quality assurance/ Inspections	WHO model quality assurance system for procurement agencies: aide-memoire for inspection	986	Annex 4	2014	EN

Category	Guideline	TRS	Annex	Year	comments
Distribution	**Procurement** (*continued*)				
Distribution/ Quality assurance/ Inspections	Système modèle d'assurance de la qualité de l'OMS pour les agences d'approvisionnement: aide-mémoire pour les inspections	986	Annex 4	2014	FR
Distribution	**Storage**				
Distribution	WHO good storage and distribution practices for medical products	1025	Annex 7	2020	
Distribution	Points to consider for setting the remaining shelf-life of medical products upon delivery	1025	Annex 8	2020	
Distribution	WHO model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products	961	Annex 9	2011	
Distribution	WHO model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products: Technical supplements	992	Annex 5	2015	
Distribution	Technical supplements to WHO Technical Report Series, No. 961, 2011: Introduction to the Technical Supplements	961	Annex 9	2011	
Distribution	*Supplement 1: Selecting sites for storage facilities*	961	Annex 9	2011	
Distribution	*Supplement 2: Design and procurement of storage facilities*	961	Annex 9	2011	
Distribution	*Supplement 3: Estimating the capacity of storage facilities*	961	Annex 9	2011	

Category	Guideline	TRS	Annex	Year	comments
Distribution	**Storage** (*continued*)				
Distribution	*Supplement 4: Building security and fire protection*	961	Annex 9	2011	
Distribution	*Supplement 5: Maintenance of storage facilities*	961	Annex 9	2011	
Distribution	*Supplement 6: Temperature and humidity monitoring systems for fixed storage areas*	961	Annex 9	2011	
Distribution	*Supplement 7: Qualification of temperature-controlled storage areas*	961	Annex 9	2011	
Distribution	*Supplement 8: Temperature mapping of storage areas*	961	Annex 9	2011	
Distribution	*Supplement 9: Maintenance of refrigeration equipment*	961	Annex 9	2011	
Distribution	*Supplement 10: Checking the accuracy of temperature control and monitoring devices*	961	Annex 9	2011	
Distribution	*Supplement 11: Qualification of refrigerated road vehicles*	961	Annex 9	2011	
Distribution	*Supplement 12: Temperature-controlled transport operations by road and by air*	961	Annex 9	2011	
Distribution	*Supplement 13: Qualification of shipping containers*	961	Annex 9	2011	
Distribution	*Supplement 14: Transport route profiling qualification*	961	Annex 9	2011	
Distribution	*Supplement 15: Temperature and humidity monitoring systems for transport operations*	961	Annex 9	2011	
Distribution	*Supplement 16: Environmental management of refrigeration equipment*	961	Annex 9	2011	

Category	Guideline	TRS	Annex	Year	comments
Inspection					
Inspection/Production	WHO general guidance on hold-time studies	992	Annex 4	2015	
Inspection	WHO guidelines for drafting a site master file	961	Annex 14	2011	
Inspection	WHO guidance on good manufacturing practices: Model inspection report	996	Annex 4, Appendix 1	2016	
Inspection	WHO good manufacturing practices on inspection: Example of a risk category assessment of the site depending on level of compliance and inspection frequency	996	Annex 4, Appendix 2	2016	
Inspection	Quality managent system requirements for national good manufacturing practice inspectorates	1025	Annex 5	2020	
Inspection	WHO guidelines on pre-approval inspections	902	Annex 7	2002	
Inspection	WHO guidelines for Inspection of pharmaceutical manufacturers	823	Annex 2	1992	
Inspection	**Desk assessment**				
Inspection/ Regulatory standards	WHO good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions	1010	Annex 9	2018	

Category	Guideline	TRS	Annex	Year	comments
Production	**WHO good manufacturing practices**				
Production	WHO good manufacturing practices for pharmaceutical products: Main principles	986	Annex 2	2014	EN
Production	Bonnes pratiques de fabrication de l'OMS des produits pharmaceutiques: Grands principes	986	Annex 2	2014	FR
Production	Frequently asked questions: WHO good manufacturing practices in pharmaceutical practice	https://www.who.int/medicines/areas/quality_safety/quality_assurance/gmp/en/			
Production	WHO good manufacturing practices for active pharmaceutical ingredients (bulk drug substances)	957	Annex 2	2010	EN
Production	Bonnes pratiques de fabrication de l'OMS pour les substances actives pharmaceutiques	957	Annex 2	2010	FR
Production	WHO good manufacturing practices for the manufacture of pharmaceutical excipients	885	Annex 5	1999	
Production	WHO good manufacturing practices for sterile pharmaceutical products	961	Annex 6	2011	
Production	WHO good manufacturing practices for biological products (jointly with the Expert Committee on Biological Standardization)	966	Annex 3	2016	
Production	WHO good manufacturing practices for blood establishments (jointly with the Expert Committee on Biological Standardization)	961	Annex 4	2011	

Category	Guideline	TRS	Annex	Year	comments
Production	**WHO good manufacturing practices** (*continued*)				
Production	WHO good manufacturing practices for pharmaceutical products containing hazardous substances	957	Annex 3	2010	EN
Production	Bonnes pratiques de fabrication de l'OMS pour les produits pharmaceutiques contenant des substances dangereuses	957	Annex 3	2010	FR
Production	WHO good manufacturing practices for the manufacture of investigational pharmaceutical products for clinical trials in humans	863	Annex 7	1996	
Production	WHO good manufacturing practices for the manufacture of herbal medicines	1010	Annex 2	2018	
Production/ Regulatory standards	IAEA - WHO good manufacturing practices for radiopharmaceutical products	1025	Annex 2	2020	
Production	WHO good manufacturing practices for water for pharmaceutical use	970	Annex 2	2012	EN
Production	Bonnes pratiques de fabrication de l'OMS pour l'eau à usage pharmaceutique	970	Annex 2	2012	FR
Production	製薬用水に対するWHO管理基準 (WHO good manufacturing practices for water for pharmaceutical use)	970	Annex 2	2012	JP
Production	Production of water for injection by means other than distillation	1025	Annex 3	2020	

Category	Guideline	TRS	Annex	Year	comments
Production	**WHO good manufacturing practices** (*continued*)				
Production	WHO good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (part 1)	1010	Annex 8	2018	
Production	WHO good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products (part 2): interpretation of guidelines	1019	Annex 2	2019	
Production/Quality assurance	WHO good manufacturing practices: Guidelines on validation	1019	Annex 3	2019	
Production	**Risk analysis**				
Production/ Regulatory standards	WHO guidelines on quality risk management	981	Annex 2	2013	
Production/Inspection	WHO good manufacturing practices on environmental aspects of manufacturing: points to consider for manufacturers and inspectors for the prevention of antimicrobial resistance	1025	Annex 6	2020	
Production	**Technology transfer**				
Production	WHO guidelines on transfer of technology in pharmaceutical manufacturing	961	Annex 7	2011	

Category	Guideline	TRS	Annex	Year	comments
Production	**Processing practices for herbals**				
Production	WHO good practices for the processing of herbal medicines	1010	Annex 1	2018	
Production	**Data management**				
Production/ Quality assurance	WHO good data and record management practices	966	Annex 5	2016	EN
Production/ Quality assurance	Bonnes pratiques de l'OMS de gestion des données et des enregistrements	966	Annex 5	2016	FR
Quality control	**Screening tests**				
Quality control	Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms	https://apps.who.int/iris/bitstream/handle/10665/42020/9241545135.pdf?sequence=1			
Quality control	**Pharmacopoeias**				
Quality control	WHO good pharmacopoeial practices	996	Annex 1	2016	
Quality control	WHO good pharmacopoeial practices: chapter on compounding	1010	Annex 6	2018	
Quality control	WHO good pharmacopoeial practices: chapter on herbal medicines	1010	Annex 7	2018	

Category	Guideline	TRS	Annex	Year	comments
Quality control	**International Pharmacopoeia and International Reference Standards**				
Quality control	*The International Pharmacopoeia (Ph. Int.)*	https://www.who.int/teams/health-product-and-policy-standards/pharmacopoeia			
Quality control	*The International Pharmacopoeia*: Procedure for the development of monographs and other texts	1025	Annex 1	2020	
Quality control	*The International Pharmacopoeia*: Revised concepts and future perspectives	1003	Annex 2	2017	
Quality control	*The International Pharmacopoeia*: Updating mechanism for the section on radiopharmaceuticals	992	Annex 2	2015	
Quality control	*The International Pharmacopoeia*: Related substances tests - dosage form monographs guidance notes	943	Annex 1	2007	
Quality control	WHO International Chemical Reference Substances (availability, price, ordering)	https://www.edqm.eu/en/WHO-ICRS-Reference-Substances-1393.html			
Quality control	Release procedure for International Chemical Reference Substances	981	Annex 1	2013	
Quality control	WHO general guidelines for the establishment, maintenance and distribution of chemical reference substances	943	Annex 3	2007	
Quality control	WHO recommendations on risk of transmitting animal spongiform encephalopathy agents via medicinal products	908	Annex 1	2003	

Category	Guideline	TRS	Annex	Year	comments
Quality control	**Analysis of Samples**				
Quality control	WHO considerations for requesting analysis of medicines samples	1010	Annex 3	2018	
Quality control	WHO model certificate of analysis	1010	Annex 4	2018	
Quality control	**Laboratory Guidelines**				
Quality control	WHO good practices for pharmaceutical quality control laboratories	957	Annex 1	2010	
Quality control	WHO good practices for pharmaceutical microbiology laboratories	961	Annex 2	2011	
Quality control/ Inspection	WHO good chromatography practices	1025	Annex 4	2020	
Quality control/ Inspection	WHO guidelines for preparing a laboratory information file	961	Annex 13	2011	
Quality control	**Plant materials**				
Quality control	Quality control methods for medicinal plant materials	https://apps.who.int/iris/bitstream/handle/10665/41986/9241545100.pdf?sequence=1			
Quality control	WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines	1003	Annex 1	2017	

Category	Guideline	TRS	Annex	Year	comments
Quality control	**Testing of suspect samples**				
Quality control/ Distribution (*Monitoring*)	WHO guidance on testing of "suspect" falsified medicines	1010	Annex 5	2018	
Regulatory standards	**Stability**				
Regulatory standards	WHO guidelines on stability testing of active pharmaceutical ingredients and finished pharmaceutical products	1010	Annex 10	2018	
Regulatory standards	Stability conditions for WHO Member States by Region - Appendix 1 to the Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (Update of 24 August 2018)			2018	
Regulatory standards	**Interchangeability**				
Regulatory standards	WHO guidelines on interchangeable multisource (generic) pharmaceutical products: registration requirements to establish interchangeability	1003	Annex 6	2017	
Regulatory standards	WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms	1025	Annex 12	2020	

Category	Guideline	TRS	Annex	Year	comments
Regulatory standards	**Interchangeability** (*continued*)				
Regulatory standards	WHO biopharmaceutics classification system: protocol to conduct equilibrium solubility experiments for the classification of active pharmaceutical ingredients for biowaiver	1019	Annex 4	2019	
Regulatory standards	WHO guidance for organizations performing in vivo bioequivalence studies	966	Annex 9	2016	
Regulatory standards	WHO list of international comparator pharmaceutical products and general background notes	1003	Annex 5	2017	
Regulatory standards	WHO guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products	992	Annex 8	2015	
Regulatory standards	List of International Comparator products (September 2016)	https://www.who.int/medicines/areas/quality_safety/quality_assurance/list_int_comparator_prods_after_public_consult30.9.xlsx?ua=1			
Regulatory standards	**Medical devices**				
Regulatory standards	WHO global model regulatory framework for medical devices including in vitro diagnostic medical devices	1003	Annex 4	2017	

Category	Guideline	TRS	Annex	Year	comments
Regulatory standards	**Others**				
Regulatory standards	WHO general guidance on variations to multisource pharmaceutical products	966	Annex 10	2016	
Regulatory standards	WHO good review practices for national and regional regulatory authorities	992	Annex 9	2015	
Regulatory standards	WHO guidelines on submission of documentation for a multisource (generic) finished product: Quality part	986	Annex 6	2014	
Regulatory standards/ Quality control	WHO recommendations for quality requirements when plantderived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients	992	Annex 6	2015	
Regulatory standards/ Quality control	UNFPA-WHO technical specifications for male latex condoms	1025	Annex 10	2020	
Regulatory standards/ Quality control	UNFPA-WHO specifications for plain lubricants	1025	Annex 11	2020	
Regulatory standards/ Distribution (***Monitoring***)	WHO guidelines for sampling of pharmaceutical products and related materials	929	Annex 4	2005	
Regulatory standards/ Inspection	WHO guidelines for drafting a site master file	961	Annex 14	2011	
Regulatory standards/ Inspection	WHO guidelines for the preparation of a contract research organization master file	957	Annex 7	2010	

Category	Guideline	TRS	Annex	Year	comments
Regulatory standards	**Others** (*continued*)				
Regulatory standards	WHO guidelines on active pharmaceutical ingredient master file procedure	948	Annex 4	2008	
Regulatory standards	International nonproprietary names for biological and biotechnological substances: a review	948	Annex 5	2008	
Regulatory standards	WHO guidelines for the registration of fixed-dose combination medicinal products	929	Annex 5	2005	EN
Regulatory standards	Corrected chinese version 固定剂量复方制剂注册指导原则 WHO guidelines for the registration of fixed-dose combination medicinal products	929	Annex 5	2005	CH
Regulatory standards/ Production	WHO guidelines on packaging for pharmaceutical products	902	Annex 9	2002	
Regulatory standards	**Collaborative procedure**				
Regulatory standards	WHO collaborative procedure in the assessment and accelerated national registration of pharmaceutical products and vaccines approved by stringent regulatory authorities	1010	Annex 11	2018	
Regulatory standards	WHO good practices of national regulatory authorities in implementing the collaborative registration procedures for medical products	1019	Annex 6	2019	
Regulatory standards	WHO guidelines on the implementation of quality management systems for national regulatory authorities	1025	Annex 13	2020	

Category	Guideline	TRS	Annex	Year	comments
Prequalification					
Prequalification	UNFPA-WHO prequalification programme guidance for contraceptive devices: Male latex condoms, female condoms and intrauterine devices	1025	Annex 9	2020	
Prequalification	WHO collaborative procedure between the WHO prequalification team and national regulatory authorities in the assessment and accelerated national registration of WHO-prequalified pharmaceutical products and vaccines	966	Annex 8	2016	
Prequalification	WHO procedure for prequalification of pharmaceutical products	961	Annex 10	2011	
Prequalification	WHO guidelines on variations to a prequalified product	981	Annex 3	2013	
Prequalification	WHO guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part	970	Annex 4	2012	
Prequalification	WHO prequalification of quality control laboratories: procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies	1003	Annex 3	2017	
Prequalification	WHO guidelines on the requalification of prequalified dossiers	957	Annex 6	2010	

Category	Guideline	TRS	Annex	Year	comments
Prequalification					
Prequalification	WHO procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products	953	Annex 4	2009	
Prequalification	WHO guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities	986	Annex 5	2014	

Annex 2

Points to consider when including Health-Based Exposure Limits (HBELs) in cleaning validation

1. Introduction and background 94

2. Scope 95

3. Glossary 95

4. Historical approach in cleaning validation 97

5. New approach using HBELs in cleaning validation 97

5.1 Documentation 98
5.2 Equipment 98
5.3 Cleaning agents 98
5.4 Sampling 99
5.5 Cleanability studies 99
5.6 Risk management 100
5.7 Guidance for Health-Based Exposure Limits (HBELs) setting 100
5.8 Acceptance criteria 102
5.9 Analytical procedures 102
5.10 Data integrity 103
5.11 Cleaning validation and cleaning verification 103
5.12 Visually clean 104
5.13 Cleaning process capability 104
5.14 Personnel 104
5.15 Life cycle 104

References 104

Further reading 106

Appendix 1 Using Health-Based Exposure Limits (HBELs) to assess risk in cleaning validation 107

1. Introduction and background

The World Health Organization (WHO) has published the guideline entitled *Good manufacturing practices for pharmaceutical products: main principles* in the WHO Technical Report Series, No. 986, Annex 2, 2014 (*1*).

The WHO *Supplementary guidelines on good manufacturing practice: validation* were published in 2006 and were supported by seven appendices. The main text (*2*) and its appendixes (*3*, *4*, *6*, *7*, *8*, *9*) were revised between 2006 and 2019. Appendix 3, relating to cleaning validation (*5*), was not updated at that time. Its revision, however, was discussed during an informal consultation held in Geneva, Switzerland, in July 2019. The outcome of the discussion was presented to the WHO Expert Committee on Specifications for Pharmaceutical Products (ECSPP) meeting in October 2019. The ECSPP acknowledged the importance of harmonization in regulatory expectations with regards to cleaning validation approaches. The Expert Committee recommended a "Points to consider" document be prepared in order to describe the current approaches used in cleaning validation and highlighting the complexities involved in order to establish a common understanding. A revision of the relevant appendix would then be considered by the Expert Committee thereafter.

Some of the main principles of good manufacturing practices (GMP) include the prevention of mix-ups and the prevention of contamination and cross-contamination. Multi-product facilities in particular, have a potential risk of cross-contamination. It is therefore important that manufacturers identify all risks relating to contamination and cross-contamination and identify and implement the appropriate controls to mitigate these risks.

These controls may include, for example, technical and organizational measures, dedicated facilities, closed systems, cleaning and cleaning validation.

It is strongly recommended that manufacturers review their existing technical and organizational measures, suitability of cleaning procedures and appropriateness of existing cleaning validation studies.

Technical controls, such as the design of the premises and utilities (e.g. heating, ventilation and air-conditioning [HVAC], water and gas), should be appropriate for the range of products manufactured (e.g. pharmacological classification, activities and properties). Effective controls should be implemented to prevent cross-contamination when air is re-circulated through the HVAC system.

Organizational controls, such as dedicated areas and utilities, dedicated equipment, procedural control, and campaign production, should be considered where appropriate as a means to reduce the risk of cross-contamination.

Measures to prevent cross-contamination and their effectiveness should be reviewed periodically in accordance with authorized procedures.

It should be noted that the above examples are described in more detail in other documents. The focus of this document is on Health-Based Exposure Limits (HBELs) setting in cleaning validation.

2. Scope

This document provides points to consider for a risk and science-based approach when considering HBELs, based on pharmacological and toxicological data, in cleaning validation.

This document further provides points to consider when reviewing the current status and approaches to cleaning validation in multiproduct facilities.

The principles described in this document may be applied in facilities where active pharmaceutical ingredients (APIs), investigational medical products (IMP), vaccines, human and veterinary medical products are manufactured. The principles may also be considered, where appropriate, in facilities where medical devices are manufactured.

This document should be read in conjunction with the main GMP text and supplementary texts on validation (*1–9*).

3. Glossary

Adjustment factor (safety factors). Numerical factor used in a quantitative risk assessment to represent or allow for the extrapolation, uncertainty, or variability of an observed exposure concentration and its associated health outcome in a particular laboratory species or exposed population to an exposure concentration for the target population (for example, from animals to human patients and short-term exposure to chronic exposure) that would be associated with the same delivered dose. Adjustment factors can also be used when dealing with clinical data, e.g. when a study population is not representative of the general population (*10*).

Cleanability. The ability of a cleaning procedure to effectively remove material, cleaning agent residue and microbial contamination.

Cleaning validation. The collection and evaluation of data, from the cleaning process design stage through cleaning at commercial scale, which establishes scientific evidence that a cleaning process is capable of consistently delivering clean equipment, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

Contamination. The presence of undesired foreign entities of a chemical, microbiological or physical nature in or on equipment, a starting material, or an

intermediate or pharmaceutical product during handling, production, sampling, packaging, repackaging, storage or transport.

Cross-contamination. Contamination of a starting material, intermediate product or finished product with another starting material or product.

Health Based Exposure Limits (HBELs). *See definition of Permitted Daily Exposure (PDE)*

Margin of safety. The margin of safety is the ratio between the cleaning acceptance limit based on HBEL and the process residue data.

Maximum safe carryover (MSC). The maximum amount of carryover of a residual process residue (API, cleaning agent, degradant, and so forth) into the next product manufactured without presenting an appreciable health risk to patients.

Maximum safe surface residue (MSSR). The MSSR is the maximum amount of process residue that can remain on equipment surfaces and still be safe to patients. The MSSR is mathematically calculated by dividing the Maximum Safe Carryover (MSC) by the total area of shared contact (MSC/Total Product Contact Surface Area).

Permitted daily exposure (PDE). PDE represents a substance-specific dose that is unlikely to cause an adverse effect if an individual is exposed at or below this dose every day for a lifetime.

Point of departure (of the HBEL calculation). The dose-response point that marks the beginning of a low-dose extrapolation to derive an HBEL. This point can be a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL), Lowest Observed Adverse Effect Level (LOAEL) or Lowest Observed Effect Level (LOEL), or Benchmark Dose Level (BMDL) for an observed effect [the highest dose at which no unwanted/adverse effect is observed (NOEL/NOAEL), or, if unavailable, the dose at which a significant adverse effect is first observed (LOEL/LOAEL)].

Verification. Evidence that the equipment is clean (i.e. that residues are reduced from prior operations to levels no higher than those that are predetermined and specified as acceptable). Appropriate methods should be used and, depending upon the circumstances, may include visual inspection, analytical and microbial (as applicable) testing of swab and/or rinse samples.

4. Historical approach in cleaning validation

For details on the historical approaches in cleaning validation, see the WHO Technical Report Series, No. 1019, Annexure 3, Appendix 3, 2019 (5).

The acceptance criteria for cleaning validation recommended in historical GMP texts did not account for HBELs. A cleaning limit based on HBELs should be calculated and compared against an existing cleaning limit. Historically established cleaning limits may be used when these are more stringent than HBELs. Any alert and action limits should not be based on historically established cleaning limits, but should be based on a statistical analysis if existing data (i.e. statistical process control).

Where the historical approach cannot be satisfactorily justified, and in view of the risks of contamination and cross-contamination, the new approaches, as described below, should be prioritized and implemented.

5. New approach using HBELs in cleaning validation

Historical cleaning validation approaches often merely showed that using a defined cleaning procedure achieved an objective of meeting historical limits. In many instances, no development work or cleanability studies were done nor was consideration given to pharmacological and toxicological data for establishing limits for cleaning residues.

Manufacturers should ensure that their cleaning procedures are appropriately developed and that their cleaning validation provides scientific evidence that residues of identified products that can be manufactured in shared facilities are removed to levels considered as safe for patients. Control measures should be implemented to mitigate the risks of contamination and cross-contamination.

This approach should include at least the following points (some of which are further described in the text below):

- risk assessment to identify cross-contamination hazards, analyse risks, and to identify risk controls;
- cleaning procedure development studies including cleanability studies, where applicable (e.g. new products or cleaning procedures);
- determination of technical and organizational controls;
- HBELs setting;
- selection of appropriate analytical procedures; and
- cleaning process control strategy.

Manufacturers should describe and implement their policy and approaches, including the points mentioned above, in a document such as a master plan.

Genotoxic and carcinogenic substances, degradants and other contaminants (if relevant) should be identified and their risks evaluated. Appropriate action should be taken where required (*11*).

5.1 Documentation

Risk management principles, as described by WHO and other guidelines on quality risk management (*12*), should be applied to assist in identifying and assessing risks. The appropriate controls should be identified and implemented to mitigate contamination and cross-contamination.

The policy and approaches in cleaning and cleaning validation require that good scientific practices should be applied (including the use of appropriate equipment and methods). This should be described in a cleaning validation master plan. Development studies, cleaning and cleaning validation should be performed in accordance with predefined, authorized standard operating procedures, protocols and reports, as appropriate. Records should be maintained and available.

The design and layout of documents, and the reporting of data and information, should be in compliance with the principles of good documentation practices (*13*) and should also meet data integrity requirements (*14*).

5.2 Equipment

Cleaning validation should cover direct product contact surfaces. Non-contact surfaces should be included in cleaning validation where these have been identified as areas of risk.

Authorized drawings of equipment should be current, accurate and available. Equipment surface area calculations should be documented and justified. The source data for these calculations should be available. The calculated values should be used in the calculations in cleaning validation.

All shared equipment and components, including those that are difficult to clean (for example sieves, screens, filters and bags [such as centrifuge bags]) should be considered in cleaning validation and calculations.

Where the need is identified, dedicated equipment and or components should be used.

5.3 Cleaning agents

Cleaning agents (including solvents and detergents used in cleaning processes) should be selected based on cleaning process development studies including cleanability studies. They should be appropriate for their intended use.

There should be proof of effectiveness and appropriateness of the selected cleaning agent.

Other points to consider include the concentration in which these are used, their composition and removal of their residues to an acceptable level.

5.4 Sampling

Historically, cleaning validation has focused mainly on product contact surface areas.

A combination of at least two or three methods should normally be used. These include swab samples, rinse samples and visual inspection. Visual inspection should always be performed where possible and safe to do so. Sampling should be carried out by swabbing whenever possible. Rinse samples should be taken for areas which are inaccessible for swab sampling. The sampling materials and method should not influence the result.

Appropriate sampling procedures, swab material and sampling techniques should be selected and used to collect swab and rinse samples. The detail should be clearly described in procedures and protocols. The number of swabs, location of swabbing, swab area, rinse sample volume and the manner in which the samples are collected should be scientifically justified.

Swab and rinse sample methods should be validated for commercial product manufacturing and verified for IMPs. Recovery should be shown to be possible from all product contact materials sampled in the equipment with all the sampling methods used.

Where microbiological sampling is carried out, a compendial or validated method should be used.

The manner in which collected samples are stored (if required) and prepared for analysis should be appropriate, described in detail and included in the cleaning validation.

5.5 Cleanability studies

Before a new cleaning procedure is validated and adopted for routine use, a cleanability study should be performed in order to determine the appropriateness of the procedure for removing for example product residue, cleaning agents and microorganisms. For cleaning procedures that have already been validated where the data show that the cleaning procedure is effective and consistent, or where risk assessment indicated that cleanability studies may not be required, this may be considered acceptable.

5.6 Risk management

Risk management should be implemented with a focus on the identification, evaluation, assessment and control of risks to mitigate the risk of contamination and cross-contamination.

Measures should include technical and organizational controls in order to deliver a verified or validated cleaning process (*12*).

5.7 Guidance for Health-Based Exposure Limits (HBELs) setting

Manufacturers should establish, document and implement a company-wide policy on HBELs setting for shared facilities.

The appropriateness of the production and control of various APIs or various products in shared facilities should be evaluated on the basis of scientific data and information.

This is applicable to products already produced in a facility as well as when new products are planned to be introduced into a facility, for example, through a change control procedure.

Procedures should be established and implemented describing how the scientific and toxicological data and information are obtained and considered and how HBELs are established.

Data and information should be gathered and critically evaluated by a qualified expert. A qualified expert is an individual with relevant qualifications including educational background (e.g. toxicology, pharmacology or related health fields), certifications (e.g. (e.g. Diplomate of the American Board of Toxicology (DABT), European Registered Toxicologist (ERT) and with adequate experience in the practice of deriving HBELs, such as occupational exposure limits (OELs), PDEs for residual solvents, elemental impurities, and product contamination/nonconformances. The data and evaluation should be presented in a report that is peer-reviewed by another qualified expert (*10*, *15*). The data and information presented should be free from bias.

Where this service is outsourced by the manufacturer, appropriate measures should be put in place in order to ensure that the data obtained are reliable. GMP requirements, such as vendor qualification, agreements and other related aspects, should be considered.

Note: The HBEL value for the same substance sometimes differs when it is determined by different individuals. The reason for the difference between the values should be clarified and investigated.

The report for each substance should include scientific detail and information, as applicable, such as:

- substance identification

- chemical structure
- clinical indication
- mode of action
- route of administration (*Note: Where there is more than one route of administration, separate HBELs should be derived for each route*)
- preclinical/nonclinical data, for example, of acute and repeat-dose toxicity data
  - genotoxicity data
  - carcinogenicity data
  - reproductive and developmental toxicity data
  - immunotoxicity and sensitization data
- clinical data
- pharmacodynamics and pharmacokinetics
- identification of the critical effect(s)
- point of departure for the HBEL calculation(s)
- adjustment factors
- justification of the selected lead rationale (if calculations with different points of departure were made).

The report should be reviewed for its completeness and appropriateness by the manufacturer's designated internal personnel or by an appointed external person. The person should have in-depth knowledge, appropriate qualifications and experience (see above). A summary document may be prepared from the report, for each relevant substance, which contains the key pharmacological/toxicological characteristics of the compound, the effect that drives the HBEL ("lead effect"), the basis of the rationale that has been used to set the HBEL and the HBEL itself including the route/s of exposure for which the HBEL(s) is/are valid (*15*, *16*, *17*, *18*, *19*).

The scientific report and calculated PDE value should be used when defining the limits used in cleaning validation.

Note: If no NOAEL is obtained, the LOAEL may be used. Alternative approaches to the NOAEL, such as the benchmark dose, may also be used. The use of other approaches to determine HBELs could be considered acceptable if adequately and scientifically justified (16, 17).

Manufacturers should periodically consider new data and information on HBELs. Appropriate action, such as the updating of PDE reports, should be taken where required.

Note: therapeutic macromolecules and peptides are known to degrade and denature when exposed to pH extremes and/or heat, and may become pharmacologically inactive. The cleaning of biopharmaceutical manufacturing equipment is typically performed under conditions which expose equipment surfaces to pH extremes and/or heat, which would lead to the degradation and inactivation of protein-based products. In view of this, the determination of health-based exposure limits using PDE limits of the active and intact product may not be required.

Where other potential routes of cross-contamination exist, the risks posed should be considered on a case-by-case basis.

5.8 Acceptance criteria

The limits established in cleaning validation should be scientifically justified.

Historically, some manufacturers have specified acceptance criteria where HBELs and related toxicity data were not included in the determination of such acceptance criteria.

Criteria such as Maximum Safe Carryover (MSC) and Maximum Safe Surface Residue (MSSR) values should be calculated. Calculations and data should be available and comply with data integrity principles. The calculation should include values of PDE, maximum daily dose, batch size and total shared equipment surface areas, sample areas, sample dilution volumes and recovery factors.

MSC and MSSR should be calculated and presented, for example, in table form listing preceding and following product values. The cleanability value obtained should be considered in determining the acceptability of the procedure(s) and whether other controls including separate, dedicated facilities are required (*for example of IMPs see EudraLex Volume 4 Part 1 Chapter 3.6, Annex 15, Annex 13*).

The margin of safety should be identified.

5.9 Analytical procedures

Samples obtained in cleaning validation should be analyzed by using procedures that are validated for their intended use. The procedures should be developed in accordance with the principles of Analytical Quality by Design.

Specific methods, such as High-performance Liquid Chromatography (HPLC), should be used where appropriate. UV spectrophotometric methods and testing for total organic carbon (TOC) may be used where indicated and where justified. Non-specific methods should only be used where specific methods cannot be employed and their use can be justified, for example, based on the outcome of risk assessment.

Where analytical procedures were developed and validated off-site, the scope and extent of validation when these are transferred to the site, should be defined and justified. This includes procedures that are transferred from research and development laboratories to site laboratories. Analytical procedures should be able to quantify residue levels at the maximum safe surface residue level. (For analytical procedure validation, see reference *6*.)

Manufacturers should ensure that the procedures remain in a validated state.

5.10 Data integrity

Data, information and results pertaining to, for example, HBELs, PDE reports, results obtained from cleaning validation and calculations, should be scientific and should be in compliance with the principles as contained in data integrity guidelines (*14*).

5.11 Cleaning validation and cleaning verification

Cleaning validation

The cleaning procedure should be validated (*5*).

Cleaning validation should include proof of, for example, the applicability of the procedure to clean equipment that:

- had been kept in an unclean state for a period of time (dirty equipment hold time);
- are used after a product is planned (e.g. change from one product to another product);
- are used in a campaign, where multiple batches of a product are produced one after the other; and/or
- are stored in a clean state for defined periods of time (clean equipment hold time).

HBELs should be considered when establishing carryover limits in cleaning validation.

Cleaning verification

The company should describe the policy and approach to cleaning verification. Cleaning verification is where the effectiveness of the validated cleaning procedure is routinely verified. The approach may include swab or rinse samples and should include the same sampling and testing procedures used in cleaning validation. The results obtained from testing on a routine basis should be reviewed and subjected to statistical trending if possible.

5.12 Visually clean

Visually clean is an important criterion in cleaning validation. It should be one of the acceptance criteria used on a routine basis. Personnel responsible for visual inspection should be appropriately trained and qualified and training records should be kept.

Where visual inspection is used as a quantitative method, then Visible Residue Limits (VRLs) should be determined. The process to determine the limit should be appropriately described in procedures and protocols covering, for example, concentrations, method of spiking, surface areas, material of construction and other conditions such as light (LUX level) and angles. The acceptability of visual inspection should be determined by comparing the VRL of that compound to the MSSR with an appropriate safety margin.

5.13 Cleaning process capability

The cleaning procedure should remain in a validated state. It is recommended that Process Capability (Cpk) be calculated and Statistical Process Control (SPC) be used to support cleaning verification results and data. For example, the results from cleaning verification sample analysis could be statistically trended. The capability (Cpk) of the cleaning process is then calculated using an appropriate statistical technique.

Data should be presented, for example, in graph form, and the capability of the process in relation to control limits and the margin of safety should be presented and discussed as part of continuous improvement over the life cycle.

5.14 Personnel

Personnel should be trained on the procedures and principles of cleaning and cleaning validation, including contamination and cross-contamination control, HBELs setting, equipment disassembly, visual inspection, sampling, testing and statistical calculations, as appropriate and based on their responsibilities.

5.15 Life cycle

Cleaning procedures, cleaning validation and cleaning verification should be included in the life cycle approach described by the company.

References

1. Guidelines on good manufacturing practices for pharmaceutical products: main principle. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/fr-trs986annex2gmp-main-principles.pdf, accessed 12 August 2020).

2. Good manufacturing practices: guidelines on validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1019/en/, accessed 2 February 2021).

3. Guidelines on heating ventilation and air-conditioning systems for non-sterile pharmaceutical products and Part 2: interpretation of guidelines on heating ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 2 (WHO Technical Report Series, No. 1019; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1010-annex8-who-gmp-heating-ventilation-airconditioning-part2.pdf, accessed 2 February 2021).

4. Good manufacturing practices: guidelines on validation. Appendix 2. Validation of water systems for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 3 (WHO Technical Report Series 1019,; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

5. Good manufacturing practices: guidelines on validation. Appendix 3. Cleaning validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

6. Good manufacturing practices: guidelines on validation. Appendix 4. Analytical procedure validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty- third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

7. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

8. Good manufacturing practices: guidelines on validation. Appendix 6. Guidelines on qualification. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

9. Guidelines on good manufacturing practices: validation, Appendix 7: non sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs1019-annex3-gmp-validation.pdf, accessed 2 February 2021).

10. ASTM E3219-20. Standard Guide for the Derivation of Health Based Exposure Limits (HBELs). West Conshohocken, PA: American Society for Testing Materials (ASTM) International.

11. ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.

12. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/production/trs981-annex2-who-quality-risk-management.pdf, accessed 2 February 2021).
13. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 996; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs966-annex05-who-record-management-practices.pdf, accessed 2 February 2021).
14. Guideline on data integrity. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fifty-fifth report. Geneva: World Health Organization; 2021: Annex 4 (WHO Technical Report Series, No.xxx, website etc) Geneva: World Health Organization; 2019 (working document QAS/19.819; https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas19-819-rev1-guideline-on-data-integrity.pdf, accessed 2 February 2021).
15. PIC/S. (2020). AIDE-MEMOIRE: Inspection of Health Based Exposure Limit (HBEL) Assessments and Use in Quality Risk Management (PI 052-1): Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-Operation Scheme.Guideline on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. EMA, 2014 (EMA/CHMP/ CVMP/ SWP/169430/2012).
16. Questions and answers on implementation of risk-based prevention of cross-contamination in production and Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities. (EMA/CHMP/CVMP/SWP/246844/2018). European Medicines Agency, 2018.
17. ASTM E3106. Standard Guide for Science-Based and Risk-Based Cleaning Process Development and Validation.
18. ISPE Baseline, Pharmaceutical Engineering Guide, Volume 7 – Risk-based manufacture of pharmaceutical products, International Society for Pharmaceutical Engineering (ISPE), Second edition, July 2017.

Further reading

- Comparison of Permitted Daily Exposure with 0.001 Minimal Daily Dose for Cleaning Validation. May 02, 2017. Ester Lovsin Barle, Camille Jandard, Markus Schwind, Gregor Tuschl, Claudia Sehner, David G. Dolan. Pharmaceutical Technology. Volume 41, Issue 5, pages 42–53.
- ICH Topic Q3A (R2). Note for guidance on impurities testing: Impurities in new drug substances (www.ich.org).
- Regulatory Toxicology and Pharmacology. ADE Supplement, Volume 79, Supplement 1, Pages S1-S94 (15 August 2016) (https://www.sciencedirect.com/journal/regulatory-toxicology-and pharmacology/vol/79/suppl/S1, accessed 25 September 2020).
- Sehner C, Schwind M, Tuschl G, Lovsin Barle E. What to consider for a good quality PDE document? Pharm Dev Technol. 2019;24(7):803-811. doi:10.1080/10837450.2019.1592188

Appendix 1

Using Health-Based Exposure Limits (HBELs) to assess risk in cleaning validation*

Permitted Daily Exposure (PDE)

The Permitted Daily Exposure (PDE) can be calculated based on the data and information obtained. For example:

$$PDE = \frac{NOAEL \times \text{weight adjustment}}{F1 \times F2 \times F3 \times F4 \times F5}$$

Where NOAEL is no-observed adverse effect level, and

F represents various adjustment factors. The value selected for each factor should be justified. All adjustment factors should ideally be compound-specific. Default values should only be used where no compound-specific data are available.

The PDE is derived by dividing the NOAEL for the critical effect by various adjustment factors (also referred to as safety-, uncertainty-, assessment- or modifying factors) to account for various uncertainties and to allow extrapolation to a reliable and robust no-effect level in the human or target animal population. (*Note: The values for the factors cited below are defaults and should only be used in the absence of compound-specific information*).

F1 to F5 are addressing the following sources of uncertainty:

- F1: A factor (values between 2 and 12) to account for extrapolation between species;
- F2: A factor of 10 to account for variability between individuals;
- F3: A factor 10 to account for repeat-dose toxicity studies of short duration, i.e., less than 4-weeks;
- F4: A factor (1-10) that may be applied in cases of severe toxicity, e.g. non-genotoxic carcinogenicity, neurotoxicity or teratogenicity;
- F5: A variable factor that may be applied if the no-effect level was not established. When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

* Barle, E.L. Using Health-Based Exposure Limits to assess risk in cleaning validation. Pharmaceutical Technology

The use of additional modifying factors to address residual uncertainties not covered by the above factors may be accepted provided they are well supported with literature data and an adequate discussion is provided to support their use (*17*).

If no NOAEL is obtained, the lowest-observed-adverse-effect level (LOAEL) may be used.

Calculating Maximum Safe Carryover (MSC) and Maximum Safe Surface Residue (MSSR)

MSC and MSSR can be calculated by using HBELs, to determine the risks associated with cleaning validation.

Step 1. Calculate MSC:

$$\text{MSC a (g)} = \frac{\text{PDE a (ug)} \times \text{Batch size b (kg)}}{\text{Maximum Daily Dose b (mg)}}$$

Where a = product a
b = product b or subsequent product

Step 2. Tabulate the data

API	PDE ug/day	MDD mg/day	Batch size Kg	Shared Equipment surface (m2)
1				
2				
3				
4				
5				

Step 3. Calculate MSSR (mg/m2)

$$\text{MSSR} = \frac{\text{MSC a (g)} \times 1000}{\text{Shared surface for b (m2)}}$$

Step 4. Tabulate the data for MSSR and identify where there is a risk, based on the MSSR that are not met when considering the cleanability of the procedure or the Visual Residue Limit of the compound / product.

MSSR		Following product b					
		1	2	3	4	5	6
Pre-Ce-ding Product a	1						
	2						
	3						
	4						
	5						
	6						

Annex 3

Good manufacturing practices: water for pharmaceutical use

Background

Unlike other product or process ingredients, water is usually drawn from an on-demand system and is not subject to testing and batch or lot release prior to use. Thus it is essential that water quality (including microbiological and chemical quality) throughout production, storage and distribution processes is controlled.

In recent years, following extensive consultations with stakeholders, several pharmacopoeias have adopted revised monographs on water for injection (WFI) that allow for production by non-distillation technologies. In 2017, the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) recommended that the WHO Secretariat collect feedback on whether or not they should revise the WHO specifications and good manufacturing practices (GMP) on WFI and, if so, how to do so. Following several consultations, the ECSPP agreed that the monograph in *The International Pharmacopoeia* (*Water for injections*) and the guideline *WHO Good manufacturing practices: water for pharmaceutical use* (*1*), should both be revised to allow for technologies other than distillation for the production of WFI.

In early 2019, the WHO Secretariat commissioned a draft guidance text for the production of WFI by means other than distillation. Following several public consultations, the text was presented to the Fifty-fourth ECSPP. The Expert Committee adopted the *Production of water for injection by means other than distillation* guideline and recommended that it should also be integrated into WHO's existing guideline on *Good manufacturing practices: water for pharmaceutical use*.

This document is a revision of *WHO Good manufacturing practices: water for pharmaceutical use*, previously published in the WHO Technical Report Series, No. 970, Annex 2, 2011.

1. Introduction and scope 113

2. Background to water requirements and uses 113

3. General principles for pharmaceutical water systems 115

4. Water quality specifications 115
4.1 Pharmacopoeial specifications 115
4.2 Drinking-water 116
4.3 Bulk purified water 118
4.4 Bulk water for injections 120
5. General considerations for water purification systems 121
6. Water storage and distribution systems 123
7. Good practices for water systems 123
8. System sanitization and bioburden control 125
9. Storage vessels 126
10. Water distribution 127
11. Operational considerations including some qualification and validation principles 128
12. Continuous system monitoring 129
13. Maintenance of water systems 130
14. System reviews 131
15. Inspection of water systems 131
References 132
Further reading 133

1. Introduction and scope

1.1 This document concerns water for pharmaceutical use (WPU) produced, stored and distributed in bulk form. It provides information on different specifications for WPU; good practices for the management of the quality of water systems; water treatment (production) systems; water storage and distribution systems; commissioning, qualification and validation; sampling and testing; and the routine monitoring of water.

1.2 The focus of this document is on the treatment, storage and distribution of treated water used in pharmaceutical applications. It excludes the production, storage and usage of water in quality-control laboratories.

1.3 This document does not cover water for administration to patients in the formulated state or the use of small quantities of water in pharmacies to compound individually prescribed medicines.

1.4 The document can be used in whole or in part, as appropriate, to the section and application under consideration.

1.5 In addition to this document, the "Further reading" section at the end of this document includes publications that can serve as additional background material when planning, installing and operating systems intended to provide WPU.

1.6 This document is supplementary to the *WHO good manufacturing practices for active pharmaceutical ingredients* (*2*), and the *WHO good manufacturing practices for pharmaceutical products: main principles* (*3*).

2. Background to water requirements and uses

2.1 Water is a widely used substance in the pharmaceutical industry and other sectors involved in manufacturing pharmaceutical products. It is extensively used as a raw material or starting material in the production, processing and formulation of active pharmaceutical ingredients (APIs), intermediates and finished pharmaceutical products (FPP), in the preparation of solvents and reagents, and for cleaning (e.g. washing and rinsing). Water has unique chemical properties due to its polarity and hydrogen bonds. These include a relatively high boiling point, high specific heat, cohesion, adhesion and density. These include contaminants that may be hazards in themselves or that may be able to react with product substances, resulting in hazards to health. Water should therefore meet appropriate quality standards to mitigate these risks.

2.2 The microbiological and chemical quality of water should be controlled throughout production, storage and distribution. While chemical test results can normally be obtained without delay, results from microbiological testing are normally available only after water has already been used as microbiological tests may require periods of incubation. The assurance of quality to meet the on-demand expectation of water is therefore essential.

2.3 To reduce the risks associated with the production, storage and distribution of water, and considering the properties and use, it is essential:

- to ensure the appropriate design, installation, operation and maintenance of WPU, pre-treatment, treatment, storage and distribution systems;
- to continuously or periodically perform sanitization;
- to take the appropriate measures in order to minimize chemical and microbial contamination; and
- to minimize microbial proliferation and endotoxin formation, where applicable.

2.4 Different grades of water quality exist. The appropriate water quality, meeting its defined specification (such as described in a pharmacopoeia), should be used for the intended application.

2.5 The application of specific types of water to processes and dosage forms should be considered.

2.6 Pharmaceutical manufacturers should use the appropriate grade of WPU during, for example, the manufacture of APIs and different dosage forms, for different stages in washing and cleaning, and in the synthesis of materials and products.

2.7 The grade of water used should take into account the nature and intended use of the intermediate or FPP and the stage in the manufacturing process at which the water is used.

2.8 Bulk water for injections (BWFI) should be used, for example, in the manufacture of injectable products, such as dissolving or diluting substances or preparations during the manufacturing of parenteral products, and for the manufacture of water for preparation of injections. BWFI should also be used for the final rinse after the cleaning of equipment and components that come into contact with injectable products, as well as for the final rinse in a washing process in which no subsequent thermal or chemical depyrogenization process is applied.

3. General principles for pharmaceutical water systems

3.1 Pharmaceutical water production, storage and distribution systems should be designed, installed, commissioned, qualified, validated, operated and maintained to ensure the consistent and reliable production of water of appropriate quality.

3.2 The capacity of these systems should be enough to meet both the minimum and peak demand. These systems should be able to operate continuously for significant periods of time in order to avoid the inefficiencies and equipment stresses that occur when equipment cycles turn on and off too frequently.

3.3 Qualification may include stages such as preparing User Requirement Specifications (URS), Factory Acceptance Tests (FAT), Site Acceptance Tests (SAT), as well as installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). The release and use of the system should be approved by the quality unit, e.g. quality assurance (QA) at an appropriate stage of qualification and validation (see section 11 below).

3.4 Water sources and treated water should be monitored regularly for chemical, microbiological and, where appropriate, endotoxin contamination. The performance of water treatment, storage and distribution systems should also be monitored. Records of the results monitored, trend analysis and any actions taken should be maintained.

4. Water quality specifications

4.1 Pharmacopoeial specifications

4.1.1 Pharmacopoeias include specifications for water used in bulk and in dosage forms. Where this document refers to specifications, such as those in pharmacopoeias, the relevant, current publications should be used. This document does not attempt to duplicate such material. Where subtle points of difference exist between pharmacopoeial specifications, the manufacturer should choose the appropriate specification in accordance with the related marketing authorization submitted to the relevant medicine's regulatory authority. Pharmacopoeial requirements or guidance for WPU are described in national, regional and international pharmacopoeias (*4*) and limits for various impurities, or classes of impurities, are either specified or recommended. Requirements or guidance are given in pharmacopoeias on the microbiological and chemical quality of water.

4.2 Drinking-water

Note: The requirements for the design, construction and commissioning of drinking water systems are usually controlled through local regulations. Drinking water systems are not usually qualified or validated, but subjected to commissioning.[1]

4.2.1 The quality of drinking-water is covered by the *WHO guidelines for drinking-water quality* (*5*) and standards from the International Organization for Standardization (ISO) and other regional and national agencies. Drinking-water should comply with the relevant regulations laid down by the relevant authority.

4.2.2 Drinking-water may be derived from a natural or stored source. Examples of natural sources include springs, wells, rivers, lakes and seas. The condition of the source water should be considered when choosing a treatment to produce drinking- water.

4.2.3 Drinking-water should be supplied under continuous positive pressure by a plumbing system free from any defects that could lead to contamination.

4.2.4 Drinking-water may be derived from a public water supply system. This includes an off-site source, such as a municipality. Appropriate drinking-water quality should be ensured by the supplier. Tests should be conducted to guarantee that the drinking-water delivered is of drinking quality. This testing is typically performed on water when taken from the water source. Where required, quality may be achieved through processing on-site.

4.2.5 Where drinking-water is purchased in bulk and transported to the user by water tankers, controls should be put into place to mitigate any associated risks. Vendor assessment and authorized certification activities, including confirmation of the acceptability of the delivery vehicle, should be undertaken in a similar way to that used for any other starting material.

4.2.6 It is the responsibility of the pharmaceutical manufacturer to assure that the source water supplying the purified water (PW) treatment system meets the appropriate drinking-water requirements. In these situations, the point at which drinking-water quality is achieved should be identified and a water sample taken and tested at defined intervals thereafter.

[1] See documents listed under Further reading.

4.2.7 If drinking-water is used directly in certain stages of pharmaceutical manufacture, such as in the production of APIs or in the feedwater for the production of higher qualities of WPU, then testing should be carried out periodically by the water user's site; for example, at the point of use, to confirm that the quality meets the standards required for drinking-water. The selection of tests to be performed, and the frequency of testing, should be based on a risk assessment.

4.2.8 Where drinking-water is produced through the treatment of raw water by a system on-site, the system configuration and water-treatment steps used should be described.

4.2.9 Examples of typical processes employed to produce drinking-water may include:

- desalination;
- filtration;
- softening;
- disinfection or sanitization, such as by ozone or sodium hypochlorite (chlorine);
- iron (ferrous) removal;
- precipitation; and
- the reduction of concentration of specific inorganic and/or organic materials.

4.2.10 Controls should be implemented to minimize the microbiological contamination of sand filters, carbon beds and water softeners. The techniques selected should be appropriate and may include backflushing, chemical and/or thermal sanitization and frequent regeneration.

4.2.11 The quality of drinking-water should be monitored routinely to account for environmental, seasonal or supply changes which may have an impact on the source water quality.

4.2.12 Where drinking-water is stored and distributed by the user, the storage and distribution systems should minimize the degradation of the water quality prior to use. After any such storage, testing should be carried out routinely and in accordance with a defined procedure. The storage and distribution of drinking-water should be done in a manner to ensure a turnover or recirculation of the water, if possible.

4.2.13 The equipment and systems used to produce and store drinking-water should be able to be drained or flushed, and sanitized.

4.2.14 Storage tanks should be closed with appropriately protected vents and should allow for visual inspection.

4.2.15 Distribution pipework should be able to be drained or flushed, and sanitized.

4.2.16 The scope and extent of commissioning for the system should be identified and justified.

4.2.17 If possible, the results from testing drinking-water should be subjected to statistical analysis in order to identify trends and changes. If the drinking-water quality changes significantly, but is still within specification, the direct use of this water as a WPU, or as the feedwater to downstream treatment stages, should be reviewed for any potential risks. The appropriate action should be taken and documented.

4.2.18 Changes to an in-house system or to its operation should be made in accordance with change control procedures.

4.2.19 Additional testing should be considered if there is any change in the raw water source, treatment techniques or system configuration.

4.3 Bulk purified water

4.3.1 Bulk purified water (BPW) should meet the relevant pharmacopoeial specifications for chemical and microbiological purity. The appropriate and applicable test procedures should be followed.

4.3.2 BPW should be prepared from drinking-water as a minimum-quality feedwater.

4.3.3 Any appropriate, qualified purification technique, or sequence of techniques, may be used to prepare BPW. BPW could be prepared by, for example, ion exchange, reverse osmosis (RO), RO/electro-deionization (EDI), ultrafiltration, or any combination of these techniques.

4.3.4 The following are examples of aspects that should be considered when configuring a water purification system or defining URS:

- the quality of feedwater and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required;
- the number and location of sampling points

- design of sampling points in such a way so as to avoid potential contamination;
- unit process steps provided and documented with the appropriate instrumentation to measure parameters such as flow, pressure, temperature, conductivity and total organic carbon;
- material of construction;
- sanitization strategy;
- main components;
- interlocks, controls and alarms; and
- appropriate software, electronic data management, system security and audit trail.

4.3.5 Ambient-temperature systems such as ion exchange and ultrafiltration are especially susceptible to microbiological contamination, particularly when equipment is static during periods of no or low demand for water. Sanitization at defined intervals (e.g. based on the data collected from the system validation and system behaviour), as well as other controls, should be defined to prevent and minimize microbiological contamination.

4.3.6 Methods for sanitizing each stage of purification should be appropriate and validated. The removal of any agents used for sanitization should be proven.

4.3.7 The following controls, for example, should be considered in order to minimize microbial contamination:

- the maintenance of water flow at all times in the storage and distribution system to prevent water from stagnating;
- control of temperature in the system, for example, by heat exchangers or room cooling in order to reduce the risk of microbial growth;
- the provision of ultraviolet disinfection at appropriate locations in the system;
- the use of water-treatment system components that can periodically be thermally sanitized above 70 °C for a defined period of time, or chemically sanitized using, for example, ozone, hydrogen peroxide and/or peracetic acid; and
- a combination of thermal and chemical sanitization, if required.

4.3.8 BPW should have appropriate alert and action limits for chemical and microbiological purity determined from a knowledge of the system and data trending. BPW should be protected from recontamination and microbial proliferation.

4.4 Bulk water for injections

4.4.1 BWFI should meet the relevant pharmacopoeial specifications for chemical and microbiological purity (including endotoxins). BWFI is the highest quality of pharmacopoeial WPU.

4.4.2 BWFI is not a final dosage form. It is an intermediate bulk product suitable to be used as an ingredient during formulation.

4.4.3 As a robust technique should be used for the production of BWFI, the following are examples of what should be considered when configuring a water purification system or defining URS:

- the quality of feedwater and its variation over seasons;
- the quantity of water required by the user;
- the required water-quality specification;
- the sequence of purification stages required, where appropriate;
- based on the selection of components, material of construction and type of system, the appropriate URS, qualification and validation;
- the optimum generator size or generators with variable control to avoid over-frequent start/stop cycling;
- blow-down and dump functions;
- cool-down venting to avoid contamination ingress;
- appropriately located sampling points designed in such a way so as to avoid potential contamination;
- appropriate instrumentation to measure parameters as required;
- sanitization strategy;
- interlocks, controls and alarms; and
- electronic data storage, system security and audit trail.

4.4.4 BWFI may be prepared, for example, by distillation as the final purification step. Alternatively, BWFI may be produced by means other than distillation. Techniques such as deionisation, electro deionization, nanofiltration, ultrafiltration, water-softening, descaling, pre-filtration and degasification, ultraviolet treatment, along with other techniques, may be considered in conjunction with a single or double pass RO system. For full details, see *Production of water for injection by means other than distillation* as published in the WHO Technical Report Series, No. 1025, Annex 3, 2020 (*6*).

4.4.5 BWFI should have appropriate microbial and chemical alert and action limits and should also be protected from recontamination and microbial proliferation.

5. General considerations for water purification systems

5.1 Pharmaceutical manufacturers should apply the current principles of quality risk management (*7*) in selecting and using the appropriate water purification systems. An appropriate method for the production of WPU should be used.

5.2 Risks and controls should be identified for each stage of the production, storage, distribution, use and monitoring of WPU.

5.3 Risks identified should be evaluated in order to determine the scope and extent of validation and qualification of the system, including the computerized systems used for the production, control and monitoring of WPU.

5.4 Risk management should be an ongoing part of the quality management process for WPU. A mechanism to review or monitor events associated with the production, storage, distribution and use of WPU should be implemented.

5.5 Procedures for managing changes and deviations should be followed. Where applicable, the appropriate risk and impact assessments should be carried out in such a way that changes and deviations are managed.

5.6 The chosen water purification system, method or sequence of purification steps must be appropriate in order to ensure the production of water of the intended grade. Based on the outcome of the risk assessment, the following should at least be considered when selecting the water treatment system and method:

- the quality of the available feedwater and the variation over time (seasonal changes);
- the availability of suitable support facilities for the system (e.g. electricity, heating, steam, chilled water and compressed air);
- the extent of pre-treatment required;
- the sequence of purification steps required;
- the design and location of sampling points;
- the sanitization strategy;

- the availability of water-treatment equipment on the market;
- the reliability and robustness of the water-treatment equipment in operation;
- the yield or efficiency of the purification system;
- the ability to adequately support and maintain the water purification equipment;
- the continuity of operational usage considering hours/days/years and planned downtime;
- the total life-cycle of the system (including capital, operation and maintenance);
- the final water quality specification; and
- the minimum, average and maximum quantity of water required by the user.

5.7 The specifications for water purification equipment, storage and distribution systems should take into account at least the following:

- the location of the plant room;
- the extremes in temperature that the system will encounter;
- the risk of contamination, for example, from materials of construction (contact materials) and the environment;
- the adverse impact of adsorptive contact materials;
- hygienic or sanitary design, where required;
- corrosion resistance;
- freedom from leakage;
- system configuration to avoid or minimize proliferation of microbiological organisms;
- tolerance to cleaning and sanitizing agents (thermal and/or chemical);
- the sanitization strategy;
- system capacity and output requirements; and
- the provision of all necessary instruments, test and sampling points in order to allow for all the relevant critical quality parameters of the complete system to be monitored.

5.8 The design, configuration and layout of the water purification equipment, storage and distribution systems should also take into account the following physical considerations:

- the ability to collect samples;

- the space available for the installation and environment around the system;
- structural loadings on buildings;
- the provision of adequate access for maintenance and monitoring; and
- the ability to safely handle regeneration and sanitization chemicals.

6. Water storage and distribution systems

6.1 Where drinking water is stored and distributed, the appropriate controls should be determined and implemented in order to mitigate risks. This applies to all stages in the supply, storage and distribution of drinking-water.

6.2 The water storage and distribution systems for PW and BWFI should be appropriately designed, installed, qualified, operated and maintained in order to ensure the storage and distribution of water is of consistent quality to the user points.

7. Good practices for water systems

7.1 The components of water systems, including but not limited to pipework, valves and fittings, seals, diaphragms and instruments, should be appropriate and remain suitable during the full range of operational conditions such as temperature and pressure of the system at rest, in operation and during sanitization. The construction materials should be of adequate quality.

7.2.1 As a minimum, the following design and construction practices should be considered.

For drinking water storage, supply and distribution systems on-site

Materials of construction should be selected based on the following requirements:

- ability to operate at the temperatures/pressures required;
- lack of impact on the final water quality;
- resistant to sanitizing chemicals;
- threaded and flanged joints are permitted; and
- sample valves should preferably be of sanitary design.

Note that the system may have a design life at the end of which it should be replaced or adequately modified.

For purified water and bulk water for injection systems

Note: Construction standards are generally aligned with potable water standards up to the process stage (e.g. RO).

- Materials of construction should be appropriate. It should be non-leaching, non-adsorbing, non-absorbing and resistant to corrosion. Stainless-steel grade 316L or polyvinylidene chloride (PVDC) is generally recommended. The choice of material should take into account the intended sanitization method.
- Stainless steel systems should be orbitally welded, with manual welds where necessary. Inter-weldability between materials should be demonstrated with the maintenance of weld quality through a defined process. Documentation for such a system should be kept and should include, as a minimum, the qualification of the welder, set-up for welding (e.g. machine), work session test pieces (coupons or weld samples), proof of quality of gas used, welding machine calibration record, weld identification and heat numbers, and logs of all welds. Records, photographs or videos of inspection of a defined proportion of welds (e.g. 100% of manual welds, 10% of orbital welds).
- Joints should be made using sanitary connections, for example, hygienic clamp joints. Threaded joints should not be permitted. Polyvinylidene fluoride or polyvinylidene difluoride (PVDF) systems should be fusion joined and visually inspected.
- Passivation should be considered for stainless steel systems, for example, for non-electropolished surfaces (after initial installation and after significant modification) in accordance with a documented procedure defining the solution to be used, its concentration, the temperature and contact time.
- Internal finish should be smooth.
- Flanges, unions and valves should be of a hygienic or sanitary design. Valves should be diaphragm type forged or machined body, with points of use constructed so that they can drain. Sample valves should be sanitary type with the surface roughness of 1.0 micrometer RA or lower for PW and WFI systems and are typically installed between process stages and on the distribution loop return. The appropriate checks should be carried out in order to ensure that the correct seals and diaphragms are used and that they are fitted and tightened correctly.
- The system should be installed to promote drainability with a recommended minimum slope of 1/100.

- Where appropriate, pressure or hydro-tests for leaks, spray-ball functionality test and flow turbulence should be considered.
- Provision should be made for in-line measurement for total organic carbon (TOC), conductivity, pressure, flow and temperature.
- Documents should provide evidence of system components and qualification. These include as applicable drawings, original or certified copies of certificates of conformity for materials of construction, records of on-site tests performed, weld/joining records, calibration certificates, system pressure test records and records of passivation.

8. System sanitization and bioburden control

8.1 Water-treatment, storage and distribution systems should be subjected to controls that will reduce the risk of contamination and the proliferation of microbiological organisms.

8.2 Controls may include using chemical and/or thermal sanitization procedures as appropriate for production, storage and distribution systems. The procedure and conditions used (such as times and temperatures, as well as the frequency), should be defined and proven to be effective for sanitizing all relevant parts of the system. The techniques employed should be considered during the design stage of the system as the procedure and technique may impact on the components and materials of construction.

8.3 Systems that operate and are maintained at elevated temperatures (e.g. > 70 °C) are generally less susceptible to microbiological contamination than systems that are maintained at lower temperatures. When lower temperatures are required due to the water treatment processes employed, or the temperature requirements for the water in use, special precautions should be taken to prevent the ingress of contaminants including microorganisms (see section 9.2 for guidance).

8.4 Where the chemical sanitization of the water systems is part of the biocontamination control programme, a validated procedure should be followed in order to ensure that the sanitizing process selected is effective and that the sanitizing agent has been effectively removed.

8.5 Records of sanitization should be maintained.

8.6 Other control techniques to be considered may include:

- The maintenance of a continuous circulation of water maintaining turbulent flow evidenced by, for example, a Reynolds number of > 4000.
- Ensuring hygienic design, including the use of zero dead leg diaphragm valves where possible, and minimizing dead legs elsewhere. Areas of possible dead legs should be measured and calculated.
- Installing pipework in a manner to allow for full drainage, if required. A guidance figure for the slope is not less than 1/100.
- Considering the use of ultraviolet lamps in the system where needed with independent monitoring.
- Maintaining the system at an elevated temperature (e.g. > 70 °C), if required.

9. Storage vessels

9.1 Storage vessels should be appropriate for their intended use.

9.2 As a minimum, the following should be considered:

- the design and shape to ensure drainage of water from the vessel, when required;
- construction materials;
- capacity, including buffer capacity, between the steady state, water generation rate and the potentially variable simultaneous demand from user points, short-term reserve capacity in the event of failure of the water-treatment system or the inability to produce water (e.g. due to a regeneration cycle);
- prevention of stagnant water in the vessel (e.g. the headspace where water droplets can accumulate) and the need for the use of a spray-ball or distributor devices to wet the inner surfaces of the vessel;
- the fitting of bacteria-retentive, hydrophobic vent filters which are tested for their integrity at appropriate intervals;
- the fitting of sanitary design pressure safety valves or bursting discs provided with external rupture indicators to ensure that loss of system integrity is detected;
- the design and sanitization, as required, of level indicators;
- the design and location of valves, sampling points and monitoring devices and sensors; and

- the need for heat exchangers or jacketed vessels. Where these are used, double tube sheet or double plate heat exchangers should be considered.

10. Water distribution

10.1 The water distribution system should be designed as a loop, with continuous circulation of BPW and BWFI. Where this is not the case, the appropriate justification for using a non-recirculating one-way system should be provided as well as robust measures implemented to monitor these.

10.2 As a minimum, the following should be considered:

- controls to minimize proliferation of contaminants;
- material of construction, joints and impact as a result of sanitization; and
- the design and location of devices, sensors and instruments such as flow meters, conductivity sensors, TOC analysers and temperature sensors.

10.3 Filtration should not be used in distribution loops or at take-off user points.

10.4 Where heat exchangers are used, they should be arranged in continually circulating loops or sub-loops in order to avoid unacceptable static water in the system.

10.5 When the temperature is reduced for processing purposes, the reduction should occur for the minimum necessary time. The cooling cycles and their duration should be proven satisfactory during the qualification of the system.

10.6 Circulation pumps should be of a sanitary design with the appropriate seals to prevent contamination of the system.

10.7 Where stand-by pumps are provided, they should be configured or managed to avoid zones where stagnant water is trapped within the system.

10.8 Consideration should be given to preventing contamination in systems where parallel pumps are used. There should be no stagnant water remaining in a pump when the pumps is not being used.

10.9 Components should be identified and labelled. The direction of flow should be indicated.

11. Operational considerations including some qualification and validation principles

11.1 Water systems should be appropriately qualified and validated (8). The scope and extent of qualification should be determined based on risk assessment. (See also point 3.3. above.)

11.2 When commissioning work is done, this should be documented. Commissioning is not a replacement for qualification.

11.3 In order to demonstrate the reliability and robustness of a system and its performance, a three-phase approach should be used for validation, covering at least one year of operation over different seasons. Tests on the source water (drinking-water) should be included within the validation programme and continued as part of the routine monitoring, and these results should meet specifications.

Note: A typical phase 1 to 3 approach for a new system is described below. When changes are made to existing systems, the phase(s) and length of each phase, as well as sampling points and frequency of sampling should be based on documented risk assessment.

Phase 1

Phase I should cover a period of at least two weeks.

Procedures and schedules should cover at least the following activities and testing approaches:

- chemical and microbiological testing in accordance with a defined plan;
- sample, test and monitoring of the incoming feedwater to verify its quality;
- sample, test and monitoring after each step in the purification process;
- sample, test and monitoring at each point of use and at other defined sample points including the end of the distribution loop;
- verification of operating ranges;
- operating, cleaning, and maintenance;
- sanitizing procedures and operating ranges;
- demonstrate the consistent production and delivery of product water of the required quality and quantity;

- establishing provisional alert and action levels; and
- test-failure procedure.

The system should be monitored intensively for its performance. Water should not be used for product manufacturing during this phase.

Phase 2

Phase 2 should cover at least a further test period of two weeks after the satisfactory completion of Phase 1. The system should be monitored while deploying all the standard operating procedures (SOPs). The sampling programme should be generally the same as in Phase 1. The use of the water for product manufacturing purposes during this phase may be acceptable, provided that Phase 1 and ongoing Phase 2 data demonstrate the appropriate water quality and the practice is approved by QA.

The approach should also:

- demonstrate consistent system operation within established ranges; and
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3

Phase 3 should follow phase 2 ensuring that the duration of Phase I, 2 and 3 cover at least 12 months. The sample locations, sampling frequencies and tests may be reduced according to a routine plan which should be based on the established procedures and data from Phase 1 and Phase 2. Data should be trended, for example, quarterly and a system review should be undertaken after the completion of Phase 3 as part of the evaluation of system performance capability. The appropriate action should be taken where such a need is identified.

Water can be used during this phase. The data and information obtained during Phase 3 should demonstrate the reliable performance of the system over this period of time covering the different seasons.

12. Continuous system monitoring

12.1 The system should be subject to continuous monitoring.

12.2 A monitoring plan should be followed where samples are collected in accordance with a written procedure.

12.3 A combination of online and offline instruments, linked to appropriately qualified alarm systems, should be used. Parameters such as flow, pressure, and temperature should be monitored with online instruments – as well as conductivity and TOC, where possible. Periodic offline testing to confirm the results from online testing is recommended. Other parameters may be monitored through offline testing.

12.4 Offline testing (including physical, chemical and microbiological attributes) should be done in accordance with a predetermined programme.

12.5 Samples should be taken from points of use and dedicated sample points where required. All water samples should be taken using the same methodology as detailed in production procedures, for example, using a hose and with a suitable flushing and drainage procedure in place.

12.6 Tests should be carried out to ensure that the relevant pharmacopoeia specification (and approved company specification, where applicable) has been met. This may include the microbiological quality of water, as appropriate.

12.7 The results for identified quality attributes should be subjected to statistical analysis at defined intervals, for example, monthly, quarterly and annually, in order to identify trends. The results should be within defined control limits, such as 3 sigma.

12.8 Alert and action levels should be established based on historically reported data.

12.9 Adverse trends and out-of-limit results should be investigated for the root cause, followed by the appropriate corrective and preventive actions. Where microbial contamination of BWFI occurs, the micro-organism should be identified.

13. Maintenance of water systems

13.1 WPU systems should be maintained in accordance with an approved and documented maintenance programme. Records should be kept.

13.2 The maintenance programme should take into account at least the following:

- defined frequency for system elements e.g. filters, instruments, gauges;
- the calibration programme;
- SOPs for specific tasks;

- the control and storage of approved spare parts;
- preventive maintenance and maintenance plan and instructions, including cleaning after maintenance;
- a review and approval of systems for use upon completion of work; and
- a record and review of problems and faults during maintenance

14. System reviews

14.1 WPU systems should be reviewed at described intervals (e.g. annually)S. The review should be documented.

14.2 The review team should be comprised of representatives from, for example, engineering, utilities, validation, QA, quality control, microbiology, production and maintenance.

14.3 Examples of matters to be included in the review are:

- changes made since the last review;
- system performance trends and capability;
- quality trends;
- failure events and alarm history;
- investigations;
- out-of-specification and out-of-limit results;
- alert and action limits;
- assessing compliance with current GMP requirements for WPU systems;
- verification of documentation being current;
- maintenance and calibration history;
- records such as log books and electronic data; and
- the appropriateness of the software and the computerized system linked to the water system, for example, SCADA (Supervisory Control and Data Acquisition), including audit trail, authorized users with access and privileges.

15. Inspection of water systems

15.1 WPU (BPW and BWFI) systems are subjected to regulatory inspections. Users should conduct audits and self-inspection of water systems at regular intervals. Records should be maintained.

15.2 This document can be used as the basis of an audit and inspection. A tour of the water system, treatment system, storage and distribution system, as well as visible pipework and user points, should be performed to ensure that the system is appropriately designed, installed, qualified, validated, maintained and monitored.

References

1. WHO Good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; https://apps.who.int/iris/bitstream/handle/10665/75168/WHO_TRS_970.pdf?sequence=1, accessed 29 July 2020).
2. WHO Good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series No. 957; https://apps.who.int/iris/bitstream/handle/10665/44291/WHO_TRS_957_eng.pdf?sequence=1, accessed 29 July 2020).
3. WHO Good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986 https://apps.who.int/iris/bitstream/handle/10665/112733/WHO_TRS_986_eng.pdf?sequence=1, accessed 29 July 2020).
4. *The International Pharmacopoeia*. Geneva, World Health Organization (https://www.who.int/medicines/publications/pharmacopoeia/en/ and https://apps.who.int/phint/2019/index.html#p/home, accessed 1 May 2020).
5. WHO Guidelines for drinking-water quality: fourth edition, incorporating the first addendum; 2017 (https://www.who.int/water_sanitation_health/publications/drinking-water-quality-guidelines-4-including-1st-addendum/en/, accessed 1 May 2020).
6. WHO Production of water for injection by means other than distillation: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 3 (WHO Technical Report Series, No. 1025; https://www.who.int/docs/default-source/medicines/who-technical-report-series-who-expert-committee-on-specifications-for-pharmaceutical-preparations/trs1025-annex3.pdf?sfvrsn=caebed51_2, accessed 29 July 2020).
7. WHO Guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981: https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2 TRS-981.pdf?ua=1, accessed 1 May 2020).
8. WHO Guidelines on validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 1 May 2020).

Further reading

- American Society of Mechanical Engineers. Bioprocessing Equipment Standard. ASME — BPE 2019.
- Banes PH. Passivation: understanding and performing procedures on austenitic stainless-steel systems. Pharmaceutical Engineering, 1990: 41.
- Guide to inspections of high purity water systems. Maryland, US Food and Drug Administration, 1993 (http://www.fda.gov/ICECI/InspectionGuides).
- Biotechnology. Equipment. Guidance on testing procedures for cleanability. British Standards Publishing. BS EN 12296, 1998.
- European Medicines Agency, 2020. Guideline on the quality of water for pharmaceutical use. EMA/CHMP/CVMP/QWP/496873/2018, Amsterdam, Netherlands (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-water-pharmaceutical-use_en.pdf).
- European Pharmacopoeia: see website for the publishers of the European Pharmacopoeia and supplements (http://www.pheur.org/).
- Harfst WH. Selecting piping materials for high-purity water systems. Ultra-pure water, May/June 1994.
- International Organization for Standardization (ISO) for drinking water ISO 24512:2007 consisting of the following International Standards:
  — ISO 24510, Activities relating to drinking water and wastewater services — Guidelines for the assessment and for the improvement of the service to users
  — ISO 24511, Activities relating to drinking water and wastewater services — Guidelines for the management of wastewater utilities and for the assessment of wastewater services
  — ISO 24512, Activities relating to drinking water and wastewater services — Guidelines for the management of drinking water utilities and for the assessment of drinking water services
- ISPE Baseline Guide Volume 4: Water and Steam Systems. International Society for Pharmaceutical Engineering, 2019.
- ISPE Baseline Guide Volume 5: Commissioning and Qualification. Second edition. International Society for Pharmaceutical Engineering, 2019.
- Noble PT. Transport considerations for microbial control in piping. Journal of Pharmaceutical Science and Technology, 1994, 48: 76–85.
- Pharmaceutical Inspection Co-operation Scheme. PIC/S; Inspection of utilities; P1 009-1. Geneva, Pharmaceutical Inspection Co-operation Scheme, 2002.
- Tverberg JC, Kerber SJ. Effect of nitric acid passivation on the surface composition of mechanically polished type 316 L sanitary tube. European Journal of Parenteral Sciences, 1998, 3: 117–124.
- US Food and Drug Administration. Guide to inspections of high purity water systems, high purity water systems (7/93), 2009 (http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074905.htm).
- US Pharmacopeia: published annually (see http://www.usp.org/).
- World Health Organization, 2018. A global overview of national regulations and standards for drinking-water quality (https://apps.who.int/iris/bitstream/handle/10665/272345/9789241513760-eng.pdf?ua=1).
- World Health Organization, 2018. Developing drinking-water quality regulations and standards: general guidance with a special focus on countries with limited resources (https://apps.who.int/iris/bitstream/handle/10665/272969/9789241513944-eng.pdf?ua=1).

- World Health Organization, 1997. Guidelines for drinking-water quality, 2nd edition: Volume 3 - Surveillance and control of community supplies (https://apps.who.int/iris/bitstream/handle/10665/42002/9241545038.pdf?sequence=1&isAllowed=y).
- World Health Organization, 2018. Management of radioactivity in drinking-water (https://apps.who.int/iris/bitstream/handle/10665/272995/9789241513746-eng.pdf?ua=1).
- World Health Organization, 2019. Microplastics in drinking water (https://apps.who.int/iris/bitstream/handle/10665/326499/9789241516198-eng.pdf?ua=1).

Annex 4

Guideline on data integrity

This document replaces the WHO *Guidance on good data and record management practices* (Annex 5, WHO Technical Report Series, No. 996, 2016) (*1*).

1. Introduction and background 137
2. Scope 137
3. Glossary 138
4. Data governance 140
5. Quality risk management 144
6. Management review 145
7. Outsourcing 146
8. Training 146
9. Data, data transfer and data processing 147
10. Good documentation practices 148
11. Computerized systems 149
12. Data review and approval 152
13. Corrective and preventive actions 152
References 153
Further reading 153
Appendix 1 Examples in data integrity management 155

1. Introduction and background

1.1. In recent years, the number of observations made regarding the integrity of data, documentation and record management practices during inspections of good manufacturing practice (GMP) (*2*), good clinical practice (GCP), good laboratory practice (GLP) and Good Trade and Distribution Practices (GTDP) have been increasing. The possible causes for this may include (i) reliance on inadequate human practices; (ii) poorly defined procedures; (iii) resource constraints; (iv) the use of computerized systems that are not capable of meeting regulatory requirements or are inappropriately managed and validated (*3*, *4*); (v) inappropriate and inadequate control of data flow; and (vi) failure to adequately review and manage original data and records.

1.2. Data governance and related measures should be part of a quality system, and are important to ensure the reliability of data and records in good practice (GxP) activities and regulatory submissions. The data and records should be 'attributable, legible, contemporaneous, original' and accurate, complete, consistent, enduring, and available; commonly referred to as "ALCOA+".

1.3. This document replaces the WHO *Guidance on good data and record management practices* (Annex 5, WHO Technical Report Series, No. 996, 2016) (*1*).

2. Scope

2.1. This document provides information, guidance and recommendations to strengthen data integrity in support of product quality, safety and efficacy. The aim is to ensure compliance with regulatory requirements in, for example clinical research, production and quality control, which ultimately contributes to patient safety. It covers electronic, paper and hybrid systems.

2.2. The guideline covers "GxP" for medical products. The principles could also be applied to other products such as vector control products.

2.3. The principles of this guideline also apply to contract givers and contract acceptors. Contract givers are ultimately responsible for the integrity of data provided to them by contract acceptors. Contract givers should therefore ensure that contract acceptors have the appropriate capabilities and comply with the principles contained in this guideline and documented in quality agreements.

2.4. Where possible, this guideline has been harmonised with other published documents on data integrity. This guideline should also be read with other WHO good practices guidelines and publications including, but not limited to, those listed in the references section of this document.

3. Glossary

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

ALCOA+. A commonly used acronym for "attributable, legible, contemporaneous, original and accurate" which puts additional emphasis on the attributes of being complete, consistent, enduring and available throughout the data life cycle for the defined retention period.

Archiving. Archiving is the process of long-term storage and protection of records from the possibility of deterioration, and being altered or deleted, throughout the required retention period. Archived records should include the complete data, for example, paper records, electronic records including associated metadata such as audit trails and electronic signatures. Within a GLP context, the archived records should be under the control of independent data management personnel throughout the required retention period.

Audit trail. The audit trail is a form of metadata containing information associated with actions that relate to the creation, modification or deletion of GxP records. An audit trail provides for a secure recording of life cycle details such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record regardless of its medium, including the "who, what, when and why" of the action.

Backup. The copying of live electronic data, at defined intervals, in a secure manner to ensure that the data are available for restoration.

Certified true copy or true copy. A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.

Data. All original records and true copies of original records, including source data and metadata, and all subsequent transformations and reports of these data which are generated or recorded at the time of the GMP activity and which

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 criticality. This is defined by the importance of the data for the quality and safety of the product and how important data are for a quality decision within production or quality control.

Data governance. The sum total of arrangements which provide assurance of data quality. These arrangements ensure that data, irrespective of the process, format or technology in which it is generated, recorded, processed, retained, retrieved and used will ensure an attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available record throughout the data life cycle.

Data integrity risk assessment (DIRA). The process to map out procedures, systems and other components that generate or obtain data; to identify and assess risks and implement appropriate controls to prevent or minimize lapses in the integrity of the data.

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

Dynamic data. Dynamic formats, such as electronic records, allow an interactive relationship between the user and the record content. For example, electronic records in database formats allow the user to track, trend and query data; chromatography records maintained as electronic records allow the user or reviewer (with appropriate access permissions) to reprocess the data and expand the baseline to view the integration more clearly.

Electronic signatures. A signature in digital form (bio-metric or non-biometric) that represents the signatory. In legal terms, it is the equivalent of the handwritten signature of the signatory.

Good practices (GxP). An acronym for 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 GLP, GCP, GMP, good pharmacovigilance practices (GVP) and good distribution practices (GDP).

Hybrid system. The use of a combination of electronic systems and paper systems.

Medical product. A term that includes medicines, vaccines, diagnostics and medical devices.

Metadata. Metadata are data that provide the contextual information required to understand other data. These include structural and descriptive metadata, which describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata that are necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in the measurement of weight, the number 8 is meaningless without metadata, such as, the unit, milligram, gram, kilogram, and so on. Other examples of metadata include the time or 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.

Raw data. The original record (data) which can be described as the first-capture of information, whether recorded on paper or electronically. Raw data is synonymous with source data.

Static data. A static record format, such as a paper or electronic record, that is fixed and allows little or no interaction between the user and the record content. For example, once printed or converted to static electronic format chromatography records lose the capability of being reprocessed or enabling more detailed viewing of baseline.

4. Data governance

4.1. There should be a written policy on data integrity.

4.2. Senior management should be accountable for the implementation of systems and procedures in order to minimise the potential risk to data integrity, and to identify the residual risk using risk management techniques such as the principles of the guidance on quality risk management from WHO (*5*) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) (*6*).

4.3. Senior management is responsible for the establishment, implementation and control of an effective data governance system. Data governance should be embedded in the quality system. The necessary policies, procedures, training, monitoring and other systems should be implemented.

4.4. Data governance should ensure the application of ALCOA+ principles.

4.5. Senior management is responsible for providing the environment to establish, maintain and continually improve the quality culture, supporting the transparent and open reporting of deviations, errors or omissions and data integrity lapses at all levels of the organization. Appropriate, immediate action should be taken when falsification of data is identified. Significant lapses in data integrity that may impact patient safety, product quality or efficacy should be reported to the relevant medicine regulatory authorities.

4.6. The quality system, including documentation such as procedures and formats for recording and reviewing of data, should be appropriately designed and implemented in order to provide assurance that records and data meet the principles contained in this guideline.

4.7. Data governance should address the roles, responsibilities, accountability and define the segregation of duties throughout the life cycle and consider the design, operation and monitoring of processes/systems to comply with the principles of data integrity, including control over authorized and unauthorized changes to data.

4.8. Data governance control strategies using quality risk management (QRM) principles (5) are required to prevent or mitigate risks. The control strategy should aim to implement appropriate technical, organizational and procedural controls. Examples of controls may include, but are not limited to:

- the establishment and implementation of procedures that will facilitate compliance with data integrity requirements and expectations;
- the adoption of a quality culture within the company that encourages personnel to be transparent about failures, which includes a reporting mechanism inclusive of investigation and follow-up processes;
- the implementation of appropriate controls to eliminate or reduce risks to an acceptable level throughout the life cycle of the data;
- ensuring sufficient time and resources are available to implement and complete a data integrity programme; to monitor compliance

with data integrity policies, procedures and processes through e.g. audits and self-inspections; and to facilitate continuous improvement of both;

- the assignment of qualified and trained personnel and provision of regular training for personnel in, for example, GxP, and the principles of data integrity in computerized systems and manual/paper based systems;
- the implementation and validation of computerized systems appropriate for their intended use, including all relevant data integrity requirements in order to ensure that the computerized system has the necessary controls to protect the electronic data (*3*); and
- the definition and management of the appropriate roles and responsibilities for contract givers and contract acceptors, entered into quality agreements and contracts including a focus on data integrity requirements.

4.9. Data governance systems should include, for example:

- the creation of an appropriate working environment;
- active support of continual improvement in particular based on collecting feedback; and
- review of results, including the reporting of errors, unauthorized changes, omissions and undesirable results.

4.10. The data governance programme should include policies and procedures addressing data management. These should at least where applicable, include:

- management oversight and commitment;
- the application of QRM;
- compliance with data protection legislation and best practices;
- qualification and validation policies and procedures;
- change, incident and deviation management;
- data classification, confidentiality and privacy;
- security, cybersecurity, access and configuration control;
- database build, data collection, data review, blinded data, randomization;
- the tracking, trending, reporting of data integrity anomalies, and lapses or failures for further action;

- the prevention of commercial, political, financial and other organizational pressures;
- adequate resources and systems;
- workload and facilities to facilitate the right environment that supports DI and effective controls;
- monitoring;
- record-keeping;
- training; and
- awareness of the importance of data integrity, product quality and patient safety.

4.11. There should be a system for the regular review of data for consistency with ALCOA+ principles. This includes paper records and electronic records in day-to-day work, system and facility audits and self-inspections.

4.12. The effort and resources applied to assure the integrity of the data should be commensurate with the risk and impact of a data integrity failure.

4.13. Where weaknesses in data integrity are identified, the appropriate corrective and preventive actions (CAPA) should be implemented across all relevant activities and systems and not in isolation.

4.14. Changing from paper-based systems to automated or computerised systems (or vice-versa) will not in itself remove the need for appropriate data integrity controls.

4.15. Records (paper and electronic) should be kept in a manner that ensures compliance with the principles of this guideline. These include but are not limited to:

- ensuring time accuracy of the system generating the record, accurately configuring and verifying time zone and time synchronisation, and restricting the ability to change dates, time zones and times for recording events;
- using controlled documents and forms for recording GxP data;
- defining access and privilege rights to GxP automated and computerized systems, ensuring segregation of duties;
- ensuring audit trail activation for all interactions and restricting the ability to enable or disable audit trails (Note: 'back-end' changes and 'hard' changes, such as hard deletes, should not be allowed). Where audit trials can be disabled then this this action should also appear in the audit trail;

- having automated data capture systems and printers connected to equipment and instruments in production (such as Supervisory Control and Data Acquisition (SCADA), Human Machine Interface (HMI) and Programme Logic Control (PLCs) systems), in , quality control, and in clinical research (such as Clinical Data Management (CDM) systems), where possible;
- designing processes in a way to avoid the unnecessary transcription of data or unnecessary conversion from paper to electronic and vice versa; and
- ensuring the proximity of an official GxP time source to site of GxP activity and record creation.

4.16. Systems, procedures and methodology used to record and store data should be periodically reviewed for effectiveness. These should be updated throughout the data life cycle, as necessary, where new technology becomes available. New technology implementation must be evaluated before implementation to verify the impact on data integrity.

5. Quality risk management

Note: documentation of data flows and data process maps are recommended to facilitate the assessment, mitigation and control of data integrity risks across the actual and intended data process(es).

5.1. Data Integrity Risk Assessment (DIRA) should be carried out in order to identify and assess areas of risk. This should cover systems and processes that produce data or, where data are obtained and inherent risks. The DIRAs should be risk-based, cover the life cycle of data and consider data criticality. Data criticality may be determined by considering how the data is used to influence the decisions made. The DIRAs should be documented and reviewed, as required, to ensure that it remains current.

5.2. The risk assessments should evaluate, for example, the relevant GxP computerised systems, supporting personnel, training, quality systems and outsourced activities.

5.3. DI risks should be assessed and mitigated. Controls and residual risks should be communicated. Risk review should be done throughout the document and data life cycle at a frequency based on the risk level, as determined by the risk assessment process.

5.4. Where the risk assessment has highlighted areas for remedial action, the prioritisation of actions (including the acceptance of an appropriate level of residual risk) and the prioritisation of controls should be documented and communicated. Where long-term remedial actions are identified, risk-reducing short-term measures should be implemented in order to provide acceptable data governance in the interim.

5.5. Controls identified may include organizational, procedural and technical controls such as procedures, processes, equipment, instruments and other systems in order to both prevent and detect situations that may impact on data integrity. Examples include the appropriate content and design of procedures, formats for recording, access control, the use of computerized systems and other means.

5.6. Efficient risk-based controls should be identified and implemented to address risks impacting data integrity. Risks include, for example, the deletion of, changes to and exclusion of data or results from data sets without written justification, authorisation where appropriate, and detection. The effectiveness of the controls should be verified (see Appendix 1 for examples).

6. Management review

6.1. Management should ensure that systems (such as computerized systems and paper systems) are meeting regulatory requirements in order to support data integrity compliance.

6.2. The acquisition of non-compliant computerized systems and software should be avoided. Where existing systems do not meet current requirements, appropriate controls should be identified and implemented based on risk assessment.

6.3. The effectiveness of the controls implemented should be evaluated through, for example:

- the tracking and trending of data;
- a review of data, metadata and audit trails (e.g. in warehouse and material management, production, quality control, case report forms and data processing); and
- routine audits and/or self-inspections, including data integrity and computerized systems.

7. Outsourcing

7.1. The selection of a contract acceptor should be done in accordance with an authorized procedure. The outsourcing of activities, ownership of data, and responsibilities of each party (contract giver and contract accepter) should be clearly described in written agreements. Specific attention should be given to ensuring compliance with data integrity requirements. Provisions should be made for responsibilities relating to data when an agreement expires.

7.2. Compliance with the principles and responsibilities should be verified during periodic site audits. This should include the review of procedures and data (including raw data and metadata, paper records, electronic data, audit trails and other related data) held by the relevant contract accepter identified in risk assessment.

7.3. Where data and document retention are contracted to a third party, particular attention should be given to security, transfer, storage, access and restoration of data held under that agreement, as well as controls to ensure the integrity of data over their life cycle. This includes static data and dynamic data. Mechanisms, procedures and tools should be identified to ensure data integrity and data confidentiality, for example, version control, access control, and encryption.

7.4. GxP activities, including outsourcing of data management, should not be sub-contracted to a third party without the prior approval of the contract giver. This should be stated in the contractual agreements.

7.5. All contracted parties should be aware of the requirements relating to data governance, data integrity and data management.

8. Training

8.1. All personnel who interact with GxP data and who perform GxP activities should be trained in relevant data integrity principles and abide by organization policies and procedures. This should include understanding the potential consequences in cases of non-compliance.

8.2. Personnel should be trained in good documentation practices and measures to prevent and detect data integrity issues.

8.3. Specific training should be given in cases where computerized systems are used in the generation, processing, interpretation and reporting of data and

where risk assessment has shown that this is required to relevant personnel. Such training should include validation of computerized systems and for example, system security assessment, back-up, restoration, disaster recovery, change and configuration management, and reviewing of electronic data and metadata, such as audit trails and logs, for each GxP computerized systems used in the generation, processing and reporting of data.

9. Data, data transfer and data processing

9.1. Data may be recorded on paper or captured electronically by using equipment and instruments including those linked to computerised systems. A combination of paper and electronic formats may also be used, referred to as a "hybrid system".

9.2. Data integrity consideration are also applicable to media such as photographs, videos, DVDs, imagery and thin layer chromatography plates. There should be a documented rationale for the selection of such a method.

9.3. Risk-reducing measures such as scribes, second person oversight, verification and checks should be implemented where there is difficulty in accurately and contemporaneously recording data related to critical process parameters or critical quality attributes.

9.4. Results and data sets require independent verification if deemed necessary from the DIRA or by another requirement.

9.5. Programmes and methods (such as processing methods in sample analysis (see also Good Chromatography Practices, TRS 1025) should ensure that data meet ALCOA+ principles. Where results or data are processed using a different method/parameters, then each version of the processing method should be recorded. Data records, content versions together with audit trails containing the required details should allow for reconstruction of all data processing in GxP computerized systems over the data life cycle.

9.6. Data transfer/migration procedures should include a rationale and be robustly designed and validated to ensure that data integrity is maintained during the data life cycle. Careful consideration should be given to understanding the data format and the potential for alteration at each stage of data generation, transfer and subsequent storage. The challenges of migrating data are often underestimated, particularly regarding maintaining the full meaning of the migrated records.

Data transfer should be validated. The data should not be altered during or after it is transferred to the worksheet or other application. There should be an audit trail for this process. The appropriate quality procedures should be followed if the data transfer during the operation has not occurred correctly. Any changes in the middle layer software should be managed through the appropriate Quality Management Systems (*7*).

10. Good documentation practices

Note: The principles contained in this section are applicable to paper data.

10.1. Good documentation practices should be implemented and enforced to ensure compliance with ALCOA+ principles.

10.2. Data and recorded media should be durable. Ink should be indelible. Temperature-sensitive or photosensitive inks and other erasable inks should not be used. Where related risks are identified, means should be identified in order to ensure traceability of the data over their life cycle.

10.3. Paper should not be temperature-sensitive, photosensitive or easily oxidizable. If this is not feasible or limited, then true or certified copies should be generated.

10.4. Specific controls should be implemented in order to ensure the integrity of raw data and results recorded on paper records. These may include, but are not limited to:

- control over the issuance and use of loose paper sheets at the time of recording data;
- no use of pencil or erasers;
- use of single-line cross-outs to record changes with the identifiable person who made the change, date and reason for the change recorded (i.e. the paper equivalent to an electronic audit trail);
- no use of correction fluid or otherwise, obscuring the original record;
- controlled issuance of bound, paginated notebooks;
- controlled issuance and reconciliation of sequentially numbered copies of blank forms with authenticity controls;
- maintaining a signature and initial record for traceability and defining the levels of signature of a record; and
- archival of records by designated personnel in secure and controlled archives.

11. Computerized systems

(Note. This section highlights some specific aspects relating to the use of computerized systems. It is not intended to repeat the information presented in the other WHO guidelines here, such as the WHO Guideline on computerized systems (3), WHO Guideline on validation (2) and WHO Guideline on good chromatography practices (7). See references.)

11.1. Each computerized system selected should be suitable, validated for its intended use, and maintained in a validated state.

11.2. Where GxP systems are used to acquire, record, transfer, store or process data, management should have appropriate knowledge of the risks that the system and users may pose to the integrity of the data.

11.3. Software of computerized systems, used with GxP instruments and equipment, should be appropriately configured (where required) and validated. The validation should address for example the design, implementation and maintenance of controls in order to ensure the integrity of manually and automatically acquired data; ensure that Good Documentation Practices will be implemented; and that data integrity risks will be appropriately managed throughout the data life cycle. The potential for unauthorized and adverse manipulation of data during the life cycle of the data should be mitigated and, where possible, eliminated.

11.4. Where electronic instruments (e.g. certain pH meters, balances and thermometers) or systems with no configurable software and no electronic data retention are used, controls should be put in place to prevent the adverse manipulation of data and to prevent repeat testing to achieve the desired result.

11.5. Appropriate controls for the detection of lapses in data integrity principles should be in place. Technical controls should be used whenever possible but additional procedural or administrative controls should be implemented to manage aspects of computerised system control where technical controls are missing. For example, when stand-alone computerized systems with a user-configurable output are used, Fourier-transform infrared spectroscopy (FTIR) and UV spectrophotometers have user-configurable output or reports that cannot be controlled using technical controls. Other examples of non-technical detection and prevention mechanisms may include, but are not limited to, instrument usage logbooks and electronic audit trails.

Access and privileges

11.6. There should be a documented system in place that defines the access and privileges of users of systems. There should be no discrepancy between paper records and electronic records where paper systems are used to request changes for the creation and inactivation of users. Inactivated users should be retained in the system. A list of active and inactivated users should be maintained throughout the system life cycle.

11.7. Access and privileges should be in accordance with the role and responsibility of the individual with the appropriate controls to ensure data integrity (e.g. no modification, deletion or creation of data outside the defined privilege and in accordance with the authorized procedures defining review and approval where appropriate).

11.8. A limited number of personnel, with no conflict of interest in data, should be appointed as system administrators. Certain privileges such as data deletion, database amendment or system configuration changes should not be assigned to administrators without justification – and such activities should only be done with documented evidence of authorization by another responsible person. Records should be maintained and audit trails should be enabled in order to track activities of system administrators. As a minimum, activity logging for such accounts and the review of logs by designated roles should be conducted in order to ensure appropriate oversight.

11.9. For systems generating, amending or storing GxP data, shared logins or generic user access should not be used. The computerised system design should support individual user access. Where a computerised system supports only a single user login or limited numbers of user logins and no suitable alternative computerised system is available, equivalent control should be provided by third-party software or a paper-based method that provides traceability (with version control). The suitability of alternative systems should be justified and documented (*8*). The use of legacy hybrid systems should be discouraged and a priority timeline for replacement should be established.

Audit trail

11.10. GxP systems should provide for the retention of audit trails. Audit trails should reflect, for example, users, dates, times, original data and results, changes and reasons for changes (when required to be recorded), and enabling and disenabling of audit trails.

11.11. All GxP relevant audit trails should be enabled when software is installed and remain enabled at all times. There should be evidence of enabling the audit trail. There should be periodic verification to ensure that the audit trail remains enabled throughout the data life cycle.

11.12. Where a system cannot support ALCOA+ principles by design (e.g. legacy systems with no audit trail), mitigation measures should be taken for defined temporary periods. For example, add-on software or paper-based controls may be used. The suitability of alternative systems should be justified and documented. This should be addressed within defined timelines.

Electronic signatures

11.13. Each electronic signature should be appropriately controlled by, for example, senior management. An electronic signature should be:

- attributable to an individual;
- free from alteration and manipulation
- be permanently linked to their respective record; and
- date- and time-stamped.

11.14. An inserted image of a signature or a footnote indicating that the document has been electronically signed is not adequate unless it was created as part of the validated electronic signature process. The metadata associated with the signature should be retained.

Data backup, retention and restoration

11.15. Data should be retained (archived) in accordance with written policies and procedures, and in such a manner that they are protected, enduring, readily retrievable and remain readable throughout the records retention period. True copies of original records may be retained in place of the original record, where justified. Electronic data should be backed up according to written procedures.

11.16. Data and records, including backup data, should be kept under conditions which provide appropriate protection from deterioration. Access to such storage areas should be controlled and should be accessible only by authorized personnel.

11.17. Data retention periods should be defined in authorized procedures.

11.18. The decision for and manner in which data and records are destroyed, should be described in written procedures. Records for the destruction should be maintained.

11.19. Backup and restoration processes should be validated. The backup should be done routinely and periodically be restored and verified for completeness and accuracy of data and metadata. Where any discrepancies are identified, they should be investigated and appropriate action taken.

12. Data review and approval

12.2. There should be a documented procedure for the routine and periodic review, as well as the approval of data. Personnel with appropriate knowledge and experience should be responsible for reviewing and checking data. They should have access to original electronic data and metadata.

12.3. The routine review of GxP data and meta data should include audit trails. Factors such as criticality of the system (high impact versus low impact) and category of audit trail information (e.g. batch specific, administrative, system activities, and so on) should be considered when determining the frequency of the audit trail review.

12.4. A procedure should describe the actions to be taken where errors, discrepancies or omissions are identified in order to ensure that the appropriate corrective and preventive actions are taken.

12.5. Evidence of the review should be maintained.

12.6. A conclusion, where required, following the review of original data, metadata and audit trail records should be documented, signed and dated.

13. Corrective and preventive actions

13.1. Where organizations use computerized systems (e.g. for GxP data acquisition, processing, interpretation, reporting) which do not meet current GxP requirements, an action plan towards upgrading such systems should be documented and implemented in order to ensure compliance with current GxP.

13.2. When lapses in GxP relevant data regarding data integrity are identified, a risk-based approach may be used to determine the scope of the

investigation, root cause, impact and CAPA, as appropriate. Health authorities, contract givers and other relevant organizations should be notified if the investigation identifies a significant impact or risk to, for example, materials, products, patients, reported information or data in application dossiers, and clinical trials.

References

1. Guidelines on good manufacturing practices for pharmaceutical products: main principle. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 986; https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS986annex2.pdf?ua=1, accessed 4 May 2020).
2. Good manufacturing practices: guidelines on validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations; fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; http://digicollection.org/whoqapharm/documents/s23430en/s23430en.pdf, accessed 5 May 2020).
3. Good manufacturing practices: guidelines on validation. Appendix 5. Validation of computerized systems. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 3 (WHO Technical Report Series, No. 1019; https://www.who.int/medicines/areas/quality_safety/quality_assurance/WHO_TRS_1019_Annex3.pdf?ua=1, accessed 4 May 2020).
4. Guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf, accessed 4 May 2020).
5. ICH harmonised tripartite guideline. Quality risk management Q9. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use; 2005 (https://database.ich.org/sites/default/files/Q9%20Guideline.pdf, accessed 12 June 2020).
6. Good chromatography practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 4 (WHO Technical Report Series, No. 1025; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 12 June 2020).
7. MHRA GxP data integrity guidance and definitions; Revision 1: Medicines & Healthcare Products Regulatory Agency (MHRA), London, March 2018 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf, accessed 12 June 2020).

Further reading

- Data integrity and compliance with CGMP guidance for industry: questions and answers guidance for industry. U.S. Department of Health and Human Services, Food and Drug Administration; 2016 (https://www.fda.gov/files/drugs/published/Data-Integrity-and-Compliance-With-Current-Good-Manufacturing-Practice-Guidance-for-Industry.pdf, accessed 15 June 2020).

- Good Practices for data management and integrity in regulated GMP/GDP environments. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S), November 2018 (https://picscheme.org/layout/document.php?id=1567, accessed 15 June 2020).
- Baseline guide Vol 7: risk-based manufacture of pharma products; 2nd edition.
- ISPE Baseline® Guide, July 2017. ISPEGAMP® guide: records and data integrity; March 2017.
- Data integrity management system for pharmaceutical laboratories PDA Technical Report, No. 80; August 2018.
- ICH harmonised tripartite guideline. Pharmaceutical Quality System Q10. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use; 2008 (https://database.ich.org/sites/default/files/Q10%20Guideline.pdf, accessed 2 October 2020).

Appendix 1

Examples in data integrity management

This Appendix reflects on some examples in data integrity management in order to support the main text on data integrity. It should be noted that these are examples and are intended for the purpose of clarification only.

Example 1: Quality risk management and data integrity risk assessment

Risk management is an important part of good practices (GxP). Risks should be identified and assessed and controls identified and implemented in order to assist manufacturers in preventing possible DI lapses.

As an example, a Failure Mode and Effects Analysis (FMEA) model (or any other tool) can be used to identify and assess the risks relating to any system where data are, for example, acquired, processed, recorded, saved and archived. The risk assessment can be done as a prospective exercise or retrospective exercise. Corrective and preventive action (CAPA) should be identified, implemented and assessed for its effectiveness.

For example, if during the weighing of a sample, the entry of the date was not contemporaneously recorded on the worksheet but the date is available on the print-out from a weighing balance and log book for the balance for that particular activity. The fact that the date was not recorded on the worksheet may be considered a lapse in data integrity expectations. When assessing the risk relating to the lack of the date in the data, the risk may be considered different (lower) in this case as opposed to a situation when there is no other means of traceability for the activity (e.g. no print-out from the balance). When assessing the risk relating to the lapse in data integrity, the severity could be classified as "low" (the data is available on the print-out); it does not happen on a regular basis (occurrence is "low"), and it could easily be detected by the reviewer (detection is "high") – therefore the overall risk factor may be considered low. The root cause as to why the record was not made in the analytical report at the time of weighing should still be identified and the appropriate action taken to prevent this from happening again.

Example 2: Good documentation practices in data integrity

Documentation should be managed with care. These should be appropriately designed in order to assist in eliminating erroneous entries, manipulation and human error.

Formats

Design formats to enable personnel to record or enter the correct information contemporaneously. Provision should be made for entries such as, but not limited to, dates, times (start and finish time, where appropriate), signatures, initials, results, batch numbers and equipment identification numbers. When a computerized system is used, the system should prompt the personnel to make the entries at the appropriate step.

Blank sheets of paper

The use of blank sheets should not be encouraged. Where blank sheets are used (e.g. to supplement worksheets, laboratory notebooks and master production and control records), the appropriate controls have to be in place and may include, for example, a numbered set of blank sheets issued which are reconciled upon completion. Similarly, bound paginated notebooks, stamped or formally issued by designated personnel, allow for the detection of unofficial notebooks and any gaps in notebook pages. Authorization may include two or three signatures with dates, for example, "prepared by" or "entered by", "reviewed by" and "approved by".

Error in recording data

Care should be taken when entries of data and results (electronic and paper records) are made. Entries should be made in compliance with good documentation practices. Where incorrect information had been recorded, this may be corrected provided that the reason for the error is documented, the original entry remains readable and the correction is signed and dated.

Example 3: Data entry

Data entry includes for example sample receiving registration, sample analysis result recording, logbook entries, registers, batch manufacturing record entries and information in case report forms. The recording of source data on paper records should be done using indelible ink, in a way that is complete, accurate, traceable, attributable and free from errors. Direct entry into electronic records should be done by responsible and appropriately trained individuals. Entries should be traceable to an individual (in electronic records, thus having an individual user access) and traceable to the date (and time, where relevant). Where appropriate, the entry should be verified by a second person or entered through technical means such as the scanning of bar-codes, where possible, for the intended use of these data. Additional controls may include the locking of critical data entries after the data are verified and a review of audit trails for

critical data to detect if they have been altered. The manual entry of data from a paper record into a computerized system should be traceable to the paper records used which are kept as original data.

Example 4: Dataset

All data should be included in the dataset unless there is a documented, justifiable, scientific explanation and procedure for the exclusion of any result or data. Whenever out of specification or out of trend or atypical results are obtained, they should be investigated in accordance with written procedures. This includes investigating and determining CAPA for invalid runs, failures, repeats and other atypical data. The review of original electronic data should include checks of all locations where data may have been stored, including locations where voided, deleted, invalid or rejected data may have been stored. Data and metadata related to a particular test or product should be recorded together. The data should be appropriately stored in designated folders. The data should not be stored in other electronic folders or in other operating system logs. Electronic data should be archived in accordance with a standard operating procedure. It is important to ensure that associated metadata are archived with the relevant data set or securely traceable to the data set through relevant documentation. It should be possible to successfully retrieve all required data and metadata from the archives. The retrieval and verification should be done at defined intervals and in accordance with an authorized procedure.

Example 5: Legible and enduring

Data and metadata should be readable during the life cycle of the data. Electronic data are normally only legible/readable through the original software application that created it. In addition, there may be restrictions around the version of a software application that can read the data. When storing data electronically, ensure that any restrictions which may apply and the ability to read the electronic data are understood. Clarification from software vendors should be sought before performing any upgrade, or when switching to an alternative application, to ensure that data previously created will be readable.

Other risks include the fading of microfilm records, the decreasing readability of the coatings of optical media such as compact disks (CDs) and digital versatile/video disks (DVDs), and the fact that these media may become brittle.

Similarly, historical data stored on magnetic media will also become unreadable over time as a result of deterioration. Data and records should be stored in an appropriate manner, under the appropriate conditions.

Example 6: Attributable

Data should be attributable, thus being traceable to an individual and where relevant, the measurement system. In paper records, this could be done through the use of initials, full handwritten signature or a controlled personal seal. In electronic records, this could be done through the use of unique user logons that link the user to actions that create, modify or delete data; or unique electronic signatures which can be either biometric or non-biometric. An audit trail should capture user identification (ID), date and time stamps and the electronic signature should be securely and permanently linked to the signed record.

Example 7: Contemporaneous

Personnel should record data and information at the time these are generated and acquired. For example, when a sample is weighed or prepared, the weight of the sample (date, time, name of the person, balance identification number) should be recorded at that time and not before or at a later stage. In the case of electronic data, these should be automatically date- and time-stamped. In case hybrid systems are to be used, including the use for an interim period, the potential and criticality of system breaches should be covered in the assessment with documented mitigating controls in place. (The replacement of hybrid systems should be a priority with a documented CAPA plan.) The use of a scribe to record an activity on behalf of another operator should be considered only on an exceptional basis and should only take place where, for example, the act of recording places the product or activity at risk, such as, documenting line interventions by aseptic area operators. It needs to be clearly documented when a scribe has been applied.

> *"In these situations, the recording by the second person should be contemporaneous with the task being performed, and the records should identify both the person performing the task and the person completing the record. The person performing the task should countersign the record wherever possible, although it is accepted that this countersigning step will be retrospective. The process for supervisory (scribe) documentation completion should be described in an approved procedure that specifies the activities to which the process applies.*" (Extract taken from the Medicines & Healthcare Products Regulatory Agency (MHRA) *GxP data integrity guidance and definitions* (*10*).)

A record of employees indicating, their name, signature, initials or other mark or seal used should be maintained to enable traceability and to uniquely identify them and the respective action.

Example 8: Changes

When changes are made to any GxP result or data, the change should be traceable to the person who made the change as well as the date, time and reason for the change. The original value should not be obscured. In electronic systems, this traceability should be documented via computer generated audit trails or in other metadata fields or system features that meet these requirements. Where an existing computerized system lacks computer-generated audit trails, personnel may use alternative means such as procedurally controlled use of log-books, change control, record version control or other combinations of paper and electronic records to meet GxP regulatory expectations for traceability to document the what, who, when and why of an action.

Example 9: Original

The first or source capture of data or information and all subsequent data required to fully reconstruct the conduct of the GxP activity should be available. In some cases, the electronic data (electronic chromatogram acquired through high-performance liquid chromatography (HPLC)) may be the first source of data and, in other cases, the recording of the temperature on a log sheet in a room – by reading the value on a data logger. This data should be reviewed according to the criticality and risk assessment.

Example 10: Controls

Based on the outcome of risk assessment which should cover all areas of data governance and data management, appropriate and effective controls should be identified and implemented in order to assure that all data, whether in paper records or electronic records, will meet GxP requirements and ALCOA+ principles. Examples of controls may include, but are not limited to:

- the qualification, calibration and maintenance of equipment, such as balances and pH meters, that generate printouts;
- the validation of computerized systems that acquire, process, generate, maintain, distribute, store or archive electronic records;
- review and auditing of activities to ensure that these comply with applicable GxP data integrity requirements;
- the validation of systems and their interfaces to ensure that the integrity of data will remain while transferring between/among computerized systems;
- evaluation to ensure that computerized systems remain in a validated state;
- the validation of analytical procedures;

- the validation of production processes;
- a review of GxP records;
- ensuring effective review and oversight of the Batch Release Systems and processes by using different oversight and review techniques to ensure that data have not changed since the original entry; and
- the investigation of deviations, out of trend and out of specifications results.

Example 11: Accuracy

Points to consider for assuring accurate GxP records:

- the entry of critical data into a computer by an authorized person (e.g. entry of a master processing formula) requires an additional check on the accuracy of the data entered manually. This check may be done by independent verification and release for use by a second authorized person or by validated electronic means. For example, to detect and manage risks associated with critical data, procedures would require verification by a second person;
- validation and control over formulae for calculations including electronic data capture systems;
- ensuring correct entries into the laboratory information management system (LIMS) such as fields for specification ranges;
- other critical master data, as appropriate. Once verified, these critical data fields should normally be locked in order to prevent further modification and only be modified through a formal change control process;
- the process of data transfer between systems should be validated;
- the migration of data including planned testing, control and validation; and
- when the activity is time-critical, printed records should display the date and time stamp.

Annex 5

World Health Organization/United Nations Population Fund Recommendations for condom storage and shipping temperatures

Background

The report of the Fifty-fourth meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in 2019 (*1*)) stated the following:

> *As agreed at the ECSPP meeting in October 2018, the United Nations Population Fund (UNFPA) and WHO have separated different aspects of the current procedures 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 revised in the first half of 2019, then sent to the Expert Advisory Panel (EAP) and put out for public consultation in July 2019. The comments received were reviewed by 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 (2);*
- *World Health Organization/United Nations Population Fund technical specifications for male latex condoms (3); and*
- *World Health Organization/United Nations Population Fund specifications for plain lubricants (4).*

The Expert Committee further recommended proceeding with the next steps as discussed.

This is one of the four remaining working documents in this series.

1. Introduction 163
2. During shipment 163
3. Warehouse storage 164
References 165
Further reading 166

1. Introduction

Good quality condoms conforming to the World Health Organization (WHO)/ United Nations Population Fund (UNFPA) technical specifications for male latex condoms (*3*) have excellent storage properties. The combination of individual condom packaging, inner boxes and shipping containers is designed to protect the condoms during shipping and storage. Nevertheless, storage under poor conditions and/or rough handling during shipping might adversely affect the properties of the condoms. Extended exposure to excessively high temperatures (over 40 °C) may adversely affect shelf life. This document provides guidance on the shipping and storage of condoms to help ensure they conform to WHO/UNFPA Specification and *ISO 4074:2015* requirements until after the manufacturer's stated expiry date.

The individual primary packages specified in the WHO/UNFPA technical specification for male latex condoms protect the condoms from exposure to oxygen, ozone and water. Nevertheless, as with all medicines and medical devices, the products should be protected for exposure to any form of contamination including dust, pests and water. Although the individual packages protect the condoms from water and moisture vapour excessively high humidity and direct exposure to water may damage the inner boxes and shipping cartons.

This guidance is to be referred along with *WHO Good distribution practices for pharmaceutical products* (*5*).

2. During shipment

Store condoms in dry conditions away from direct sources of heat and sunlight.

The mean kinetic temperature[1] (MKT) during shipment should not exceed 30 °C. Peak temperatures should not exceed 50 °C[2]. The use of calibrated data loggers to monitor all shipments that originate, terminate or transit hot climatic zones is recommended. WHO maintains a list of suitable prequalified data loggers[3].

---

[1] Temperatures during shipping can be monitored using data loggers. Most modern data loggers can automatically calculate and print out the mean kinetic temperature (MKT) (in some cases, data has to be downloaded and analysed using provided software).

[2] Brief, short term temperature excursions up to 50 °C have limited impact on MKT. If during shipping the MKT exceeds 30 °C and/or peak temperatures exceed 50 °C, a risk assessment should be conducted to assess whether or not the properties of the condoms in the consignment have been compromised. Random sampling and testing of condoms for burst properties is recommended to support the risk assessment.

[3] https://apps.who.int/immunization_standards/vaccine_quality/pqs_catalogue/categorypage.aspx?id_cat=35

Ideally, data loggers can calculate the MKT either automatically or by using software supplied with the data loggers after data has been downloaded.

3. Warehouse storage

Store in well ventilated, dry conditions away from direct sources of heat, including sunlight.

Long-term (i.e. one month to a year) average storage temperature should be less than 30 °C. Short-term (i.e. up to one month) temperature excursions should not exceed 40 °C. The recommended limit for short term exposure is cumulative over the total period of storage.

Condom factories prequalified by UNFPA will have provided evidence to verify the claimed shelf life of the product. The shelf life is determined by accelerated and real-time studies, conducted at or referenced to a specific temperature (30 +5/ −2 °C) because this is the MKT of the most extreme climate in climatic zones III and IV[4]. Research has demonstrated that properly packaged good-quality condoms stored at average temperatures in tropical climates do not deteriorate during storage. More information about the recommendations for storage and shipment, and the rationale for choosing 30 + 5/ −2 °C as the storage temperature for stability studies, is given in the Technical Basis Paper of the WHO/UNFPA *technical specifications for male latex* condoms (*3*).

Since the shelf life of the condoms will have been determined at 30 + 5/ −2 °C, air-conditioned storage is not necessary but it would be an advantage in hot climates, if available. In hot climates, it is important that condoms are stored in a well-ventilated environment away from direct sunlight and other sources of heat in order to minimize the exposure of the condoms to high temperatures. Similar precautions should be taken during transportation and delivery. In general, the storage temperature should be as low as can practically be achieved. Condoms stored outdoors in shipping containers are particularly vulnerable as the temperatures inside containers can be substantially above ambient temperatures resulting in faster deterioration.

Storage time in shipping containers should be minimized. The condoms are sealed in individual foil packages which are themselves packed in cardboard. The cardboard storage containers are vulnerable to moisture and should be stored in a dry storeroom away from walls and placed on pallets to protect against rising damp. Ideally, cartons should be stored at least 10 cm off the floor, 30 cm away from the walls and stacked no more than 2.4 metres high. It should

[4] More details on climatic zones can be found in *WHO Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (*6*).

be ensured that the floor of the storage area is paved with concrete and the walls and floor should not get damp due to seepage of water or rain water condensate. The ambient temperature in the warehouse should be recorded.

Condoms are fully protected by the individual foil package. However, cosmetic damage to the foil and damage to the outer packaging can make the product appear damaged and therefore less acceptable to the user.

In accordance with good storage practices, potential contaminants of any sort (e.g. powders or liquids) should be avoided to reduce risk to the end users of the condoms.

Condoms should be left in their original cartons and inner boxes until needed for distribution. The cartons should be positioned so that the lot number and expiry date are visible. If any additional information, such as local registration identification numbers, is required this should be affixed to the shipping cartons adjacent to the lot numbers and expiry dates to permit all the information to be readily seen during storage. The cartons should be identified and their locations recorded to ensure that specific lots can be located. Lots should be released on a first expiry—first out basis (FEFO).

Recalled, damaged or expired condoms should be clearly labelled and kept in a separate, clearly identified and segregated quarantine area. The disposal of such condoms should be in accordance with local procedures for the disposal of damaged medical devices.

References

1. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
2. World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 9 (WHO Technical Report Series, No. 1025; trs1025-annex9.pdf (who.int), accessed 14 January 2021).
3. World Health Organization/United Nations Population Fund Technical specifications for male latex condoms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 10 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
4. World Health Organization/United Nations Population Fund UNFPA-WHO specifications for plain lubricants. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 11 (WHO Technical Report Series, No. 1025; trs1025-annex11.pdf (who.int), accessed 14 January 2021).
5. WHO Good Storage and Distribution Practices for Medical Products published in WHO Technical Report Series, No. 1025, 2020 Annex 7 trs1025-annex7.pdf (who.int) , accessed 14 January 2021).

6. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report. Geneva: World Health Organization; 2018: Annex 10 (WHO Technical Report Series, No. 1010; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1010-annex10-who-stability-testing-of-active-pharmaceutical-ingredients.pdf, accessed 2 February 2021).

Further reading

- UNFPA-published Condom programming for HIV prevention—An operations manual for programme managers and PATH's procurement capacity toolkit: Tools and resources for procurement of reproductive health supplies and safe disposal and management of unused, unwanted, contraceptives (http://www.unfpa.org/resources/safe-disposal-and-management-unused-unwanted-contraceptives, accessed 20 May 2020).

Annex 6

World Health Organization/United Nations Population Fund Guidance on testing of male latex condoms

Background

The report of the Fifty-fourth meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in 2019 (*1*) stated the following:

> *As agreed at the ECSPP meeting in October 2018, the United Nations Population Fund (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 revised in the first half of 2019, then sent to the Expert Advisory Panel (EAP) and put out for public consultation in July 2019. The comments received were reviewed by 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 (2);*
- *World Health Organization/United Nations Population Fund technical specifications for male latex condoms (3); and*
- *World Health Organization/United Nations Population Fund specifications for plain lubricants (4).*

The Expert Committee further recommended proceeding with the next steps as discussed.

This is one of the four remaining working documents in this series.

1. Introduction 170

2. Determination of length 170

3. Determination of width 171

4. Determination of thickness 171

4.1 Mass method 172
4.2 Micrometer method 173

5. Determination of bursting volume and pressure 174

5.1 Loading of the condom onto the mandrel 175
5.2 Ensuring the correct inflation length 175
5.3 Checking that the condom does not slip during inflation 176
5.4 Calibrating the volume and pressure measuring equipment 176
5.5 Correcting for variations in atmospheric pressure owing to the altitude of the test laboratory 177
5.6 Other factors to consider in the burst testing of condoms 177
5.7 Cleanliness of the air supply hole in the mandrel 178
5.8 Maintenance of the supply air pressure and the air flow rate 178
5.9 Maintenance of the air temperature from the compressor 178

6. Determination of stability and shelf life 178

7. Freedom from holes 181

7.1. The water leak test (hang and roll) 181
7.2 The electrical test 182
7.3 The water leak test (hang and squeeze) 183

8. Visibly open seals (*ISO 4074:2015*, Annex N) 183

9. Visible defects (*ISO 4074:2015*, Annex M and *WHO/UNFPA Technical specifications for male latex condoms*) 183

10. Determination of package seal integrity 184

References 186

1. Introduction

Condoms, procured as part of a public procurement programme or otherwise, are tested as per the World Health Organization (WHO)/United Nations Fund Population (UNFPA) specification by independent laboratories. In addition, there may be specific programme requirements which would have been incorporated in the purchase orders. These testing laboratories have to be accredited to the current version of *ISO 17025 General requirements for the competence of testing and calibration laboratories* (*5*), and use the test methods in the current version of *ISO 4074 Natural rubber latex male condoms – Requirements and test methods* (*6*), in order to be considered for testing services. The following guidance has been developed to assist the laboratories to standardize testing and reduce variability. This guidance is intended to supplement the information on conducting the tests specified in *ISO 4074:2015* (*6*).

2. Determination of length

Condom length can be measured manually, using a suitable calibrated mandrel, or automatically, using one of the dedicated automatic instruments now available (*ISO 4074:2015*, Annex D).

The automatic methods have the advantage that data can usually be transferred directly to any computerized record system, although it is important that the equipment is validated for the correct handling of the data and regularly calibrated following the methods recommended by the manufacturer.

A standard mandrel, described in *ISO 4074:2015* (*6*), is used to normalize the measurements as different condom designs can have different shapes at the teat and closed end.

As a rolled condom can retain the memory of the roll when unrolled, it is permitted to stretch the condom a little (no more than 20 mm, and not more than twice) when unrolled to help remove any wrinkles persisting after the unrolling.

Condoms can be measured without removing the lubricant but handling a lubricated condom can be difficult as the lubricant can cause the condom to stick to itself in pleats or creases. A lubricated condom may also not hang freely over the mandrel and, if stretched, can be held in the extended state by the lubricant. The condom can be powdered to ease the handling problems, as described in the standard, with or without removal of the lubricant.

Owing to the way the bead is formed, the condom length may not be exactly the same at all points around the condom. It is important to measure the length at several points and record the minimum. The instrumental methods may do this automatically.

When measuring the length manually, it is important that the measurement is taken with the bead of the condom at eye level to avoid any

parallax errors. It may be easier to position the mandrel on a stand to bring it up to the eye level of the operator. Again, the instrumented methods will take this into account. While fixing the length mandrel, it should be ensured that it is fixed on a horizontal plane without slanting.

Note that measurement of condom length should be rounded to the nearest 1 mm.

3. Determination of width

Condom width can be measured directly, using a ruler, or automatically using one of the dedicated automatic instruments now available (*ISO 4074:2015*, Annex E).

The automatic methods have the advantage that data can usually be transferred directly to any computerized record system, although it is important that the equipment is validated for correct handling of the data and regularly calibrated following the methods recommended by the manufacturer.

When measuring directly, using a ruler calibrated in mm, it is important that the condom is positioned so that the axis of the condom is exactly perpendicular to the ruler.

Note that the end of a ruler can get worn and the corners rounded so it is better to position the condom to use another point (e.g. the 10, 20 or 100 mm index) as the zero. The condom should be measured at the narrowest point within the range 20 to 50 mm from the open end.

Condoms can be measured without removing the lubricant but handling a lubricated condom can be difficult as the lubricant can cause the condom to stick to itself in pleats or creases. Gently manipulate the condom to smooth out any such creases, ensuring that the condom is not stretched as sometimes the lubricant can hold the condom in an extended state. It may be better to remove the lubricant and lightly powder the condom, especially if the same condoms will be used for the determination of length.

Note that the condom width should be measured to the nearest 0.5 mm which will require the measurement to be interpolated if the scale is in whole mm.

4. Determination of thickness

ISO 4074:2015 Annex F (*6*) allows two methods for the measurement of thickness, one based on the direct measurement by a micrometer, and the other by mass. The mass method was introduced owing to the fact that the precision and reproducibility of the micrometer method was found to be relatively poor.

One of the reasons for this is to accommodate condoms where the surface is not smooth and, also, it is thought that the pressure applied by the foot of the micrometer to ensure good contact with the material under test can compress the film slightly. In some cases, this pressure has also been found to be well outside the specified range.

Any lubricant on the condom is removed by washing or wiping the condom with propan-2-ol, and removing the lubricant can make the condom difficult to handle. If any powder is added to facilitate handling and sample preparation, this must be removed before measuring.

The thickness of a condom can vary along and around the condom and, for this reason, thickness is measured at three points on the condom: the mid-point (± 5 mm) of the condom, 30 ± 5 mm from the closed end and 30 ± 5 mm from the open end. If the micrometer method is used, then three measurements, approximately equally spaced around the condom, are taken at each location and averaged. The mass method, of course, will give the average thickness of the sample being measured. For textured condoms, the thickness is usually measured using the micrometer method at the point specified and agreed between the manufacturer and the buyer of the condoms.

4.1 Mass method

The mass method calculates the volume of the sample by dividing the mass of the sample by the density of natural rubber. If the length and width of the sample are known, then the thickness can be simply calculated.

The formula, as given in Annex F of *ISO 4074:2015*, is:

$$\text{Thickness (in mm.)} = \frac{1}{0.92} \times \frac{1}{A} \times m$$

using a density of 0.92 g/cm^3, and where A is the area of the test piece (length in mm. x 20) in mm^2 and m is the mass of the sample in mg. If the condom is not parallel-sided, then measure both of the long sides and use the average.

The method specifies the test piece for tensile testing as the sample. This has the advantage that many laboratories already have the cutting die to give a 20 mm wide ring test piece from a condom.

Whilst there will be very slight differences in the density of the condom, caused by differences in the formulations, these will not cause any significant changes in the calculated thickness.

4.2 Micrometer method

The micrometer method measures the thickness of the sample directly using a calibrated dial or digital micrometer capable of reading to the nearest 0.001 mm. If the condom is textured, then micrometer measurements on the textured portion can give false results. In this case, measure the condom at a non-textured region as close as possible to the specified points (and report this with the results). Alternatively, the mass method could be used. Zero the gauge after measuring each sample.

Because of the compressibility of rubber, it is essential that the foot pressure is within the specified range of 22 ± 5 kPa and measuring the foot pressure should form part of the regular calibration procedure for the gauge. Note that powder or lubricant on the shaft of the gauge may increase friction when the gauge is used, altering the foot pressure. For this reason, it is important to ensure that the gauge is kept clean.

It is essential that the foot of the micrometer is exactly parallel to the platen. If not, then the edge of the foot, rather than the face, will contact the sample. Under the defined load, the edge can dig into the sample and give a false reading. A photograph of an incorrectly adjusted gauge is shown in *figure 1*. Correct alignment can be checked by measuring a slip gauge or a feeler gauge using several positions around the very edge of the foot of the micrometer (*figure 2*). If the micrometer is correctly set up, the readings will be the same from all sides of the foot.

Fig. 1
The foot of this micrometer is incorrect and will give the wrong reading

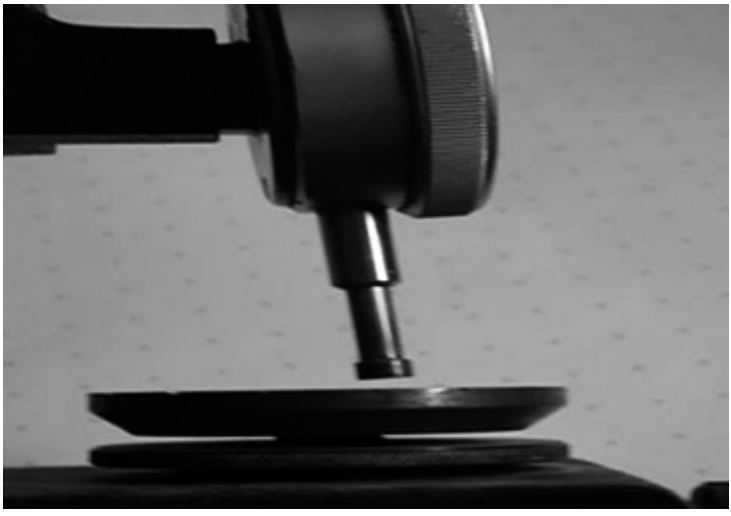
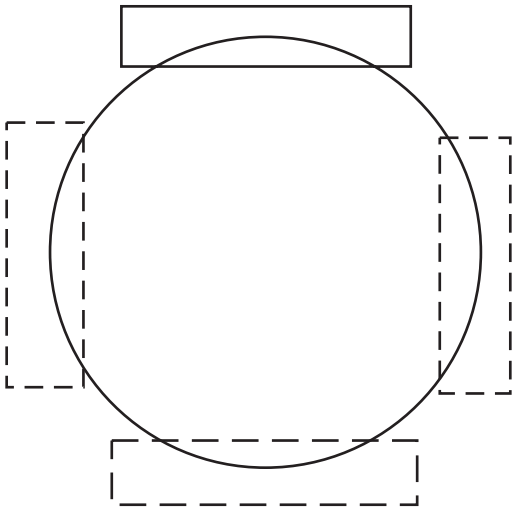


Fig. 2
Showing the measurement positions to confirm that the foot is parallel to the platen
Note that, according to clause 6.4.12 of *ISO 17025:2017* (*5*), "The laboratory shall take practicable measures to prevent unintended adjustments of equipment from invalidating results". It is therefore recommended that parts of the gauge that should not be adjusted during routine use, such as the gauge mount, are made tamper-evident. A small sticky label signed by an authorized person and placed over the part is a simple way to achieve this.



5. Determination of bursting volume and pressure

The burst properties of condoms are important and are frequently one of the parameters that show up differences in inter-laboratory testing (*ISO 4074:2015*, Annex H). There can be many reasons for testing variability of which the following are thought to be the most important.

- loading of the condom onto the mandrel;
- correct inflation length;
- slippage of the condom during inflation;
- correct calibration of pressure and volume measuring equipment;
- any corrections for variations in atmospheric pressure owing to the altitude of the test laboratory;
- cleanliness of the air supply hole in the mandrel;
- maintenance of the supply air pressure and the air flow rate; and
- maintenance of the air temperature from the compressor.

Note that recommendations for calibrating the air inflation equipment are given in Annex O of *ISO 4074:2015*.

5.1 Loading of the condom onto the mandrel

Condoms are almost always tested lubricated and a lubricated condom can be difficult to handle. One of the problems resulting from this is that the condom may be stretched too far on loading. In this situation, especially with burst test machines that use a wide supporting mandrel, the lubricant can cause the condom to stick to the mandrel or inflation cuff, preventing the extended condom from recovering fully. As a result, the tested length of the condom is less than it should be. This will lead to a falsely low burst volume and a higher burst pressure.

Note: The opposite situation can occur, especially if the operator is trying too hard to avoid stretching the condom. This can give a condom that is positioned too loosely on the mandrel. In this case, the tested length will be greater than specified giving burst volumes that are erroneously high and burst pressures too low.

The correct way to load the condoms is as follows:

- Remove the condom from the pack, taking care not to damage it (it is recommended that gloves or finger cots are worn).
- Whilst it is permitted to unroll the condom before loading, it will generally be much easier to unroll the condoms directly onto the supporting rod or mandrel.
- Place the rolled condom onto the top of the supporting rod or mandrel and, using the finger tips, stroke the condom down a little at a time, allowing the condom to relax for a few seconds after each stroke.
- Ensure that the condom is not stretched as it is unrolled over the supporting rod/mandrel.

5.2 Ensuring the correct inflation length

As described in 5.1 above, ensuring the correct length of the condom to be inflated is important. Assuming that the condom is loaded correctly, this length will be dictated by the length of the supporting rod or mandrel. This will generally be adjustable and can be checked using the following method or one recommended by the equipment manufacturer:

- Load the condom onto the test machine.
- Clamp the condom.

- Mark the condom, using a suitable pen or marker, as closely as possible to the top of the external clamping collar. Depending on the type of burst test machine, clamping the condom will also start the inflation. In this case, the inflation needs to be stopped as soon as possible so the condom can be marked, or the condom marked as soon as possible and the test aborted so that the condom is not inflated and burst. Some burst testing machines release the condom as soon as inflation is stopped. If this function cannot be temporarily disabled for calibration purposes, it may be necessary to mark the correct inflation length on the condom first.
- Measure the length of the condom to the mark using the condom length measuring mandrel described in Annex D of *ISO 4074:2015* (*6*). The length to the mark should be 150 ± 3 mm.
- If the tested length is outside of these limits, adjust the machine and repeat the measurement to confirm that the tested length is correct.
- Repeat for each inflation head on the test equipment.

5.3 Checking that the condom does not slip during inflation

Most air inflation equipment clamps the condom by inflating an elastic cuff against a rigid collar, clamping the condom in between.

Obviously, no matter how carefully the condom has been loaded onto the test equipment, if it is not firmly held by this clamping mechanism and the condom slips during the test, then errors will be introduced into the results. The effectiveness of the clamping system can be checked in a similar fashion to the inflation length described in 5.2 above. In this case, after marking the condom, allow it to inflate whilst watching the mark. Any slippage in the clamping mechanism will be shown by the mark moving upwards (usually erratically) as the condom inflates. It is also important to check if the machine has inflation cuffs that these do not leak air into the condom, as any unmonitored air entering the condom will give false results. This can be checked by inflating the cuff, turning off the air supply (if the machinery will allow this) and checking that the cuff remains inflated over a period of several minutes. If the testing machine does not permit the cuff to remain inflated when the air supply is turned off, a systematic difference between the volume readings for different test heads may indicate that a cuff is leaking.

Again, check all the inflation heads on the test equipment.

5.4 Calibrating the volume and pressure measuring equipment

Owing to the different types of condom burst equipment used in the industry, no recommendations on the calibration and verification procedures can be

made here, other than to calibrate the machines following the manufacturer's instructions. The calibration interval again can be specified by the manufacturer, and will typically be between one and four times a year, although, if the equipment is subject to heavy use, it may be worth calibrating more frequently. If there are any reasons to suspect that the results from a particular machine or test head are not accurate, then investigation and re-calibration should be undertaken immediately.

5.5 Correcting for variations in atmospheric pressure owing to the altitude of the test laboratory

The calibration procedure for inflation test machines will often require the average atmospheric pressure to be entered. It is important that this is adjusted accordingly, especially for test laboratories situated at high altitudes. More detailed instructions will usually be found in the manufacturer's support literature or can be sought directly from the manufacturer.

5.6 Other factors to consider in the burst testing of condoms

- Ensure that the flow rate is within the specified range of 24-30 dm^3/min.
- When a condom is inflated, there is a region of high stress between the part of the condom that is firmly clamped and the adjacent freely expanding part. Owing to the characteristics of latex dipping, this zone is also usually the thinnest. Care must be taken to remove any potential for damage in this area. *ISO 4074:2015* (*6*) specifies that the edge of the rigid collar is rounded with no sharp edges but this edge should be checked regularly to ensure that it has not been nicked or damaged and is still adequately smooth.
- Inflation testing machines can test a lot of condoms between service intervals and in general these condoms will be lubricated. It is not uncommon for lubricant to build up in the various holes supplying air to the condom or the piping connecting the condom to the pressure transducer. Not only can this lubricant build-up affect the accuracy of the test procedures, but contamination of the pressure transducer by lubricant can mean an expensive replacement. Powder and fragments of rubber can also partially or completely block these apertures. It is recommended that there is a daily inspection and cleaning of these apertures, and that the piping to the transducer is inspected and cleaned regularly.

- Be aware of the possibility that the test heads in a multi-headed inflation test machine can differ. Monitor the individual heads and, if any of them appear to be giving consistently different results to the others investigate, and rectify if necessary.
- Consider storing a batch of control condoms and testing a few of them every day, depending on the number of test heads on the machine, before starting to use the inflation equipment. If the results from these control condoms are within the expected trend, that gives an assurance that the equipment is working properly. It can also be useful in detecting and quantifying any differences between operators. Graphing the results on, say, a mean and range chart will help identify if any significant changes occur.

5.7 Cleanliness of the air supply hole in the mandrel

The air supply point in the mandrel should be cleaned regularly to avoid partial blockage by accumulated powder and lubricant.

5.8 Maintenance of the supply air pressure and the air flow rate

A dedicated air compressor should be provided for the inflation tester. Using a compressor that may not have adequate capacity to meet with the demand of maximum use by other operations in the laboratory could cause the air pressure in the inflation tester to have momentary fluctuation and variations from the time of daily calibration checks.

5.9 Maintenance of the air temperature from the compressor

The air compressor for inflation tester should be located in such a manner that it is not subject to extreme variations during the operation during the day, which could affect the density of the air.

6. Determination of stability and shelf life

A requirement of *ISO 4074:2015* annexes K and L (*6*) is that condoms should comply with the key physical property requirements (that is, burst volume and pressure, freedom from holes and package integrity) throughout their claimed shelf life. The shelf life can only be established by a real-time study carried out at 30° C (+5, −2° C). However, a provisional shelf life can be claimed whilst the real-time study is in progress, provided that satisfactory data from accelerated ageing studies are available to support the claim. A full description of the requirements for real-time and accelerated ageing stability studies is given in Annexes K and L of *ISO 4074:2015* (*6*).

The following are points to note when conducting these ageing studies:

- The condoms used in the studies must comply with the requirements of *ISO 4074:2015* (*6*). The studies can only be done with condoms that have been stored in bulk for the maximum period of time specified by the manufacturer between dipping and packaging in individual sealed containers. *ISO 4074:2015* (*6*) specifies that this period shall not exceed two years. WHO/UNFPA technical specifications, however, specify a maximum storage period of six months. By agreement with UNFPA, it is acceptable for manufacturers to conduct stability studies on condoms that have been stored for six months between dipping and packaging to verify shelf life claims for procurement under the WHO/UNFPA prequalification scheme.

  Some manufacturer's formulation may require a certain time period of maturation of condoms before their burst properties could stabilize. It is recommended to allow the required maturation time before the condoms are foiled and this minimum maturation time be validated and applied while conducting stability studies.
- Minimum stability requirements (clause 11.2) (*6*) must be established.
- Three different lots of condoms must be used in the studies. These production lots from where samples are drawn for stability studies should represent the actual normal commercial batch sizes of the manufacturer and not just three sub-lots of the manufacturer.
- Select and condition sufficient extra condoms to cover repeat testing if necessary.
- Ensure that there are contingency arrangements in place in case of equipment breakdown or power failures. You do not want to have to start the studies again from scratch.
- Ensure that the calibration and measurement of temperature are monitored correctly and the trends are reviewed to pick up early warning signals for initiating appropriate corrective and preventive actions.
- Ensure that the system of recording temperature and raising alerts in case of outages in temperature conditions are in a good state of repair throughout the long period of stability studies and the alert signals are responded to immediately.
- The claimed shelf life cannot exceed five years from the date of manufacture.
- The date of manufacture can be either the date of dipping or the date the condoms were sealed in their individual containers. Note

that the labelled date of manufacture cannot be more than two years from the date of dipping or six months to comply with UNFPA requirements, as noted above.

- Monitor the physical properties of the condoms at intervals during the real-time study. Two methods are described in clause K.2.4 (*6*) of the standard. These are:
  - Measure the airburst properties of a sample of 125 condoms from each lot and compare against the requirements of the standard, using the Acceptance Quality Limit (AQL) of 1.5 (accept on five failures or fewer, reject on six or more). If one of the three lots of condoms fails, carry out an investigation and analyse the root cause of failure. Investigation could also be carried out by analysing more samples from that batch representing that time point. If the root cause is common to the other two batches as well, the stability studies should be stopped. If there are no assignable causes for variation at any one specific time point, the study can continue but must be stopped if more than one set of samples fail. At the end of the proposed or claimed shelf life, carry out the test with larger sample sizes as per the requirements of *ISO 4074:2015* (*6*).
  - Alternatively, measure the airburst properties of a set of 32 condoms from each lot. Calculate the standard deviation (or 95% confidence interval) for burst volume and pressure. If the mean value, minus three times the standard deviation, approaches the minimum limits defined in the standard (as described in the note to clause K.2.4 {*6*}), this can indicate that the condoms will not pass the requirements of the standard if the study is continued and the stability study should be terminated.
- If the manufacturer has condoms where the shelf life has been confirmed by a real-time study, then these condoms can be used as controls in an accelerated ageing study of a new or modified condom, as described in clause L.3 (*6*).
- If there are no condoms to act as controls in this way, then the provisional shelf life must be estimated following the procedures in clause L.2 (*6*).
- Existing condoms whose shelf lives were established following the procedures of earlier versions of *ISO 4074* (i.e. 2002 {*7*} and 2014 {*8*}) can be considered to be compliant. However, considering the several changes that have taken place between 2002 and now, the manufacturer should initiate fresh real time stability studies as per

the requirements of *ISO 4074:2015* (*6*), for the products that are currently being manufactured.

- If any significant changes are made to the condom formulation, manufacturing procedures or packaging, then the shelf life will need to be re-confirmed. A significant change, as explained in *ISO 16038, Rubber condoms – Guidance on the use of ISO 4074 in the quality management of natural rubber latex condoms* (*9*), is one that can be regarded as having the potential to affect performance adversely. If a change is deemed by the manufacturer not to require confirmation of shelf life, the reasons for this decision and all supporting test data shall be documented.

7. Freedom from holes

The *ISO 4074:2015* Annex M (6) standard has two methods for performing the test for holes. The volume of water dispensed is dependent upon the average length and average width (taken at 75 ± 5 mm from the closed end excluding the reservoir tip) of 13 condoms as described in the standard.

7.1. The water leak test (hang and roll)

A suspended condom is filled with a specified volume of water and examined for visible water leakage through its walls. In the absence of any visible leakage, the condom is then rolled on coloured absorbent paper which is subsequently examined for signs of leakage of water from the condom. Condoms with visible holes less than 25 mm from the open end are not considered as defective in this test. The test must be carried out exactly as described in the Standard.

Points to note:

- Before testing, using a calibrated apparatus, ensure that the volume and temperature of the water dispensed are within the specified limits for the test.
- Ensure that the condom is secured on the mount in such a way as to avoid slippage during water dispensation, especially for the condoms that need volumes of more than 300 dm^3.
- The condom may be tapped gently to remove air bubbles present on the inner surface of the condom.
- It is essential that the rolling is carried out correctly. The water-filled condom must be rolled for a distance sufficient to allow the whole surface of the condom to contact the paper. This distance is frequently underestimated. When training operators, it can be

helpful to mark the condom to show how far the condom must be rolled. The condom must be rolled through at least two complete revolutions (WHO/UNFPA do not recommend rolling more than 10 revolutions).

- Ensure that the correct amount of pressure is applied to the condom. The hand (with fingers spread) should be maintained 25 to 35 mm above the paper.
- When testing the closed end of the condom, maintain a similar level of pressure as when rolling and do not slide the condom over the paper.
- The coloured absorbent paper should be one that makes it easy to identify the blots made by the presence of holes on the condom wall. It should also allow for the rolling of the condom body for the required revolutions as per ISO 4074. Under no circumstances shall multiple absorbent papers be joined using adhesive tape.
- The condom walls may be carefully wiped with soft absorbent cloth or paper to remove excess moisture and lubricant thus allowing for easier detection of leaks.

7.2 The electrical test

Points to note:

- The equipment should be routinely calibrated and/or verified for effectiveness, and maintained as per manufacturer's specifications. This includes routine changing of the electrolyte solution as build-up of lubricant may affect the efficacy of the test. In addition to calibration, the equipment and the technique should be verified routinely for effectiveness in detecting the holes.
- The different parameters that affect the test, such as voltage, should be checked before each batch/lot test, using calibrated apparatus, for conformity to specified limits.
- Not more than 25 mm of the condom should be left unexposed to the electrolyte.
- Any leaks detected by the system should always be confirmed by the rolling method described in the Water Leak Test. Note that *ISO 4074:2015* (*6*) specifies the Hang and Roll method must be used - not the *ASTM D3492* Hang and Squeeze method (*10*).
- Note that the condoms have to be observed during filling in order to detect any holes (see M 3.3.7, third line {*6*})

7.3 The water leak test (hang and squeeze)

This method is very similar to the Hang and Roll method except that the condom is not rolled. Instead, pressure is applied to the condom by gently squeezing it whilst it is hanging, full of water, on the test equipment. The test must be carried out exactly as described in the *ASTM D3492 – 15 Annex A3* (*10*) Standard.

Points to note when using this method are:

- After filling with water, the body of the condom should be tapped gently to dispel any air bubbles present on the inner surface of the condom.
- Do not apply too much pressure by squeezing too hard. The correct amount of distension of the filled condom is shown in *figures A3.3* to *A3.5* in the ASTM Standard (*10*).
- When checking the body of the condom, gently rotate the condom so that the entire surface is inspected.
- When examining the condoms for signs of leakage, ensure that any water droplets on the outside of the condom are the result of leakage and not water splashed onto the condom from any external source. If necessary, gently dry the outside of the condom with a paper towel and re-check.

8. Visibly open seals (*ISO 4074:2015*, Annex N)

This test is performed using samples that are drawn for conducting the tests for Freedom from Holes and Visible Defects.

The individual sealed containers are examined by visual observation for any visibly open seals. Defects may include improperly formed seals, condoms getting trapped in sealing area, uneven or very narrow sealing edges leading to open seals and leakages. However, it should be noted that these packaging "defects" are not specified in *ISO 4074:2015* (*6*).

It is recommended that the test laboratory has the display of defects related to visibly open seals to serve as examples of workmanship criteria so that consistency is maintained in conducting the test. The defective condoms observed should be preserved for reference.

9. Visible defects (*ISO 4074:2015*, Annex M and *WHO/UNFPA Technical specifications for male latex condoms*)

The test for visible defects is conducted on the same set of samples taken for the test for Freedom from Holes.

After performing the test for visibly open seals, the individual sealed containers are opened by pushing the condoms to one side of the pack and opening the seals, taking care that the condom is not damaged by the rough edges of the seals, nor sharp instruments such as scissors or finger nails. On no account should any sharp implement (scissors, scalpels, etc.) be used to open the condom packs. The condoms are unrolled and examined by visual observation under bright light, which should completely cover all parts of the condom. Visual defects are classified as Critical and Noncritical defects with corresponding AQLs of O.4 and 2.5. The section on Workmanship and Visible Defects on the WHO/UNFPA Specification (*6*) details the list of Critical and Noncritical defects. This section also lists minor imperfections, which do not affect the properties of the condoms, but are considered as potential points for elimination with appropriate quality improvement projects. Personnel should be trained for the ability to detect the visible defects and to correctly classify them. Having an approved workmanship criteria album will be useful to avoid any disputes. It is recommended to have a display of specific visual defects in the laboratory for the operators to easily identify and classify the defects.

10. Determination of package seal integrity

Unless specified otherwise in the procurement contract and purchase order, the Package Integrity test[1] specified in Annex N of *ISO 4074:2015* Annex N (*6*) shall be used to test package integrity. For condoms intended for distribution to high altitude regions or to be distributed by air freight, the alternative "dry vacuum method" described in Annex 2 of the revised *World Health Organization/United Nations Population Fund Technical specifications for male latex condoms* (*3*) may be specified.

When conducting the test according to the method specified in Annex N of *ISO 4074:215* (*6*), the following points should be noted:

- Working with a vacuum is potentially dangerous. Eye protection should be used when carrying out this test.

[1] The seal on the individual condom container, whether of the standard foil pack or the "butter dish" container can, at times, be compromised. This can be caused by several factors, including misaligned sealing jaws, excessive lubricant, a misaligned or poorly rolled condom being trapped in the seal, etc. In addition, the foil may contain pinholes or, if the information on the foil is stamped on, rather than ink-jet printed, the stamping may damage the foil. All in all, there are many ways in which the individual condom container can contain small holes. A consequence of this is that lubricant can leak out and, if not detected, can contaminate all the other condom containers within the same pack. In addition, a compromised foil can expose the condom to oxygen which could cause premature degradation. For this reason, it is necessary to test the integrity of the packages.

- The vacuum chamber should be closable with an air tight transparent lid so that the defective packs can be easily observed during the test.
- A vacuum level of 20 ± 5 kPa absolute must be used. That is approximately 20% of normal atmospheric pressure at sea level. Unfortunately, some gauges will read from 0 to 100 kPa whilst others may read from 100 (or −100) to 0 kPa (see *figure 3*). This can be confusing. If the gauge reads from 0 to 100, the correct level of vacuum will be the figure of 20 kPa: if the gauge reads the other way, the correct vacuum level will be 80 (or −80) kPa (*figure 3*). In case of doubt, remember that it is the greater level of vacuum that must be used. It will typically take at least 20 seconds – often considerably longer – for a vacuum pump to evacuate the chamber to this level. Changes in the time taken to reach the desired vacuum level can be indicative of complications in the test system or an inaccurate level of vacuum being used.
- The water level should be such that the condom packages are at least 25 mm below the surface.
- The number of packages in the chamber should be restricted so that all the packages can be clearly observed.
- A dye is often used to help detect leakage into the containers and the amount used should not obscure observation of the packages.
- If a dye is used, it should be easily washable and should not leave any deposit of colour building up as that would obstruct the observation of leakages. The vacuum container and the lid should be maintained clean.
- Observe the condom packages as soon as the vacuum pump starts – do not wait until the specified vacuum level has been reached to start the observation. By that time, all the air in a defective package may have been expelled and the stream of bubbles will have ceased.
- All of the individual containers must be opened to check for the presence of water inside. This is where the dye can be helpful, to distinguish between lubricant and any water that may have entered the pack.

Fig. 3
A pressure gauge reading from −100 to 0 kPa. In this case, the correct vacuum level for the test would be −80 kPa (red numerals)

References

1. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
2. World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 9 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
3. World Health Organization/United Nations Population Fund Technical specifications for male latex condoms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 10 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
4. World Health Organization/United Nations Population Fund Specifications for plain lubricants. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 11 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
5. ISO/IEC 17025:2017(en). General requirements for the competence of testing and calibration laboratories. International Standard ISO/IEC 17025. Geneva: International Organisation for Standardisation, 2017 (https://www.iso.org/standard/66912.html, accessed 21 May 2020).
6. ISO 4074:2015(en). Natural rubber latex male condoms – Requirements and test methods. International Standard ISO 4074. Geneva: International Organisation for Standardisation, 2015 (https://www.iso.org/standard/67615.html, accessed 21 May 2020).
7. ISO 4074:2002(en). Natural rubber latex male condoms – Requirements and test methods. International Standard ISO 4074. Geneva: International Organisation for Standardisation, 2002 (https://www.iso.org/standard/27418.html, accessed 21 May 2020).

8. ISO 4074:2014(en). Natural rubber latex male condoms – Requirements and test methods. International Standard ISO 4074. Geneva: International Organisation for Standardisation, 2014 (https://www.iso.org/standard/59718.html, accessed 21 May 2020).

9. ISO 16038:2005(en). Rubber condoms – Guidance on the use of ISO 4074 in the quality management of natural rubber latex condoms. International Standard ISO 16038. Geneva. International Organisation for Standardisation, 2005 (https://www.iso.org/standard/ 37078.html, accessed 21 May 2020).

10. ASTM D3492 – 16(en). Standard specification for rubber contraceptives (male condoms). Active Standard ASTM D3492/Developed by Subcommittee: D11.40. ASTM International, 2016 (https://www.astm.org/Standards/D3492.htm, accessed 21 May 2020).

Annex 7

World Health Organization/United Nations Population Fund guidance on conducting post-market surveillance of condoms

Background

The report of the Fifty-fourth meeting of the World Health Organization (WHO) Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) in 2019 (*1*)) stated the following:

> *As agreed at the ECSPP meeting in October 2018, the United Nations Population Fund (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 Expert Advisory Panel (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 (2);*
- *World Health Organization/United Nations Population Fund technical specifications for male latex condoms (3); and*
- *World Health Organization/United Nations Population Fund specifications for plain lubricants (4).*

The Expert Committee further recommended proceeding with the next steps as discussed.

This is one of four remaining working documents in this series.

1. Introduction 191
2. Sampling 191
3. Testing 193
4. Selection of laboratories 194
5. Interpretation of results 194
References 195

1. Introduction

Good quality condoms conforming to the *World Health Organization (WHO)/ United Nations Population Fund (UNFPA) technical specifications for male latex condoms* (*3*) have excellent storage properties. The combination of individual condom packaging, inner boxes and shipping containers is designed to protect the condoms during shipping and storage. Nevertheless, storage under poor conditions and/or rough handling during shipping might adversely affect the properties of the condoms. Exposure to such adverse conditions is potentially more likely once the condoms have left control of the purchaser and are in the wider distribution chain. For this reason, periodic surveillance testing of product recovered from the field is recommended to confirm that the condoms still conform to the requirements of the *World Health Organization/United Nations Population Fund technical specifications for male latex condoms* (*3*) and *ISO 4074, Natural rubber latex male condoms – Requirements and test methods* (*5*). Surveillance testing may also be conducted to determine if there has been a significant deterioration in condom properties relative to retained samples kept under controlled conditions.

It is recommended that prequalified manufacturers conduct periodic surveillance testing on condoms that are nearing their expiry date and have been stored in hot regions to support the shelf life claims made on the basis of real time and accelerated stability studies. Surveillance testing may have to be undertaken when there are complaints about condoms, particularly if the complaints are clustered and associated with one specific product or even a single lot of product. In such cases, sample sizes can be severely limited and it may be necessary to limit testing to just one property. The selection of sample sizes for such testing can be challenging and the results may be of limited use if only a small number of samples are available.

2. Sampling

In order to conduct post-market surveillance testing on male latex condoms, it might be necessary to recover condoms from any of the following locations:

- warehouses;
- distribution centres;
- wholesalers;
- clinics; and
- retail outlets.

Key issues when recovering samples for surveillance testing are often the sample size and lot integrity. If single lots are being tested, for example, one lot each from a number of manufacturers, then ideally the sampling schemes given in Annex B of *ISO 4074* (*5*) should be used. If possible, samples should be taken from at least three lots from each manufacturer to give an indication about lot-to-lot homogeneity. If multiple lots from a single manufacturer are being evaluated, then the sampling schemes of Annex A of *ISO 4074* (*5*) are acceptable. If sample sizes are limited then it may be necessary to test only for selected properties.

Sample only for the tests that are needed to check on the parameters in question. Obtaining sufficient samples from warehouses, distribution centres and wholesalers is not usually problematic but sampling from clinics and retail outlets often means that sample sizes have to be restricted. This may limit the types and numbers of tests that can be completed. If an adequate number of samples from one batch is not available at any particular retail outlet or clinic, it may be possible to obtain more samples of the same batch from a nearby retail store or clinic in the region.

If sample sizes are restricted, then they should still be selected from *ISO 2859-1, Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality level (AQL) for lot-by-lot inspection – Amendment 1* (*6*). Whenever possible, select sampling schemes that have at least a 95% probability of acceptance if the quality of submitted lots is at the limit of the specified AQL (refer to tables X-A through to X-R of *ISO 2859-1* (*6*) for the operating characteristic curves and acceptance probabilities of the sampling schemes). Use sample sizes that are consistent with *ISO 2859-1* (*6*). Sample sizes that fall between the specified sample sizes in the tables should not be used (for example, Table II-A) since it may not possible to make a statistically valid decision about whether or not the product sampled conforms to the specification. If there are insufficient samples available to use a specified sample size, the next lowest specified sample size, for which there are enough samples and corresponding to that AQL, should be used.

For performance requirements, such as burst properties, freedom from holes and package integrity, avoid zero accept sampling schemes whenever possible (for example, a sample size of 50 for an AQL of 0.25 with an acceptance number of 0). These sampling schemes generally have poor operating characteristic curves which can lead to type I and type II errors (i.e. an incorrect rejection of a true null hypothesis and failure to reject a false null hypothesis respectively, or more simply, false positive and false negative results). If forced to use zero accept sampling schemes, due to a shortage of samples, then be cautious about any conclusions that are reached.

At the time of sampling, full details about the lots being sampled, including the lot numbers, expiry dates and storage conditions, should be noted. Whenever possible, a sampling agency should be used and samples should be taken from lots using procedures to ensure the random selection of condoms from within the lot.

In some cases, it may be necessary to combine samples from more than one lot in order to achieve an adequate sample size for testing. This should be regarded as a last resort situation and is best avoided. Full details of the lots sampled must be recorded and the expiry date noted for each lot sampled. If possible, samples from the different lots that are to be combined should be kept separate throughout the testing process in order to facilitate analysis of the final results. It may be possible, for example, to show that the different lots sampled have very similar properties and so justify using the overall result as an estimate of the quality of all of the lots sampled.

If the test laboratory is located some distance from the location at which the condoms are being sampled, then the transport arrangements needed to deliver the condoms to the laboratory should be considered. It is essential to ensure that the condoms will be not be subjected to any adverse conditions in transit that could affect the results of the tests. Sending samples by air freight might, for example, compromise the outcome of any testing for package integrity. The use of data loggers to monitor temperatures during shipment should be used, particularly if the condoms are being shipped from or through countries with hot climates.

3. Testing

The primary focus for testing natural rubber latex male condoms should be the critical performance parameters, i.e. burst properties, freedom from holes and package integrity. Other properties, such as dimensions, are unlikely to change during storage or shipping. Burst properties can be evaluated on a variables basis as well as on an attribute basis (i.e. conformance to the 1.5 AQL for burst properties). Information about average burst volume and pressure, their associated standard deviations and the frequency distributions of the results can be extremely useful in trying to determine if any significant changes have occurred. Comparisons can be made with the original manufacturer's data and the pre-shipment test results. The statistical significance of any changes in properties can be readily assessed by the t-test or analysis of variance (ANOVA). Using such methods may be particularly informative in situations where there are insufficient samples available to make reliable estimates of conformity to the AQLs on an attribute basis.

4. Selection of laboratories

The laboratories used for surveillance testing shall be accredited to *ISO 17025* (*7*) for the tests being carried out. The laboratories should also participate in an appropriate international inter-laboratory proficiency scheme. Ideally, the same laboratory that did the original pre-shipment testing should be used. This makes the comparison of results much easier and more reliable and permits samples that have been retained under controlled conditions by the test laboratory to be re-tested if necessary.

For more information about the selection of laboratories, please refer to *World Health Organization/United Nations Population Fund Condom quality assurance* (*8*).

When selecting test laboratories, consideration should also be given to any local customs and import restrictions. Some countries have restrictions on the import of condoms without testing and these rules can even be applied to samples being imported solely for test purposes. One should confirm with the laboratory whether or not there are any rules relating to the import of samples for testing prior to sending the samples.

5. Interpretation of results

Although lot conformity is assessed on an attribute basis, the use of means and standard deviations whenever possible is recommended. This primarily applies to burst testing. Trends in burst properties, particularly when compared to the results from pre-shipment testing, can provide early warning of potential problems.

Reviewing the burst result histograms can reveal very interesting information. Bimodal (or even polymodal) distributions of burst pressure and/or volume are indicators of poor homogeneity within the lot. In some cases, this might indicate that the product is substandard and/or falsified; for example, the lot in question may consist of mixed condoms from different lots or even condoms from different manufacturers. If substandard and falsified medical product is suspected, then forward all of the details to the manufacturer whose name is marked on the pack. The manufacturer should be able to determine the authenticity of the product from the lot number. Producers of substandard and falsified medical products commonly make small mistakes with labelling so return samples of the packaging, and any information received, with the product to the manufacturer for checking. Following confirmation from the manufacturer that the product is falsified, inform the WHO team working on substandard and falsified medical products at rapidalert@who.int.

If regular post-market surveillance testing is being carried out on products from a specific manufacturer, then analysis of trends over time can

provide extremely useful information. Plotting charts, as described in the document *World Health Organization/United Nations Population Fund Condom quality assurance*, Annex 2 (*8*), for example, is a very powerful method of identifying any concerning trends in product quality. Early identification of an unacceptable trend might, for example, permit a manufacturer to carry out corrective and preventative actions before the product goes out of specification and lots are rejected. Charts can also be used to identify situations where manufacturers may have made changes to the product or production processes and failed to inform the purchaser. Comparing trends for pre-shipment test results with those from surveillance testing might also identify problems relating to the shipping and storage of a product.

References

1. WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
2. World Health Organization/United Nations Population Fund Prequalification Programme guidance for contraceptive devices: male latex condoms, female condoms and intrauterine devices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 9 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
3. World Health Organization/United Nations Population Fund technical specifications for male latex condoms. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 10 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
4. World Health Organization/United Nations Population Fund specifications for plain lubricants. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva: World Health Organization; 2020: Annex 11 (WHO Technical Report Series, No. 1025; https://www.who.int/publications-detail/978-92-4-000182-4, accessed 20 May 2020).
5. ISO 4074:2015(en). Natural rubber latex male condoms – Requirements and test methods. International Standard ISO 4074. Geneva: International Organisation for Standardisation, 2015 (https://www.iso.org/standard/67615.html, accessed 21 May 2020).
6. ISO 2859-1:1:1999/AMD 1:2011(en). Sampling procedures for inspection by attributes - Part 1: Sampling schemes indexed by acceptance quality level (AQL) for lot-by-lot inspection – Amendment 1. International Standard ISO 2859-1. Geneva: International Organisation for Standardisation, 1999/2011 (https://www.iso.org/standard/53053.html, accessed 21 May 2020).
7. ISO/IEC 17025:2017(en). General requirements for the competence of testing and calibration laboratories. International Standard ISO/IEC 17025. Geneva: International Organisation for Standardisation, 2017 (https://www.iso.org/standard/66912.html, accessed 21 May 2020).
8. World Health Organization/United Nations Population Fund Condom quality assurance. Geneva: World Health Organization; 2019 (working document QAS/19.807; https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas19-807-condom-quality-assurance.pdf, accessed 2 February 2021).

Annex 8

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 198

2. WHO solubility classification for biowaiver 198

3. Scope 199

4. Methodology 199

5. Results 200

References 203

Further reading 204

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 classes I and III according to the Biopharmaceutical 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). 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.

In addition, the present list replaces the existing literature-based compilation published in 2006 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*) based on data extracted from the public domain (i.e. solubility data published by different authors using inconsistent experimental conditions).

The WHO Biowaiver Project is organized into study cycles. Previous and current cycles are summarized below in order to provide an overview of the project development:

- 2018: cycle I; also referred to as the pilot phase.
- 2019: cycle II.
- 2020: cycle III. The new results presented in this updated document (in Table 1 highlighted in bold) come from cycle III.

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 WHO Model List of Essential Medicines (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 centers 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.

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* (*2*) 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 potential source of variability among centres and studies.

To date, all APIs studied in cycles I, II and III 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 1 provides an overview of the APIs studied by WHO during cycles I, II and III. The new APIs studied in cycle III are reported in bold.

Table 1
WHO solubility classification of active pharmaceutical ingredients prioritized from the *WHO Model List of Essential Medicines* (*3*)

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]	API PQ EOI / PQ	WHO classification[c]
aciclovir	Antiviral medicines	Antiherpes medicines	800	No	II/IV*
amoxicillin (trihydrate)	Antibacterials	Antibiotics	3000	Yes	II/IV*
azithromycin (dihydrate)	Antibacterials	Antibiotics	2000	Yes	II/IV
cefixime (trihydrate)	Antibacterials	Antibiotics	400	No	II/IV
chloroquine phosphate	**Antiprotozoals medicines**	**Antimalarial medicines**	**1 g salt (= 600 mg base)**	**No**	**I/III**
codeine (phosphate hemihydrate)	Medicines for pain and palliative care	Opioid analgesics	60	No	I/III
cycloserine hydrochloride	**Antibacterials**	**Antituberculosis medicines**	**1 g**	**Yes**	**I/III**
daclatasvir (dihydrochloride)	Antiviral medicines	Medicines for hepatitis C	60	Yes	II/IV **
darunavir (ethanolate)	Antiviral medicines	Antiretrovirals (HIV)	800	Yes	II/IV **

Table 1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]	API PQ EOI / PQ	WHO classification[c]
dexamethasone	**(1) Gastrointestinal medicines (2) Immunomodulators and antineoplastics (3) Medicines for pain and palliative care (4) *Corticosteroids for COVID-19*[d]**	**(1) Antiemetic medicines (2) Acute lymphoblastic leukaemia (2) Multiple myeloma (3) Medicines for other common symptoms in palliative care (4) *Treatment of patients with severe and critical COVID-19*[d]**	**(1) (3) 0.5 to 10 mg a day depending on the disease being treated (2) 40 mg (4) *6 mg a day*[d]**	**Yes**	**I/III ****
dolutegravir	Antiviral medicines	Antiretrovirals (HIV)	50	Yes	II/IV**
efavirenz	Antiviral medicines	Antiretrovirals (HIV)	600	Yes	II/IV
emtricitabine	**Antiviral medicines**	**Antiretrovirals (HIV)**	**200 mg**	**Yes**	**I/III****
entecavir	**Antiviral medicines**	**Antihepatitis medicines**	**1 mg**	**Yes**	**I/III ****
ethionamide	Antibacterials	Antituberculosis medicines	500–1000	Yes	II/IV*
furosemide	Cardiovascular medicines	Medicines used in heart failure	80	No	II/IV
mefloquine hydrochloride	**Antiprotozoals medicines**	**Antimalarial medicines**	**1250 mg (as hydrochloride)**	**Yes**	**II/IV**

Table 1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]	API PQ EOI / PQ	WHO classification[c]
methyldopa sesquihydrate	**Cardiovascular medicines**	**Pregnancy-induced hypertension**	**500 mg**	**No**	**I/III**
oseltamivir phosphate	**Antiviral medicines**	**Influenza virus**	**75 mg (as phosphate)**	**Yes**	**I/III ****
paracetamol	**Medicines for pain and palliative care/ Antimigraine medicines**	**Non-opioids and non-steroidal anti-inflammatory medicines / Treatment of acute attack**	**1 g**	**No**	**I/III**
primaquine (phosphate)	Antiprotozoal medicines	Antimalarial medicines (curative treatment of *P. vivax* and *P. ovale* infections)	15	Yes	I/III
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
sofosbuvir	**Antiviral medicines**	**Medicines for hepatitis C**	**400 mg**	**Yes**	**II/IV****

Table 1 *continued*

Medicine[a]	Therapeutic area	Indication	Highest therapeutic dose (mg)[b]	API PQ EOI / PQ	WHO classification[c]
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] *WHO Model List of Essential Medicines* (*3*).

[b] According to Summary of Product Characteristics from WHO-PQ or National/Regional Regulatory Authority.

[c] 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.

[d] "Corticosteroids for COVID-19. WHO Living guidance" September 2020) https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 (accessed 30 September 2020)

* Change in solubility class compared to WHO 2006 classification.

** APIs characterized for the first time within the WHO Biowaiver Project.

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

1. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 6 (WHO Technical Report Series, No. 1003; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex6-who-multisource-pharmaceutical-products-interchangeability.pdf, accessed 2 February 2021).
2. Protocol to conduct equilibrium solubility experiments for the purpose of Biopharmaceutics Classification System-based classification of active pharmaceutical ingredients for biowaiver. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-third report. Geneva: World Health Organization; 2019: Annex 4 (WHO Technical Report Series, No. 1019; https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 18 November 2019).
3. WHO Model List of Essential Medicines, 21st list. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1, accessed 4 November 2019).

Further reading

- Guidance for organizations performing in vivo bioequivalence studies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fiftieth report. Geneva: World Health Organization; 2016: Annex 9 (WHO Technical Report Series, No. 996; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs966-annex9-invivo-bioequivalence-studies.pdf, accessed 18 November 2019).
- General background notes and list of international comparator pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report. Geneva: World Health Organization; 2017: Annex 5 (WHO Technical Report Series, No. 1003; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs1003-annex5-who-list-international-comparator.pdf, accessed 18 November 2019).
- Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015; https://www.who.int/docs/default-source/medicines/norms-and-standards/guidelines/regulatory-standards/trs992-annex8-who-comparators-multisource.pdf, accessed 18 November 2019).
- List of international comparator products (September 2016). Geneva: World health Organization; 2016 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/list_int_comparator_prods_after_public_consult30.9.xlsx, and WHO list of international comparator pharmaceutical products and general background notes Annex 5, WHO Technical Report Series 1003, 2017, trs1003-annex5-who-list-international-comparator.pdf, accessed 2 February 2021).

Annex 9

Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce

1.	**Introduction**	206
2.	**Background**	206
3.	**Provisions and objectives**	207
4.	**Membership**	208
5.	**Requesting a certificate**	210
6.	**Issuing a certificate**	213
7.	**Notifying and investigating a quality defect**	215
References		215
Appendix 1	Model certificate of a pharmaceutical product	218
Appendix 2	Model batch certificate of pharmaceutical products	223
Appendix 3	Glossary	226
Appendix 4	(Draft) model notification to the Director-General of the World Health Organization	233

1. Introduction

The World Health Organization (WHO) Certification Scheme on the quality of pharmaceutical products moving in international commerce (hereinafter referred to as the "Scheme") is an international voluntary agreement to provide assurance to countries participating in the Scheme about the quality of pharmaceutical products moving in international commerce. The primary document of the Scheme is the certificate of a pharmaceutical product (CPP).

2. Background

The Scheme has been in operation since 1969 (World Health Assembly resolution WHA 22.50) and was amended in 1975 (WHA 28.65), 1988 (WHA 41.18), 1992 (WHA 45.29) and 1997 (WHA 50.3) (*1*–*5*). In 2007, the Forty-second ECSPP discussed and identified a number of perceived problems with the operation of the Scheme (*6*).

In 2008, a WHO consultation was held to make recommendations for consideration during the Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP), taking into account the WHO working document QAS/07.240 which contains key issues and possible action (*7*). The report of the consultation was the working document QAS/08.279 (*8*). In light of the changing environment, including the rapid globalization of the pharmaceutical manufacturing sector, coupled with changes in the make-up of both the regulators and the groups involved in procurement, the Forty-third ECSPP endorsed the following recommendations (*9*):

> "1. The *WHO Certification Scheme on the quality of Pharmaceutical products moving in international commerce* should be revised.
> 2. The proposal for revision of the Scheme and modification of the guidelines should be discussed by the relevant WHO Governing Bodies – the Executive Board and the World Health Assembly – and in consultation with WHO's Legal Counsel.
> 3. In the interim, a question and answer (Q&A) paper should be prepared on the function of the Scheme."

Based on the above recommendations, as an interim measure, a Q&A document on the function of the Scheme was developed in 2010 and revised in 2015 (*10*, *11*). However, the Scheme has not been revised since 1997.

In 2017, the Fifty-second ECSPP recommended that "the WHO Secretariat should prepare a proposal for revision of the Scheme for public consultation" (*12*).

The draft working document, which includes the proposed revision of the Scheme, was prepared by the WHO Secretariat and it was discussed during an informal consultation that took place from 19 to 20 May 2018.

The draft working document was circulated twice to the Member States and other interested parties for public consultation to prepare a version of the working document for endorsement by the Fifty-fifth ECSPP in 2020.

During the revision process, consideration was given to including reference to the Global Benchmarking Tool (GBT) (*13*) and the concept of WHO Listed Authorities (*14*). However, it was considered that since the GBT details are still under discussion, it was too early to add it in the Scheme. Additional wording was instead added to section 2.2 indicating that a Member State or a regional authority should possess an effective marketing authorization, vigilance and market surveillance and control systems for pharmaceutical products.

3. Provisions and objectives

3.1 A comprehensive system of certification must be founded on a reliable system of marketing authorization and independent analysis of the pharmaceutical product, as well as upon assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as "good manufacturing practices" (GMP), and also within relevant provisions already approved in the marketing authorization.

3.2 In 1969, the Twenty-second World Health Assembly, by resolution WHA22.50, endorsed requirements for *Good practices in the manufacture and quality control of drugs* (*15*) (referred to henceforth as "GMP as recommended by WHO"). These comprise internationally-recognized and respected standards that all Member States are urged to adopt and to apply. These requirements have since been revised several times.

3.3 These standards provide the basis for the the Scheme recommended initially in resolution WHA22.50 (*15*). The Scheme is an administrative instrument that requires each participating Member State or regional authority, upon application by a commercially interested party, to attest to the competent authority of another participating Member State or regional authority that:

- a specific product is authorized to be placed on the market within its jurisdiction or, if it is not thus authorized, the reason why that authorization has not been accorded;

- the manufacturing site is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP (*16*) as recommended by the WHO in accordance with its current publication;
- the actual status of commercialization of the certified product on the market of the certifying authority, when authorized; and
- all product information submitted, including labelling, is currently authorized by the certifying authority.

Additionally, the Scheme facilitates the exchange of information related to the investigation of serious quality defects reported in product exported in accordance with its provisions, reliance on the results of GMP inspections performed by other authorities, and also on the results of the assessment of the dossier with the requirements of the certifying authorities.

3.4 The Scheme, as amended in 1975 (*17*), 1988 (*18*), 1992 (*19*) and 1997 (*20*), by resolutions WHA28.65, WHA41.18, WHA45.29 and WHA50.3, is applicable to finished dosage forms of pharmaceutical products intended for administration to human beings or to food-producing animals.

3.5 Provisions for certification of starting materials (active pharmaceutical ingredients {APIs} and excipients) for exporting purposes are provided in separate guidelines (*21*).

4. Membership

4.1 Any Member State, as well as regional authority that has the legal right to control the regulation of pharmaceutical products, is eligible to participate on a voluntary basis in the Scheme as a requesting authority. In order to participate, a certifying authority should comply, additionally, with the requirements stipulated in section 2.2. Membership can be voluntarily withdrawn at any time by written notification to the Director-General of WHO.

4.2 A Member State or a regional authority intending to become a certifying member should possess:

- an effective marketing authorization, vigilance and market surveillance and control systems for pharmaceutical products, including the responsible manufacturers and licensing of distributors;
- GMP requirements, consistent with those recommended by WHO in accordance with its current publication, to which all

manufacturers of finished pharmaceutical products (FPP) are required to conform;

- effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country or region, including access to an independent medicine testing laboratory;
- a pharmaceuticals inspectorate, operating as an arm of the national or regional medicines regulatory authority, and having the technical competence, experience and resources to assess whether or not GMP and other controls are being effectively implemented, and the legal power to conduct or to coordinate appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples; and
- an efficient surveillance system, administrative capacity and good regulatory practices compliance to issue the required certificates efficiently, to detect and institute inquiries in the case of complaint, and to expeditiously notify WHO and, when possible, the competent authority in the Member State or region known to have imported a specific product, or publish the information on the website about the product that is associated with a potentially serious quality defect or other hazard in a timely manner.

4.3 Membership as a certifying member and/or requesting member should be declared by notifying in writing to the Director-General of the WHO of:

- its willingness to participate in the Scheme as a certifying member and/or a requesting member;
- any significant reservations it intends to observe relating to this participation;
- the commitment of implementing the WHO guideline ¨*WHO Certification scheme on the quality of pharmaceutical products moving in international commerce*", the WHO Model Certificates (WHO template) and provision of the certificates when requested by a requesting member;
- the name and address (including email address, telephone and website address) of its medicines regulatory authority or other competent authority;
- the commitment to notify any change of the information submitted related to the certifying and/or requesting member details; and
- a declaration to comply with the requirements for a certifying member as stipulated in section 2.2.

4.4 A consolidated list of information on the notification submitted by Member States and regional authorities in accordance with the provision in sections 2.3 and 2.5 will be available through WHO's official website (see also section 3.3).

4.5 A Member State or regional authority should inform the WHO of any change of the information notified to the Director-General of the WHO.

5. Requesting a certificate

5.1 Two documents, if available by the certifying authority, can be requested within the scope of the Scheme:

- a certificate of a pharmaceutical product (CPP) and;
- a batch certificate of a pharmaceutical product (*for more details, please see sections 3.14 and 3.15 and the Explanatory notes in Appendix 2*).

5.2 The proposed formats for these documents are provided in appendices 1 and 2 of these guidelines. All participating Member States and regional authorities are henceforth urged to adopt these formats without deletion in order to facilitate the harmonization and interpretation of certified information. A CPP with any deleted sections is no longer considered a "CPP".

The explanatory notes attached to the two documents referred to above are very important. Whilst they are not part of the document to be certified, they should always be attached to the certificate.

5.3 A list of addresses of national and regional authorities participating in the Scheme that are responsible for the registration of pharmaceutical products for human and/or veterinary use, together with details of any reservations they have declared regarding their participation in the Scheme, will be available on the WHO official website as indicated in section 2.4.

5.4 Each authority should issue appropriate guidelines to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, in order to explain the contribution of certification to the medicine regulatory process and the circumstances in which each of the two types of documents will be required, the requesting information and the methodology to follow.

Certificate of a pharmaceutical product

5.5 The certificate of a pharmaceutical product (CPP) (*Appendix 1*), issued by the certifying authority, is intended for use by the requesting authority in two situations:

- when the product in question is under consideration for a marketing authorization that will authorize its importation and sale, including the GMP compliance of the manufacturer and information on the marketing status of a product in the country of the certifying authority; and
- when administrative action is required to renew, extend, modify or review such a marketing authorization.

5.6 The CPP is intended to facilitate the trade of pharmaceutical products. Its use should have an impact for regulatory authorities and regional bodies in terms of quality and time on the assessment of dossiers for the marketing authorization. The Scheme facilitates reliance among the participating authorities and its use will enable a timely access to medicines.

5.7 All requests for CPPs should be channeled through the applicant. The applicant may submit the following information for each product to the certifying authority:

- the marketing authorization number, name and dosage form of the FPP;
- the name and amount of active ingredient(s) per unit dose (International Nonproprietary Name(s) (INN(s)) where such exist(s));
- the name and address of the marketing authorization holder;
- the name and address of the manufacturing site(s);
- the unit formulation (complete quantitative composition including all excipients);
- the product information for health professionals, the Summary of Product Characteristics (SPC), and for the public (patient information leaflets) as approved by the certifying authority; and
- the packaging of the FPP.

The name(s) and address(es) of manufacturing site(s) that could be submitted to the certifying authority are referred to the FPP, bulk finished product, solvent and diluents, quality control of the FPP, batch release, primary and secondary packaging.

For the product information to be attached to the certificate, please see section 4.7.

5.8 The certificate is a confidential document which may be issued by the certifying authority only with the permission of the applicant or of the marketing authorization holder.

5.9 The certificate is intended to be incorporated into a marketing authorization application to the requesting authority. Once prepared, it is transmitted to the requesting authority through the applicant and, when applicable, the agent in the importing country.

5.10 When any doubt arises about the status or validity of a certificate, the requesting authority should request verification of the validity of the certificate from the certifying authority, as provided for under section 4.8 of these guidelines.

5.11 In the absence of any specific agreement, each certificate will be prepared always in the working language(s) of the certifying authority. Certifying authorities are encouraged to issue bilingual certificates, including English as the second language, if applicable. The applicant will be responsible for providing any certified translation that may be required by the requesting authority.

5.12 Since the preparation of certificates imposes a significant administrative load on certifying authorities, the service may need to be financed by charges levied upon applicants.

5.13 Additional information is not within the scope of the Scheme. The certifying authority is under no obligation to supply additional information.

Batch certificate

5.14 A batch certificate of a pharmaceutical product (Appendix 2) refers to an individual batch of a pharmaceutical product and is a vital instrument in the procurement of medicines. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.

5.15 A batch certificate is normally issued by the manufacturer and must accompany and provide an attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already obtained marketing authorization in the importing country. The batch certificate shall include all the parameters (attributes), with acceptance criteria, of the release specification of the pharmaceutical product at

the time of batch release and the results. In most circumstances, these certificates are issued by the manufacturer to the importing agent (i.e. the marketing authorization holder in the importing country), but they must be made available at the request of – or in the course of any inspection made on behalf of – the competent authority.

Note: the following are examples of statements and certificates issued in connection with the Scheme. These are not considered to be part of the Scheme:

- ***Statement of marketing authorization status of pharmaceutical product(s)*** – attests only that a marketing authorization has been issued for a specified product, or products, for use in the certifying country or within the jurisdiction of the certifying regional authority. It is intended for use by importing agents when considering bids made in response to an international tender, in which case it should be requested by the agent as a condition of bidding. It is intended only to facilitate the screening and preparation of information.
- ***Batch (lot) release certificate*** (*22*, *23*) – issued by the competent authority or competent national laboratory in the certifying country or regional authority, and it refers to the results of a batch or several batches which comply with established specifications and provisions to assure the quality, safety and efficacy (QSE) of the concerned vaccines and vaccine's individual components, as well as with WHO's good manufacturing practices (GMP) for pharmaceutical products and biological products.

6. Issuing a certificate

6.1 The certifying authority is responsible for assuring the authenticity of the certified data. Certificates should not bear the WHO logo, but a statement should always be included to confirm that the document is issued in the format recommended by WHO.

6.2 When manufacture takes place in a country other than that from which the CPP is issued, an attestation relevant to compliance of the manufacture with GMP should still be provided on the basis of inspections undertaken for registration purposes by the same authority or by another authority.

6.3 When the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy, before attesting compliance with GMP, that the applicant:

(a) applies identical GMP standards to the production of all batches of pharmaceutical products manufactured within the site, including those destined exclusively for export; and

(b) consents, in the event of identification of a quality defect consistent with the criteria set out in section 5.1, to relevant inspection reports being released, in confidence and where possible, to the requesting authority, should the latter so require.

6.4 When the applicant is not the manufacturer of the finished dosage form, the certifying authority should similarly satisfy – in so far as it has the authority to inspect the records and relevant activities of the applicant – that it has the applicant's consent to release relevant reports on the same basis, as described in section 4.3 (b) above.

6.5 Whenever a product is purchased through an intermediary, or when more than one set of premises has been involved in the manufacture and packaging of a product, the certifying authority should consider whether or not it has received sufficient information to satisfy that those aspects of the manufacture of the product have been undertaken in compliance with GMP as recommended by WHO.

6.6 The certifying authority should officially stamp and date any certificates issued or certify using a secure electronic system/electronic certificate (e-certificate). Every effort should be made to ensure that certificates and all annexed documentation are consistent with the version of the marketing authorization operative on the date of issue. Nevertheless, requesting authorities are discouraged to introduce legalization procedures or any form of authentication procedures such as notarization, embassy legalization and apostillation that may cause the undue delay of certificates.

6.7 To avert any potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous, and to enable the certifying authority to maintain comprehensive records of countries to which certificates have been issued, each certificate should identify the requesting authority and be issued in such a way that the authenticity of the certificate can be verified using appropriate tools, such as, for example, certification and validation using a secure electronic system.

If requested, an identical copy, clearly marked as a duplicate, may be forwarded by the certifying authority without any undue delay, ideally within 20 working days.

6.8 The certifying authority should establish a standard time frame for the issuance of certificates, ideally within 30 working days. It should endeavor to issue a certificate within this period, as soon as the applicant submits sufficient documents, as requested in section 3.7.

7. Notifying and investigating a quality defect

7.1 Each certifying authority undertakes to investigate any quality defect reported in a product exported in accordance with the provisions of the Scheme, on the understanding that:

- the complaint is transmitted, together with the relevant facts, through the requesting authority;
- the complaint is considered to be of a serious nature in terms of risk by the latter authority; and
- the defect, if it appeared after the delivery of the product into the importing country, is not attributable to local climatic or storage conditions.

7.2 In case of doubt, a participating national or regional authority may request WHO to assist in identifying an independent quality control laboratory to carry out tests for the purposes of quality control.

7.3 Each certifying authority undertakes to inform WHO and, when possible, all national and regional competent authorities of any serious hazard newly associated with a product exported under the provisions of the Scheme or of any criminal abuse of the Scheme, or publish the information on the website about the product. In the case of substandard or falsified pharmaceutical products, the WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products, should be used to send the notification to WHO (*24*). Upon receipt of such notification, WHO will inform the competent authority as appropriate and/or issue a WHO Medical Product Alert (*25*).

7.4 WHO stands prepared to offer advice should difficulty arise in implementing any aspect of the Scheme or in resolving a complaint, but it cannot be a party to any resulting litigation or arbitration.

References

1. World Health Assembly resolution WHA22.50 (1969).
2. World Health Assembly resolution WHA28.65 (1975).
3. World Health Assembly resolution WHA41.18 (1988).

4. World Health Assembly resolution WHA45.29 (1992).
5. World Health Assembly resolution WHA50.3 (1997).
6. Forty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva (WHO Technical Report Series, No. 948; 2008 (https://www.who.int/medicines/publications/pharmprep/OMS_TRS_948.pdf, accessed 2 February, 2021).
7. Proposal for improvement of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (working document QAS/07.240).
8. Draft report to the Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations. Recommendations for improvement of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce (working document QAS/08.279) (2008).
9. Forty-third WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva (WHO Technical Report Series, No. 953 {2009}, untitled (who.int), accessed 2 February 2021).
10. WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce: Question and Answers (Q&A) (QAS/10.374, 2010).
11. WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce: questions and answers (Q&A) (WHO Drug Information, Vol. 30, No. 3, 2016, WHO | WHO Drug Information, accessed 2 February 2021).
12. Fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 1010 {2018}, WHO | WHO Expert Committee on Specifications for Pharmaceutical Preparations, accessed 2 February 2021).
13. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems https://www.who.int/medicines/regulation/benchmarking_tool/en/ Link accessed 23/10/2020.
14. Concept note: A framework for evaluating and publicly designating regulatory authorities as WHO-listed authorities (QAS/19.808), https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/qas19-808-who-listed-authorities.pdf?sfvrsn=e5b350f3_2 Link accessed 23/10/2020
15. Quality control of drugs. In: Twenty-second World Health Assembly, Boston, Massachusetts, 8-25 July 1969. Part 1: Resolutions and decisions, annexes. Geneva, World Health Organization; 1969:99-105 (Official Records of the World Health Organization, No. 176).
16. WHO good manufacturing practices: Health product and policy standards. Geneva: World Health Organization (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/gmp, accessed 6 February, 2021).
17. WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: Twenty-eighth World Health Assembly, Geneva, 13-30 May 1975. Part 1: Resolutions and decisions, annexes. Geneva, World Health Organization; 1975:94-95 (Official Records of the World Health Organization, No. 226).
18. Resolution WHA41.18 WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: Forty-first World Health Assembly, Geneva, 2-13 May 1988. Resolutions and decisions, annexes. Geneva, World Health Organization; 1988:53-55 (WHA41/1988/REC/1).
19. Resolution WHA45.29. Proposed guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. In: Forty-fifth World Health Assembly, Geneva, 4-14 May 1992. Resolutions and decisions, annexes. Geneva, World Health Organization; 1992:155-165 (WHA41/1992/REC/1).

20. Resolution WHA50.3 Guidelines for implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce. In: Forty-fifth World Health Assembly, Geneva, 5-14 May 1997. Resolutions and decisions, annexes. Geneva, World Health Organization; 1997:2-3 (WHA50/1997/REC/1).

21. WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-eighth Report. Geneva: World Health Organization: 2004: Annex 3 (WHO Technical Report Series, No. 917), ECS cover (7.4mm) (who.int), accessed 2 February 2021).

22. Guidelines for independent lot release of vaccines by regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 978,).

23. Model Certificate proposed by the WHO National Control Laboratory Network for Biologicals and published in its second meeting report, 2018: (https://www.who.int/immunization_standards/vaccine_quality/Report_WHO-NNB2018.pdf?ua=1), accessed 2 February 2021).

24. WHO Global Surveillance and Monitoring System (https://www.who.int/medicines/regulation/ssffc/surveillance/en/, accessed 2 February 2021).).

25. WHO Medical Product Alerts (https://www.who.int/medicines/publications/drugalerts/en/, accessed 2 February 2021).).

Appendix 1

Model certificate of a pharmaceutical product

Certificate of a pharmaceutical product

This certificate conforms to the format recommended by the World Health Organization (WHO). It establishes the status of the pharmaceutical product and of the applicant for the certificate by the national certifying authority in the country or within the jurisdiction of the regional certifying authority. It is for a single product only since the manufacturing arrangements and approved information for different dosage forms and different strengths can vary. (*General instructions and explanatory notes are attached.*)

No. of certificate: _____

Certifying country or regional certifying authority: _____

Requesting country(countries) or regional authority(authorities):

_____

1. Basic information

1.1. Name: (International Nonproprietary Name (INN)/generic/chemical name); brand name of the pharmaceutical product as it is declared in the marketing authorization certificate and used within the territory of the certifying authority and, if possible, the brand name for the foreign country as declared by the requester, (if different); and, the dosage form of the finished pharmaceutical product (FPP): _____

_____

_____

_____

_____

1.2. Composition: active pharmaceutical ingredient name(s) using if possible, INNs or national nonproprietary names,. Unit formulation (complete quantitative composition including all excipients);[1]: _____

_____

_____

_____

_____

1.3. Is this product authorized by the certifying authority to be marketed in the certifying country or within the jurisdiction of the certifying regional authority? Yes/No (*key in as appropriate*).

1.3.1 Are there restrictions of the sale, distribution or administration of the product specified in the marketing authorization? Yes/No (k*ey in as appropriate*). See attached information if Yes.

1.4. Is this product actually on the market in the certifying country or within the jurisdiction of the certifying regional authority? Yes/No/Unknown (*key in as appropriate*).

Sections 2A and 2B below are mutually exclusive, therefore:

- If the answer to 1.3 above is yes, continue with section 2A and omit section 2B.
- If the answer to 1.3 above is no, omit section 2A and continue with section 2B

2. Information on marketing authorization

2.A. Product that is authorized for marketing by the certifying authority.

2.A.1. Number of marketing authorization and date of issue. (*Indicate, when applicable, if the marketing authorization is provisional and the marketing authorization pathway, e.g. abridged, etc*): _____

_____

2.A.2 Marketing authorization holder (name and address): _____

_____

_____

_____

2.A.3. Status of marketing authorization holder (*one of the options of 3.1, if manufacturer, or specify the status as importer or any other*):

_____

2.A.4. Is a summary basis for approval appended? Yes/No (*key in as appropriate*). See attached information if answer is Yes.

2.A.5. Is the attached officially approved product information complete and consistent with the marketing authorization (*such as the Summary of Product Characteristics – SPC- or similar*)? Yes/No/Not provided (*key in as appropriate*). See attached information if answer is Yes.

2.A.6. Name and address of applicant for the certificate as provided by the marketing authorization holder, if different: _____

_____

2.A.7. Web-link to the product marketing authorization information (if available) _____

_____

2.B. Product that is not authorized for marketing by the certifying authority.

2.B.1. Applicant for certificate (name and address): _____

_____

_____

_____

2.B.2. Why is marketing authorization lacking?
Not required/Not requested/Under consideration/Refused/ Withdrawal for commercial reasons/Withdrawal for sanitary reasons (*key in as appropriate*)

2.B.3. Reason provided by the applicant for not requesting registration.

(a) The product has been developed exclusively for the treatment of conditions (e.g. tropical diseases – not endemic in the exporting country): _____

_____

_____

(b) The product has been reformulated - please specify: _____

_____

_____

(c) Any other reason, please specify: _____

_____

_____

3. Information on manufacturing and inspections

3.1. List of name and address of the manufacturing site(s) and activities:

a) manufacturing of all steps of the finished pharmaceutical product (FPP);

b) manufacturing the bulk finished product;

c) manufacturing of solvent and diluents;
d) quality control of the FPP;
e) batch release of the FPP;
f) primary packaging of the dosage form;
g) secondary packaging of the product;
h) other(s) (specify and list in new arrows).

Name of manufacturing site	Address	Activity

3.2. Does the certifying authority arrange for periodic inspection of the manufacturing site in which the of the FPP is produced? Yes/No (*key in as appropriate*). If not, proceed to question 4.

3.3. Periodicity of routine inspections: _____

3.4. Has the manufacturer of the dosage form of the FPP been inspected? Yes/No (*key in as appropriate*). If Yes, when feasible, insert date of inspection(s) (*dd/mm/yyyy*).

3.5. Do the facilities and operations of the manufacturer of the FPP conform to good manufacturing practices (GMP) as recommended by WHO?[2] Yes/No (*key in as appropriate*).

3.6. It is recommended that for products approved, but not manufactured in the country of the certifying authority, the source of information that assures the GMP compliance of the manufacturer(es) is declared.

4. Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product? Yes/No (*key in as appropriate*)[3]. If the answer is No, please explain: _____

_____

_____

_____

Address of certifying authority: _____

_____

_____

Telephone number: _____ Website: _____
Email address: _____
Name and job title of authorized person: _____

_____

Validity of the certificate[4] (optional): _____
Signature: _____
Stamp and date (*electronic whenever possible*): _____

_____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

1 Details of quantitative composition are preferred but their provision is subject to the agreement of the marketing authorization holder.

2 The requirements for good practices in the manufacture and quality control of pharmaceutical products referred to in the certificate, are those included in the Thirty-second report of the Expert Committee on Specifications for Pharmaceutical Preparations, WHO Technical Report Series, No. 986, 2014, Annex 2 (*WHO Good manufacturing practices for pharmaceutical products: main principles*). Recommendations specifically applicable to biological products have been formulated by the WHO Expert Committee on Biological Standardization (*WHO Good manufacturing Practices for biological products*, WHO Technical Report Series, No. 996, 2016, Annex 3).

3 It is of particular importance when contractors are involved in the manufacture of the product. The applicant should supply the certifying authority with information in order to identify the contracting parties responsible for each stage of manufacture of the finished dosage form and the extent and nature of any controls exercised over each of these parties.

4 A period of validity can be provided by the authority on the certificate.

Appendix 2

Model batch certificate of pharmaceutical products

Manufacturers/official[1] batch certificate of a pharmaceutical product

This certificate conforms to the format recommended by the World Health Organization (WHO) (*general instructions and explanatory notes are attached*).

1. No. of certificate: _____

2. Importing (requesting) authority: _____

3. Name: (International Nonproprietary Name (INN)/generic/chemical name); brand name of the pharmaceutical product as it is declared in the marketing authorization certificate and, if possible, brand name for the foreign country, if different. _____

   _____

   _____

   3.1. Dosage form: _____

   3.2. Composition: Active pharmaceutical ingredient name(s) using, if possible, International Nonproprietary Names (INNs) or national nonproprietary names. Unit formulation (complete quantitative composition including all excipients): _____

   _____

   _____

   3.2.1 Is the composition of the product identical to that registered in the country of export? *Yes/No/Not applicable* (*key in as appropriate*)[2] _____

   If No: please attach the formula (including excipients) of both products.

4. Marketing authorization holder[3] (name and address): _____

   _____

   _____

   4.1 Marketing authorization number[3]: _____

   4.2 Date of issue[3]: _____

   4.3 Marketing authorization issued by[3]: _____

4.4 Certificate of a pharmaceutical product (CPP) number[3,4]: _____

_____

5. Pharmaceutical product information:

5.1 Batch number: _____
5.2 Date of manufacture: _____
5.3 Shelf life (years): _____
5.4 Contents of container: _____
5.5 Nature of primary container: _____
5.6 Nature of secondary container/wrapping: _____
5.7 Specific storage conditions: _____
5.8 Temperature range: _____

6. Quality analysis: _____

_____

_____

6.1 What specifications apply to this dosage form? Either specify the pharmacopoeia or append company specifications.[5] _____

_____

6.1.1 In the case of a product registered by the certifying country or regional authority, have these company specifications[5] been accepted by the competent authority? Yes/No (*key in as appropriate*) _____

6.2 Does the batch comply with all parts of the above specifications? Yes/No (*key in as appropriate*) _____

6.3 Append certificate of analysis. Identify and explain any discrepancies from specifications.

It is hereby certified that the above declarations are correct and that the results of the analyses and assays on which they are based will be provided on request to the competent authorities in both the importing and exporting countries.

Name and address of authorized person: _____

_____

_____

Validity of the certificate[6]: _____

Telephone number: _____ Website: _____

Email address: _____

Signature of authorized person: _____

Stamp and date (*electronic whenever possible*): _____

General instructions

Please refer to the guidelines for full instructions on how to complete this form and for information on the implementation of the Scheme.

Additional sheets should be appended, as necessary, to accommodate remarks and explanations.

Explanatory notes

The certification of individual batches of a pharmaceutical product is only undertaken on an exceptional basis by the competent authority. Even then, it is rarely applied other than to biological products, such as vaccines, blood and plasma derivatives. For other products, the responsibility for any requirement to provide batch certificates rests with the marketing authorization holder in the certifying country or within the jurisdiction of the certifying regional authority. The responsibility to forward certificates to the competent authority in the importing country is most conveniently assigned to the importing agent.

Any inquiries or complaints regarding a batch certificate should always be addressed to the certifying competent authority. A copy should also be sent to the marketing authorization holder.

[1] Strike out whichever does not apply.

[2] "Not applicable" means that the product is not registered in the country of export.

[3] All items under 4 refer to the marketing authorization or the certificate of a pharmaceutical product (CPP) issued in the certifying country or within the jurisdiction of the certifying regional authority.

[4] This refers to the CPP as recommended by WHO.

[5] For each of the parameters to be measured, specifications give the values that have been accepted for batch release at the time of product registration.

[6] The validity of the certificate should not be confused with the expiry period of the batch/lot.

Appendix 3

Glossary

In order to facilitate understanding, this glossary explains terms in the guidelines and/or refers to relevant sections. It is considered as supplementary information and not as being a formal part of the World Health Organization (WHO) Certification Scheme on the quality of pharmaceutical products moving in international commerce (hereinafter referred to as the "Scheme").

abuse of Scheme. Actions addressed to the falsification of the certificates of the Scheme, its traceability, to issue them by non-authorized authorities or individuals, and any other activity against the authenticity of the certificates.

active pharmaceutical ingredient (API). Any substance or mixture of substances intended to be used in the manufacture of a finished pharmaceutical product (FPP) and that, when used in the production of a pharmaceutical product, becomes an active ingredient of the FPP. 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.

applicant. The party applying for a certificate of a pharmaceutical product (CPP). This is normally the agent responsible for importing pharmaceutical products, the marketing authorization holder or other commercially-interested party. In all instances, having regard to the commercial confidentiality of certain data, the certifying authority must obtain permission to release these data from the marketing authorization holder or, in the absence of a marketing authorization holder, from the manufacturer.

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

batch certificate (synonym: lot certificate). A document containing information, as set out in Appendix 2 of the guidelines for use, will normally be issued for

each batch by the manufacturer. Furthermore, exceptionally, a batch certificate may be validated or issued by the competent authority, particularly for vaccines, sera and other biological products. The batch certificate travels with every major consignment as a vital instrument in the procurement of medicines. The provision of a batch certificate is usually a mandatory element in tender and procurement documents.

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

bulk product. Any product that has completed all processing stages up to, but not including, final packaging.

certificate of a pharmaceutical product (CPP). A document containing the information as set out in Appendix 1 of the guidelines that is validated and issued for a specific product by the competent authority of the issuing country or regional authority and intended for use by the competent authority in the importing country/region or, in the absence of such an authority, by the procurement agency.

certifying authority. This is the competent authority in the Member State and regional authority that issues certificates. It shall ensure that it possesses the capacities listed in section 2.2 of the guidelines.

charges for CPPs. Charges levied upon applicants for the issue of a CPP to be paid to the certifying authority due to the significant administrative load imposed to these authorities during the service of preparation of certificates.

competent authority. This is the national or regional authority, as identified in the formal notification to the WHO Director-General, in which each Member State or regional authority informs WHO of its intention to participate in the Scheme. The competent authority can issue or receive certificates. The extent of participation should be indicated in the notification to the WHO Director-General as stipulated in section 2.3 of the guidelines. WHO makes available a continuously updated list of addresses of competent authorities and the specific conditions for participation (*see section 2.5 of the guideline*).

dosage form (synonym: pharmaceutical form). The form of the completed pharmaceutical product (e.g. tablet, capsule, elixir, suppository).

expiry date. The date given on the individual container (usually found on the label) of a pharmaceutical 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 pharmaceutical product. A pharmaceutical product that deliberately or fraudulently misrepresents their identity, composition or source. Any consideration related to intellectual property rights does not fall within this definition. Such deliberate or fraudulent misrepresentation refers to any substitution, adulteration, reproduction of an authorized pharmaceutical product or the manufacture of a pharmaceutical 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 pharmaceutical product.
>
> "Composition" shall refer to any ingredient or component of the pharmaceutical product in accordance with applicable specifications authorized/recognized by a national or regional regulatory authority (NRRA).
>
> "Source" shall refer to the identification, name and address of the marketing authorization holder, manufacturer, importer, exporter, distributor or retailer, as applicable.
>
> A "pharmaceutical product" should not be considered as falsified solely on the grounds that they are unauthorized for marketing in any given country.

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.

good manufacturing practices (GMP). That part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

importer. An individual or company or similar legal entity importing or seeking to import a medical product. A "licensed" or "registered" importer is one who has been granted a licence for such purpose.

importing agents, guidelines for. Guidelines on import procedures for pharmaceutical products issued for certifying authorities to all agents responsible for importing pharmaceutical products for human and/or veterinary use that operate under its jurisdiction, including those responsible for public sector purchases, to explain the contribution of certification to the medicine regulatory process and the circumstances in which each of the three types of documents will be required.

intermediaries. Intermediaries in the purchasing of pharmaceutical products for human use. Within the scope of the Scheme, they are responsible for supplying sufficient information to the national or regional certifying authorities to satisfy that those aspects of the manufacture of the product, for which the applicant is not directly responsible, have been undertaken in compliance with good manufacturing practice (GMP) as recommended by WHO.

international nonproprietary name (INN). The shortened scientific name based on the active ingredient. WHO is responsible for assigning INNs to pharmaceutical substances.

manufacture. All operations of the purchase of materials and products, production, quality control, release, storage, distribution of pharmaceutical products and related controls.

manufacturer. A company that carries out operations such as the production, packaging, repackaging, labelling and relabelling of the finished pharmaceutical product and the issuing of the certification.

marketing authorization. A legal document issued by the competent medicines regulatory authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy 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 (INNs) or national generic names where they exist), the shelf life and storage conditions and packaging characteristics. 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". Marketing authorization may occasionally also be referred to as a "licence" or "product licence".

marketing authorization holder. An individual or a corporate entity being in possession of a marketing authorization of a pharmaceutical product.

medicines regulatory authority. A national or regional body that administers the full spectrum of medicine regulatory activities, including at least all of the following functions in conformity with national or regional medicine legislation:

- the marketing authorization of new products and variations of existing products;
- quality control laboratory testing;
- the monitoring of adverse drug reactions;
- the provision of information on medicines and the promotion of rational use of medicines;
- good manufacturing practice (GMP) inspections and licensing of manufacturers, wholesalers and distribution channels;
- enforcement operations; and
- the monitoring of drug utilization.

notarization, embassy legalization or apostillation. Processes of authentication or legalization of certificates addressed to avert the potential abuse of the Scheme, to frustrate attempts at falsification, to render routine authentication of certificates by an independent authority superfluous, and to enable the certifying authority to maintain comprehensive records of countries to which specific products have been exported. In addition, this is also for ensuring that certificates and all annexed documentation are consistent with the version of the marketing authorization operative on the date of issue. It is considered enough for that goal that the complete identification of the requesting authority, and the official seal of the certifying authority (or to certify using a secure electronic system/electronic certificate) be stamped on each page. These traditional legal methods are highly discouraged in the context of the Scheme because they have caused undue delays and have not helped to afford the desired objectives.

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 information. This is the approved product information referred to in section 3.7 of the guidelines and item 2.A.4 of the product certificate. It normally consists of information for health professionals and the public (patient information leaflets) as approved by the related medicines regulatory authority and, when available, a data sheet or a summary of product characteristics approved by the medicines regulatory authority.

production. All operations involved in the preparation of a pharmaceutical product, from receipt of materials through processing, packaging and repackaging, labelling and relabelling, to completion of the finished product.

registration (synonym: marketing authorization). ***See marketing authorization.*** As a process, it is any statutory system of approval required at national or regional level as a precondition for introducing a pharmaceutical product onto the market. The result of the process could be a certificate of registration or certificate of marketing authorization.

regional authority. A group of countries in the same geographical region to achieve an integrated marketing authorization system. A regional authority that is willing to participate in the Scheme as a certificating member needs to possess a legal authority stipulated in section 2.2 by itself or through its legal framework.

reliance. An act whereby a regulatory authority in one jurisdiction may take into account or give significant weight to work performed by another regulator, or other trusted institution, in reaching its own decision.

requesting authority. This is the competent authority in the Member State and regional authority that requests certificates.

specifications. A list of tests, references to analytical procedures and appropriate acceptance criteria that are numerical limits, ranges or other criteria for the test described. It establishes the set of criteria to which a material should conform in order to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

substandard pharmaceutical product. Also called "out of specification", these are authorized pharmaceutical products that fail to meet either their quality standards or their specifications, or both. When the authorized manufacturer deliberately fails to meet these quality standards or specifications due to the misrepresentation of identity, composition or source, then the pharmaceutical product should be considered "falsified".

summary basis of approval. This refers to the document prepared by some medicines regulatory authorities that summarizes the technical basis on which the product has been licensed (*see section 4.6 of the guidelines and Explanatory note 3 of the product certificate contained in Appendix 1*).

summary product characteristics (SPC). Product information as approved by the medicines regulatory authority. The SPC serves as the basis for production

of information for health personnel as well as for consumer information on labels and leaflets of medicinal products and for control of advertising (*see also product information*).

References for Appendix 3

1. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva, World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
2. WHO good storage and distribution practices for medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report. Geneva, World Health Organization; 2020: Annex 7 (WHO Technical Report Series, No. 1025).
3. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-seventh report. Geneva, World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981).
4. WHO good manufacturing practices for pharmaceutical products: main principles. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva, World Health Organization; 2014: Annex 2 (WHO Technical Report Series, No. 986).
5. WHO model quality assurance system for procurement agencies. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-eighth report. Geneva, World Health Organization; 2014: Annex 3 (WHO Technical Report Series, No. 986).
6. Resolution WHA70. WHO Member States mechanism on substandard and/spurious/falsely-labelled/ falsified/counterfeit (SSFFC) medical products, working definitions. In: Seventieth World Health Assembly, Geneva, 22-31 May 2017. World Health Organization; 2017: Annex 12 (WHA70/2017/REC/1).

Appendix 4

(Draft) model notification to the Director-General of the World Health Organization

*[**Note** This Annex 4 is not a part of the "*Guidelines on the implementation of the WHO Certification Scheme on the quality of pharmaceutical products moving in International commerce*"].*

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) would like to inform the Director-General of the World Health Organization (WHO) that _____ (*name of country or regional authority*) would like to participate/continue to participate in the *WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce* (referred to henceforth as the " Scheme") as a:

- ☐ Certifying member
- ☐ Requesting member
- ☐ Certifying member and requesting member (*choose only one*).

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) hereby confirms that the competent authority(ies) mentioned in the Attachment to this Annex 2 is(are) the legally established authority(-ies) to regulate/control pharmaceutical products.

(Only for certifying members)
In addition, we hereby declare that our certifying authority(-ies) in the Attachment possess(es):

- an effective marketing authorization system for pharmaceutical products, including the responsible manufacturers and licensing of distributors;
- Good manufacturing practices (GMP) requirements, consistent with those recommended by WHO in accordance with its current publication, to which all manufacturers of finished pharmaceutical products are required to conform;

- effective controls to monitor the quality of pharmaceutical products registered or manufactured within its country or region, including access to an independent quality control laboratory;
- a pharmaceuticals inspectorate, operating as an arm of the national or regional medicines regulatory authority, and having the technical competence, experience and resources to assess whether or not GMP and other controls are being effectively implemented, and the legal power to conduct or to coordinate the appropriate investigations in order to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;
- an efficient surveillance system, administrative capacity and good regulatory practices compliance to effectively issue the required certificates; to detect and institute inquiries in the case of complaint and to expeditiously notify WHO and, when possible, the competent authority in the Member State or region known to have imported a specific product; or publish the information on the website about the product that is associated with a potentially serious quality defect or other hazard in a timely manner.

The Ministry of Health of the Government of _____ (*name of country*) / _____ (*name of regional authority*) would once more like to express its gratitude to the World Health Organization for this opportunity to participate/continue to participate in the Scheme.

We also confirm that any change of information in the Attachment will be promptly communicated to the WHO Secretariat.

Signature		Date	
Name and title			

[STAMP]

Attachment

Information on certifying/requesting authority(-ies)

☐ Certifying authority ☐ Requesting authority ☐ Certifying and requesting authority *(choose only one)*	
Name of the authority	
Address of the authority	
Telephone number	
Email address	
Website address	
Reservation as per section 2.3 of the Scheme for posting on the WHO website (if any)	
Other remarks (*if any*)	

(Add tables as necessary)

Annex 10

Good reliance practices in the regulation of medical products: high level principles and considerations

Background

WHO supports reliance on the work of other regulators as a general principle in order to make the best use of available resources and expertise. This principle allows leveraging the output of others whenever possible while placing a greater focus at national level on value-added regulatory activities that cannot be undertaken by other authorities, such as, but not limited to: vigilance, market surveillance, and oversight of local manufacturing and distribution. Reliance facilitates timely access to safe, effective, quality-assured medical products (see section 3. Scope) and can support regulatory preparedness and response, particularly during public health emergencies.

Good reliance practices (GRelP) are anchored in overall good regulatory practices (GRP) (*1*), which provide a means for establishing sound, affordable, effective regulation of medical products as an important part of health system strengthening. If implemented effectively, GRP can result in consistent regulatory processes, sound regulatory decision-making, increased efficiency of regulatory systems and better public health outcomes. NRAs are encouraged to adopt GRP to ensure that they are using the most efficient regulatory processes possible.

WHO is establishing and implementing a framework for evaluating regulatory authorities and designating those that meet the requirements as "WHO-listed authorities" (WLA) (*4*). Using the WHO Global Benchmarking Tool (*5*) and performance evaluation, WHO will assess the maturity and performance of a regulatory authority to determine whether it meets the requirements of a WLA and thereby provide a globally recognized, evidence-based, transparent system that can be used by NRAs as a basis for selecting reference regulatory authorities to practise reliance. A list of reference regulatory authorities is available on the WHO website (*6*).

In September 2019, WHO held a consultation to solicit input on the nature, structure and overall content of a document outlining GRelP. The meeting concluded that the concept note and recommendations on regulatory reliance principles of the Pan American Health Organization (PAHO) and the Pan American Network for Drug Regulatory Harmonization (*7*) should be used as a basis for the WHO document on GRelP. The high-level document would be complemented by a repository of case studies, practice guides and examples of practical application of GRelP.

Abbreviations to Annex 10 239

1. Introduction 240

2. Purpose 241

3. Scope 241

4. Glossary 242

5. Key concepts 245

5.1 Reliance versus recognition 245
5.2 Unilateral versus mutual reliance or recognition 246
5.3 Life cycle approach 246
5.4 Risk-based approach 246
5.5 Regional reliance mechanisms 247

6. Principles of good reliance practices 248

6.1 Universality 248
6.2 Sovereignty of decision-making 248
6.3 Transparency 248
6.4 Respect of national and regional legal bases 249
6.5 Consistency 249
6.6 Competence 250

7. Considerations 250

7.1 General considerations 250
7.2 Potential barriers 253
7.3 Enablers 254

8. Conclusions 256

References 257

Appendix 1 Examples of use of reliance 258

Abbreviations to Annex 10

AMRH	African Medicines Regulatory Harmonisation
APEC	Asia-Pacific Economic Cooperation
API	active pharmaceutical ingredient
ASEAN	Association of Southeast Asian Nations
CRP	collaborative registration procedure
GRP	good regulatory practices
ICH	International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMDRF	International Medical Device Regulators Forum
NRA	national regulatory authority; for the purpose of this document, the term also refers to regional regulatory authorities such as the European Medicines Agency
OECD	Organisation for Economic Co-operation and Development
PAHO	Pan American Health Organization
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co operation Scheme
ZAZIBONA	Zambia, Zimbabwe, Botswana and Namibia; initial participants in the Southern African Development Community collaborative procedure for joint assessment of medicines

1. Introduction

The United Nations Sustainable Development Goals and the drive for universal health coverage require that patients have access to quality-assured, effective and safe medical products. Strong regulatory systems for medical products remain a critical element of well-functioning health systems and important contributors to improving access and ultimately achieving universal health coverage.

Establishing and sustaining mature regulatory systems requires adequate resources, including skilled, capable human resources and a significant financial investment. The globalization of markets, the sophistication of health technologies, the rapid evolution of regulatory science and the increasing complexity of supply chains have shown regulators the importance of international cooperation in ensuring the safety, quality, efficacy or performance[1] of locally used products. In view of the extent and complexity of the regulatory oversight required to address these challenges, NRAs must consider enhanced, innovative, more effective forms of collaboration to make the best use of the available resources and expertise, avoid duplication and concentrate their regulatory efforts and resources where they are most needed.

Reliance represents a smarter, more efficient way of regulating medical products in the modern world. Countries are therefore encouraged to formulate and implement strategies to strengthen their regulatory systems consistent with GRP, including pursuing regulatory cooperation and convergence, as well as reliance. Reliance benefits patients and consumers, industry, national governments, the donor community and international development partners by facilitating and accelerating access to quality-assured, effective and safe medical products.

The use of reliance to enhance the efficiency of regulatory systems has a long history. The WHO Certification scheme on the quality of pharmaceutical products moving in international commerce (*8*), introduced in 1969, is a form of reliance, as it provides assurance to countries that participate in the Scheme of the quality of pharmaceutical products. The European Union introduced the "mutual recognition procedure" for marketing authorizations between its member states in 1995, and the outcomes of good manufacturing practices inspections have been shared for years in the context of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) (*9*) and mutual recognition agreements.

WHO investigated the use of reliance more recently in a survey conducted on behalf of the International Pharmaceutical Regulators Programme (*10*). The

[1] "Efficacy" applies to medicines and vaccines and "performance" to medical devices, including in-vitro diagnostics.

results showed that regulatory reliance is broadly accepted and widely practised with regard to medical products, especially among well resourced regulatory authorities. The responses also reflected an evolving situation, with varying experience and promise in the use of reliance-based approaches. While use of reliance may be an emerging trend in some regions, the commonly stated goals are to increase efficiency, help to strengthen regulatory systems and optimize the use of resources. The results and suggestions from the survey were taken into account in preparation of this document.

In view of the increasing prevalence and importance of reliance in the regulation of medical products, Member States have requested WHO to prepare practical guidance on the topic while ensuring that the approaches meet the intended objectives. This document and additional guidance that follow are intended to assist countries in implementing a sound, evidence-based, practical, effective approach to reliance.

2. Purpose

The purpose is to promote a more efficient approach to regulation, thereby improving access to quality-assured, effective and safe medical products. The document presents the overarching principles of regulatory reliance in the oversight of medical products and use of reliance to enhance the effectiveness and efficiency of regulatory oversight. It provides high-level guidance, definitions, key concepts and considerations to guide reliance mechanisms and activities, illustrative examples of reliance approaches and conclusions. It will be complemented by a "reliance toolbox", consisting of practice guides, case studies and a more comprehensive repository of examples.

3. Scope

The document covers reliance activities in the field of regulation of medical products (i.e. medicines, vaccines, blood and blood products and medical devices including in-vitro diagnostics), addressing all the regulatory functions in the full life cycle of a medical product, as defined in the Global Benchmarking Tool (*5*): registration and marketing authorization, vigilance, market surveillance and control, licensing establishments, regulatory inspection, laboratory testing, clinical trials oversight and NRA lot release. The document is intended for all NRAs, irrespective of their level of maturity or resources, and also for policy-makers, governments, industry, other developers of medical products and other relevant stakeholders.

The concept of reliance covers all types of medical products and regulatory activities. Reliance approaches should be given consideration in

particular for medical products for priority diseases for which there are unmet medical needs, medical products to be used in public health emergencies or during shortages and also for orphan and paediatric medical products.

4. Glossary

Definitions are essential to ensure a common understanding of concepts and clarity in interpreting guidance on reliance. In addition to the definitions provided below, reference is made to the WHO document on good regulatory practices (*1*), which includes definitions of harmonization, convergence and other relevant terms.

Abridged regulatory pathways. Regulatory procedures facilitated by reliance, whereby a regulatory decision is solely or partially based on application of reliance. This usually involves some work by the national regulatory authority (NRA) that is practising reliance (see section 5.4 Risk-based approach). It is expected that use of reliance in these pathways will save resources and time as compared with standard pathways, while ensuring that the standards of regulatory oversight are maintained.

Assessment. For the purpose of this document, this term covers any evaluation conducted for a regulatory function (e.g. evaluation of a clinical trial application or of an initial marketing authorization for a medical product or any subsequent post-authorization changes, evaluation of safety data, evaluation as part of an inspection).

Equivalence of regulatory systems. Implies strong similarity between two regulatory systems, as mutually established and documented through objective evidence. Equivalence can be established using criteria and approaches such as similarity of the regulatory framework and practices, adherence to the same international standards and guidelines, experience gained in use of assessments for regulatory decision making, joint activities and exchanges of staff. It is expected that equivalent regulatory systems will result in similar standards and levels of regulatory oversight or "control".

International standards and guidelines. For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant internationally recognized standards (e.g. International Organization for Standardization or pharmacopoeial standards) and guidelines (e.g. International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] or guidelines of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co operation Scheme [PIC/S]).

Mutual recognition agreement. According to a definition issued by the Organisation for Economic Co-operation and Development (OECD), a mutual recognition agreement is:

> a principle of international law whereby states party to mutual recognition agreements recognize and uphold legal decisions taken by competent authorities in another member state. Mutual recognition is a process which allows conformity assessments (of qualifications, product…) carried out in one country to be recognized in another country (*2*).

Recognition. Acceptance of the regulatory decision of another regulator or trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Reference regulatory authority. For the purpose of this document, a national or regional authority or a trusted institution such as WHO prequalification (WHO PQ) whose regulatory decisions and/or regulatory work products are relied upon by another regulatory authority to inform its own regulatory decisions.

Regional regulatory system. A system composed of individual regulatory authorities, or a regional body composed of individual regulatory authorities, operating under a common regulatory framework but not necessarily under a common legal framework. The common framework must at least ensure equivalence among the members in terms of regulatory requirements, practices and quality assurance policies. The system or regional body may have enforcement powers to ensure compliance with the common regulatory framework.

Reliance. The act whereby the regulatory authority in one jurisdiction takes into account and gives significant weight to assessments performed by another regulatory authority or trusted institution, or to any other authoritative information, in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

Sameness of product. For the purpose of this document, sameness of product means that two products have identical essential characteristics (i.e. the product being submitted to the relying authority and the product approved by the reference regulatory authority should be essentially the same). All relevant

aspects of drugs, medical devices and in vitro diagnostics, including those related to the quality of the product and its components, should be considered to confirm that the product is the same or sufficiently similar (e.g. same qualitative and quantitative composition, same strength, same pharmaceutical form, same intended use, same manufacturing process, same suppliers of active pharmaceutical ingredients, same quality of all excipients). Additionally, the results of supporting studies of safety, efficacy and quality, indications and conditions of use should be the same. The impact of potential, justified differences should be assessed by the manufacturer (for the purpose of this document, manufacturer also means marketing authorization holder) and the relying national regulatory authority (NRA) in determining the possibility of using foreign regulatory assessments or decisions.

Stringent regulatory authority. A regulatory authority which is: (a) a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), being the European Commission, the US Food and Drug Administration and the Ministry of Health, Labour and Welfare of Japan also represented by the Pharmaceuticals and Medical Devices Agency (as before 23 October 2015); or (b) an ICH observer, being the European Free Trade Association, as represented by Swissmedic, and Health Canada (as before 23 October 2015); or (c) a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement, including Australia, Iceland, Liechtenstein and Norway (as before 23 October 2015) (*3*).

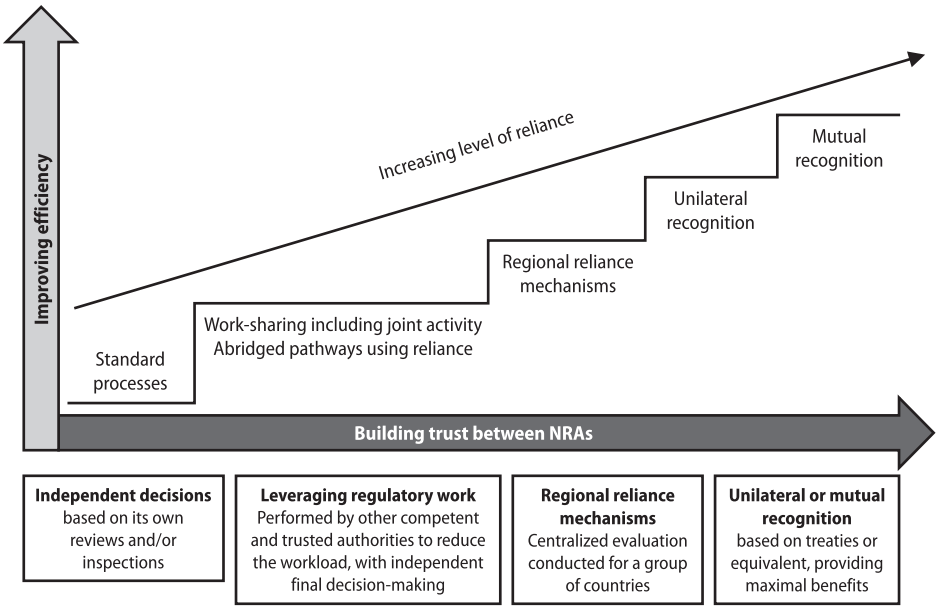
Work-sharing. A process by which NRAs of two or more jurisdictions share activities to accomplish a specific regulatory task. The opportunities for work-sharing include joint assessment of applications for authorization of clinical trials or marketing authorizations, joint inspections for good practices, joint post marketing surveillance of the quality and safety of medical products, joint development of technical guidelines or regulatory standards and collaboration on information platforms and technology. Work-sharing also entails exchange of information consistent with the provisions of existing agreements and compliant with each agency's or institution's legislative framework for sharing such information with other NRAs. A joint activity is a form of work-sharing whereby a regulatory task is conducted by two or more NRAs in collaboration in order to share their assessments, benefit from each other's expertise and discuss any shortcomings of the data evaluated. For example, a joint assessment is a procedure in which the same application is submitted simultaneously to two or more NRAs so that they conduct their evaluations in parallel and share their scientific assessments (e.g. the different modules for quality, nonclinical and clinical data can be assigned to different NRAs for review). The NRAs participating in a joint assessment can combine their lists of questions or

deficiencies to the manufacturer and base their respective independent regulatory decisions on the outcome of these assessments. Similarly, a joint inspection is one in which two or more NRAs share the activities and assessments performed during an inspection.

5. Key concepts

Fig. 1 illustrates some of the key concepts explained in the document, notably how NRAs can gain efficiency in regulatory operations and how to avoid duplication by using reliance approaches.

Fig. 1
Key concepts of reliance



5.1 Reliance versus recognition

Reliance may take many forms and be applied to varying degrees in recognizing or taking account of the assessments, decisions or other authoritative information of other authorities and institutions. Recognition may be seen as a special and more formalized approach to reliance, whereby one regulatory authority recognizes the decisions of another regulatory authority, system or institution, obviating additional regulatory assessment to reach its own decision. Recognition usually requires formal and binding legal provisions.

5.2 Unilateral versus mutual reliance or recognition

Reliance and recognition may be unilateral, for example, when a country chooses to rely on or formally recognize an assessment from another country unilaterally and without reciprocity. In other cases, mutual recognition may be based on binding mutual agreements or treaties negotiated at the level of governments. Such agreements take considerable time and resources to set up, as the regulatory systems involved must be mutually assessed and shown to be equivalent before agreement can be reached. A demonstration of the equivalence of regulatory systems is usually a prerequisite for mutual reliance or recognition. Work-sharing and joint activities are examples of mutual reliance.

5.3 Life cycle approach

The concept of reliance for regulation of medical products should be applied throughout the life cycle of medical products and in all regulatory functions (see 3. Scope). While reliance approaches are widely used for the initial authorization of medical products, they should also be used for vigilance and other post-authorization activities (e.g. post approval changes, inspections and lot release), in view of the substantial regulatory resources required for evaluating safety and post-approval changes during a product's life cycle. Review of post approval changes to a product that was approved by a different authority may present challenges. Assuring "sameness of product" (see 4. Glossary) is essential for the use of reliance. If an NRA has relied on another NRA's assessment for its initial approval, use of similar reliance measures for post approval changes and vigilance activities is beneficial, as long as the sameness of the product from the initial authorization is maintained. This also avoids the situation in which different changes are accepted in originating and in receiving countries over time.

5.4 Risk-based approach

Each NRA should define its own strategy for an appropriate risk-based approach to reliance, which includes factors such as the type and source of products evaluated, the level of resources and expertise available in the NRA, the public health needs and priorities of the country and opportunities for reliance. Using marketing authorization as an example, four different reliance based regulatory pathways and levels of reliance could be envisaged, with increasing degrees of assessment by the relying NRA:

- verification of sameness of the medical product to ensure that it is the same as that assessed by the reference regulatory authority (see section 7.1.4 Sameness of a product in different jurisdictions). Sameness should always be verified in any of the reliance approaches listed here.

- confirmation of the applicability of the assessment outcomes of another authority for regulatory decision making in the national context, for example, in terms of legal and regulatory settings, benefit–risk assessment, co-morbidities, unmet medical needs, risk management plans and any quality-related specificities such as climatic zones for product stability. In case of differences, such as in target population, epidemiology and other features of the disease, medicines used concomitantly and other factors that can substantially affect the benefit–risk profile of a medicine, as well as quality parameters, especially in relation to the stability under different climatic conditions, appropriate evidence should be provided by the manufacturer.
- abridged assessment of data on quality, safety and efficacy or performance, taking into account information in the assessment reports of the reference regulatory authority; and
- joint assessment or work-sharing between two or more regulatory authorities. This may take various forms, including a primary review by one authority followed by a joint assessment session to finalize the report and comments or distribution of the modules (quality, non-clinical and safety or efficacy) between the authorities.

Regardless of the approach, it is expected that the timelines will be shorter than the standard timelines and resources will be used more effectively when reliance is used. The reduction in timelines will depend on the level of reliance and any additional assessment required locally. It is important that the timeline established for reliance procedures should be sufficient for the relying authority to properly review the assessment of the reference authority and perform the necessary local assessments, including of local labelling, product sameness and the applicability of the data to the country.

Similar reliance-based regulatory pathways can be used for other regulatory functions, such as inspection, lot release or import testing.

5.5 Regional reliance mechanisms

In some regions, medical products can be assessed centrally in a regional regulatory system. In some regional reliance mechanisms, the regional decision is binding on the member states (e.g. European Union). In others, regional decisions are recommendations that member states take into consideration when making national regulatory decisions (e.g. the Southern African Development Community collaborative procedure ZAZIBONA [Zambia, Zimbabwe, Botswana and Namibia; initial participants in the Southern African Development Community collaborative procedure for joint assessment of medicines], the Gulf Health Council and the Caribbean Regulatory System).

6. Principles of good reliance practices

In developing a strategy on the use of reliance in regulatory functions and activities, an NRA should consider the needs and characteristics of the national health and regulatory systems. A decision to practise reliance should consider existing capacity, regulatory systems' needs, the availability of an authority on which the NRA can rely with confidence and how reliance could complement the capacity to increase efficiency and make optimal use of resources. Reliance is not a lesser form of regulatory oversight but rather a strategy for making the best use of the available resources in any setting. This would allow the allocation of resources to other regulatory functions, such as in-country vigilance and post authorization activities, thereby increasing the effectiveness of local regulatory oversight. In addition, reliance can result in more evidence-based, better-quality decisions.

The following principles are meant to complement and extend the basic principles of GRP. They are based on the principles presented in the concept note and recommendations on regulatory reliance principles of PAHO and the Pan American Network for Drug Regulatory Harmonization (*7*).

6.1 Universality

Reliance applies to all NRAs, irrespective of their levels of maturity or resources. Lack of resources or capacity are not the exclusive drivers for reliance. Different NRAs use reliance for different reasons. Some use it to increase or build in-house capacity when there is the requisite expertise but not enough to perform their regulatory work as efficiently as they would like. Others use reliance to gain expertise that they do not have locally. Reliance is relevant for all resource settings.

6.2 Sovereignty of decision-making

The decision to practise reliance and how best to do so rests with the national health regulatory authority. Reliance does not imply dependence; it is not an agency out-sourcing its decision-making authority or responsibility. In applying reliance in daily practice, NRAs maintain independence, sovereignty and accountability in regulatory decision-making.

6.3 Transparency

Transparency is a key enabler to adopting new, more efficient ways of conducting regulatory operations, both locally and internationally. NRAs should be transparent about the standards, processes and approaches they adopt in implementing reliance measures. The basis and rationale for relying on a specific entity should be disclosed and fully understood by all parties. NRAs should

engage with all stakeholders, including industry, to ensure the appropriateness and awareness of reliance processes.

Furthermore, NRAs should conduct transparent regulatory operations and decision-making, not only as a fundamental principle of GRP but also to build trust and maximize opportunities for cooperation and reliance as part of a shared regulatory community responsibility. Transparency measures should be encouraged through the publishing and sharing of regulatory information to facilitate information exchange among NRAs. NRAs that seek to act as reference agencies are encouraged to issue public assessment reports in a common language to document their regulatory decisions. Relying NRAs should use such reports as the primary source of information for assessments. If no public assessment reports are available or when additional information of a confidential nature is required, the manufacturer should provide an assessment report when available to them. If the relying NRA requests non public assessment reports from a reference agency, they may be provided with the consent of the manufacturer, if necessary.

6.4 Respect of national and regional legal bases

Reliance practices should be coherent with national and regional legal frameworks and policies on medical products, supported by clear mandates and regulations that ensure efficient implementation of reliance as part of government policy on good regulation. The reasons for adopting such legal frameworks should be the efficiency and capacity to be gained and not minimization of resources for regulatory functions. Use of reliance does not obviate the need for a capable local regulatory authority; on the contrary, it should be used to maintain and build local capacity for regulatory decision-making. When regulations do not make explicit provision for the application of reliance, it may be adopted through interpretation of existing regulations, if the legal framework does not explicitly preclude application of reliance approaches by the NRA. Reliance can be implemented through policy change, as long as it is broadly consistent with national legislation. If application of reliance is prohibited, revision of the legislation should be considered within a reasonable timeframe.

6.5 Consistency

Reliance on an assessment or decision from another authority should be established for specific, well-defined categories of products and processes. The scope of regulatory activities in which reliance may be practised should be clearly defined, and the practise of reliance should be transparent and predictable. Thus, reliance should be expected to be applied consistently for products and processes in the same categories.

6.6 Competence

Implementation of reliance approaches requires that NRAs have the necessary competence for critical decision-making. Introduction of the reliance approach usually requires the involvement of senior regulatory staff, managers and experts who are competent to make the best use of foreign information in the local context. NRAs should maintain the appropriate scientific expertise of their staff for activities in which they do not apply reliance, such as monitoring local adverse events, market surveillance and control, national labelling and product information activities and for oversight of locally manufactured products.

Equally, the authorities being relied upon should have and maintain competence and operate within a robust, transparent regulatory system based on international standards and guidelines, as well as GRP, and a well-functioning quality management system (*11*). Competence may be benchmarked through transparent processes for developing trust and building confidence in the reference authorities.

7. Considerations

A number of considerations can guide reliance approaches and facilitate their implementation. These include general aspects, barriers that NRAs may have to overcome and enablers for implementing reliance approaches. The non-exhaustive list of considerations below will be further elaborated in case studies, practice guides and the reliance repository.

Reliance is encouraged in any setting when supported by a common legal or regulatory framework in a regional regulatory system, by bilateral agreements, by mutual recognition agreements or on a purely voluntary, networking or ad-hoc basis. It is recommended that reliance be based on the original assessment. In some cases, however, it may be based on a decision made by reliance on another assessment.

7.1 General considerations

7.1.1 Reliance anchored in a national regulatory authority strategy

Application of reliance should have not only a legal basis that supports or at least does not preclude it (see section 6. Principles of good reliance practices) but should also be anchored in high-level national policy and the NRA strategy endorsed by senior management. This is necessary to provide a mandate for, direction to and expectations of NRA staff, to guide them in their daily work. The strategy should be detailed in procedures and integrated into processes to ensure the maximum benefits. It should include a sustainable funding model when implementing reliance, so that it does not negatively impact the financial sustainability and competence of the NRA. The strategy should be published

in order to make it accessible and understandable to external stakeholders. Implementation of reliance should be supported by training and periodic reviews to ensure that the standards are being maintained, to assess whether the objectives are being met and to revise it when warranted.

NRAs that practise reliance should establish and publish a list of reference regulatory authorities, with the criteria used in identifying them. They should decide and establish the criteria they will use for selecting reference authorities, such as application of international standards, long standing recognition in the international community, proximity and commonality of medical products. To qualify reference regulatory authorities or specific oversight of a regulatory function, an NRA may refer to an assessment by an independent organization (e.g. WHO benchmarking, WHO-listed authority, International Organization for Standardization accreditation, the Medical Device Single Audit Program, PIC/S).

WHO encourages NRAs to monitor and evaluate the impact of regulatory reliance, including its benefits, in their country and region and to share their experiences with other regulatory authorities. When possible, the impact should be measured specifically, and the NRA should establish the metrics they will use to measure the impact of using reliance in regulatory decision-making and the time for conducting the assessment. The metrics may include costs saved, efficiency in the number of products reaching the market or time to market, and redirection of scarce resources to areas of higher regulatory risk. NRAs should consider methods for sharing best practices and experience in establishing reliance arrangements in international forums for regulation of medical products to increase understanding of the opportunities and challenges of reliance, subject to agreement with the other party(s) involved and information disclosure requirements.

7.1.2 Cultural change

Use of reliance approaches means moving to a more innovative, effective way of working, based on trust and relying on the outputs of other NRAs. The benefits must be understood and supported at operational level, and the staff who are expected to implement reliance approaches must contribute to their development. This will require engagement, willingness, effective preparation, messaging and support from management and peers on the importance of reliance in better addressing workload pressures without minimizing the rigor of regulatory work or losing scientific or regulatory competence or capacity. Use of assessments and information from other trusted regulatory authorities can help build capacity and competence (e.g. through exposure to the reviews and decisions of the reference authority, networking, twinning, staff visits and exchanges). Furthermore, as effective use of such information in the local context requires skill, ability and experience, the skill set and competence necessary to practise reliance will have to be developed in the NRA workforce.

Senior management, reviewers, inspectors and other staff should build confidence and trust in the work done by other NRAs or trusted authorities. This will take time and require a change in the culture of the relying NRA. The experience of regulatory authorities and systems that already practise reliance should be leveraged to promote acceptance and avoid pitfalls. Trust should also be built with the public, health care professionals and the industry by assuring them that reliance offers more efficient regulatory oversight.

7.1.3 Flexibility in approach: "one size doesn't fit all"

In accordance with the principles outlined above, reliance strategies should be tailored to the needs of the national health and regulatory systems. NRAs may choose to rely on others in routine regulatory oversight and/or in special circumstances, such as a public health emergency. Reliance offers flexibility to NRAs. When adopting reliance, whatever the approach, the NRA should consider its capacity, establish clear goals and efficient processes and ensure that the standards and criteria are transparent and well established.

7.1.4 Investment of resources and time in implementing reliance

As stated above, reliance should increase the efficiency of a regulatory system in a country or region. Nevertheless, implementation of reliance approaches will first require investment of resources and time for activities such as legislative changes, preparation of guidance documents and approaches, pathways and processes, building confidence by preparing parallel or joint reviews supported by staff exchanges, training staff, dialogue with industry and other stakeholders and establishment of or access to information-sharing platforms, communication links and networks with other NRAs.

7.1.5 "Sameness" of a product in different jurisdictions

A critical aspect of the application of reliance is verification of the "sameness" of a medical product (see 4. Glossary and section 5.4 Risk-based approach) in different jurisdictions. Reliance can be practised only if the NRA that intends to use a foreign assessment as the basis for its own assessment and regulatory decision making has the assurance that the medical product being assessed is essentially the same as the one submitted to the reference NRA. The role of the manufacturer is essential to confirm the sameness of a product and to provide the same documentation to different NRAs, except for additional country-specific information submitted for review, such as product stability data according to the stability zone and the local product label. The manufacturer should confirm in the application that the product is the same and that the application contains essentially the same information, taking into consideration any potential national requirements. If the application is not submitted simultaneously to the

agencies, the manufacturer should highlight any new information about the product acquired since the application was submitted to the reference agency, with the corresponding assessment.

7.1.6 The role of industry

Industry plays a crucial role in successful use of reliance mechanisms by NRAs. While industry widely supports reliance as a concept and practice that can increase efficiency, it must have clear guidance on its application and see meaningful benefits. Industry support and stringent adherence to the factors that validate the reliance process are essential for filing applications in several countries or regions to ensure the sameness of products submitted to reference regulatory authorities and relying NRAs. They should share complete, unredacted information.

Review and discussion of pilot programs to quickly adapt and improve guidance will be key to benefit from key learnings and improve implementation. Collaboration and dialogue among all stakeholders participating in regulatory reliance activities will help to create and build trust, which is the foundation of regulatory reliance. Transparent publication of an NRA's reliance framework and strategies, including the metrics used and benefits achieved, will encourage industry to support and promote the reliance approach.

7.1.7 Reliance in a public health emergency

In case of a public health emergency, reliance approaches are even more essential and should be given more importance in order to accelerate access to the medical products required.

7.2 Potential barriers

7.2.1 Lack of political will

Lack of political will and government support can make it difficult for NRAs to implement or facilitate reliance in their daily practice, even if a legal basis is established that supports (or does not preclude) reliance and if NRAs support reliance as a strategy and approach.

7.2.2 Lack of accessible information and confidentiality of information

Lack of access to complete assessments of reference regulatory authorities can be a major barrier to effective reliance. Reference regulatory authorities should make their assessments and other regulatory information publicly available. Non-public regulatory reports might be available directly from the manufacturer when the company is able to access these reports from the reference regulatory authority. If this is not possible, the relying NRA should approach the reference

regulatory authority. In these cases, arrangements among NRAs on the exchange of confidential information would facilitate the reliance process.

Sensitive, non-public information in unredacted assessment or inspection reports can also be shared between regulatory authorities upon request. This may include confidential commercial information, trade secrets or personal information. In some circumstances, the sharing of such information may require the consent of the manufacturer. Sharing of personal information may also require consent from individuals in order to comply with data protection regulations. Given the sensitivity of such non-public information, NRAs may require that confidentiality agreements be signed that govern the exchange, management and disclosure of such information to ensure that the confidentiality of the information is protected by the relying NRA. Such information should always be exchanged through secure channels or on information-sharing platforms.

7.2.3 Other barriers

Additional potential barriers include issues such as lack of a common language, difficulties in or the cost of translation, differences in national regulatory requirements and evidentiary standards, lack of regulatory alignment of product risk classifications, inconsistent practices regarding modifications to medical devices (including in-vitro diagnostics), the lack of acceptance of foreign clinical data and real world evidence, the level of detail in regulatory reports, different levels of competence and, as previously noted, internal resistance and insufficient knowledge of the reference regulatory authority and how it operates. All such factors should be considered in developing appropriate reliance strategies, as will be further elucidated in the additional guidance documents to follow.

7.3 Enablers

7.3.1 Trust

Trust is a critical element, as reliance requires confidence that the regulatory outcome is based on strong regulatory processes and standards and is, thus, trustworthy. Consequently, initiatives to foster trust among regulatory authorities are essential. Trust develops with increasing familiarity and understanding of what is behind regulatory outputs. Confidence can be built throughout the organization by sharing information, including the standards applied to regulatory decisions, working together and learning each other's ways of working, which then leads to effective use of reliance in regulatory work. Trust can be built in phases, starting with exchange of assessment reports and moving to work-sharing or joint assessments. Regulatory authorities may consider initiating reliance processes with applications for medical products of lower risk.

In addition, industry and other stakeholders must trust regulatory authorities, for example, to respect the confidentiality of information.

7.3.2 Convergence and harmonization

Convergence and harmonization of requirements, standards and guidelines are important enablers of regulatory cooperation and reliance. The more similar requirements, standards and guidelines are, the greater the opportunity for collaboration and reliance. Use of the ICH Common Technical Document (CTD) and the electronic CTD (eCTD) as a common format for regulatory submissions around the globe is one example of how harmonization can facilitate and enable reliance.

Differences in standards and practices, however, do not prevent one authority from relying on another, particularly when the relying authority has limited capacity and expertise. The system on which an NRA relies should be at least equivalent to or superior to the standards it applies. As a matter of good practice, NRAs should rely on assessments or decisions from reference regulatory authorities that apply international standards and guidelines.

7.3.3 Information-sharing and dialogue among regulators

Information-sharing is an essential part of reliance, and NRAs are encouraged to share information and good practices with other NRAs. Increasing dialogue among regulators is seen in the growing number of international initiatives such as the International Pharmaceutical Regulators Programme and in networks for sharing regulatory information and work such as the Pan American Network for Drug Regulatory Harmonization, the Southeast Asia Regulatory Network, regulatory networks in the Regional Economic Communities under the African Medicines Regulatory Harmonisation (AMRH) Initiative and the Association of Southeast Asian Nations (ASEAN) Pharmaceutical Products Working Group, the International Coalition of Medicines Regulatory Authorities, the Caribbean Community and Common Market's (CARICOM) Caribbean Regulatory System, the Western Pacific Region Alliance of NRAs for Medical Products and others, which greatly facilitate reliance.

Scientific and technical events, such as the International Conference of Drug Regulatory Authorities, ICH and PIC/S, are platforms for disseminating regulatory information and for building knowledge and trust among NRAs.

7.3.4 Economic or legal integration

When there is economic or legal integration in a region or a group of countries, reliance is facilitated and strengthened by the existing mutual provisions. Examples are the Asia–Pacific Economic Cooperation (APEC), ASEAN, CARICOM, the European Union, the Eurasian Economic Union, the Gulf Cooperation Council,

the Pacific Alliance, the Regional Economic Communities in Africa and the Southern Common Market (MERCOSUR).

7.3.5 Engagement of stakeholders

All relevant stakeholders, including industry, health care professionals, policy-makers and the public, should be engaged and informed in order to increase their understanding and acceptance of reliance approaches and the clear benefits they present for all parties. Communication and engagement with stakeholders should be tailored to each target audience.

8. Conclusions

Reliance is being practised by a growing number of regulatory authorities as a means of improving the effectiveness and efficiency of regulation of medical products. It allows NRAs to make the best use of resources, build expertise and capacity, increase the quality of their regulatory decisions, reduce duplication of effort and, ultimately, promote timely access to safe, effectiveand quality assured medical products. Adoption of reliance measures whenever possible, in a well structured framework underpinned by national or regional policies and strategies, will allow regulators to focus their resources on activities that contribute to public health that cannot be undertaken by others.

Reliance represents a "smarter" form of regulatory oversight, based on constructive regional and international collaboration, that will facilitate and promote convergence and the use of common international standards and guidelines, resulting in more predictable, faster approval to improve access to quality-assured medical products for patients worldwide.

Reliance does not represent a less stringent form of regulatory oversight or outsourcing of regulatory mandates, nor does it compromise independence. On the contrary, a decision to "regulate through reliance" is the hallmark of a modern and efficient regulatory authority.

NRAs are encouraged to include reliance-related provisions as part of their flexible regulatory pathways, and reliance should be considered in all regulatory functions of the life cycle of a medical product, as appropriate.

The principles and considerations presented in this document should be considered in implementing regulatory reliance frameworks or strategies. Effective implementation of reliance will benefit not only NRAs but also patients, health care providers and industry.

While reliance may be viewed as particularly useful for low-resourced regulatory authorities, it is equally relevant for well-resourced NRAs. Reliance is an approach to be used by all NRAs and should therefore become an integral part of regulatory operations.

References

1. Good regulatory practices: guidelines for national regulatory authorities for medical products. Draft working document. Geneva: World Health Organization; 2016 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS16_686_rev_3_good_regulatory_practices_medical_products.pdf?ua=1, accessed 29 January 2021).
2. Definition of a mutual recognition agreement. Paris: Organization for Economic Co-operation and Development; 2020 (https://www.oecd.org/gov/regulatory-policy/irc6.htm, accessed 29 January 2021).
3. Definition of stringent regulatory authority. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-first report (WHO Technical Report Series, No. 1003). Geneva: World Health Organization; 2017:34–5 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1003/en/, accessed 29 January 2021).
4. Policy evaluating and publicly designating regulatory authorities as WHO-listed authorities. Draft working document. Geneva: World Health Organization; 2019 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS19_828_Rev1_Policy_on_WHO_Listed_Authorities.pdf, accessed 29 January 2021).
5. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems. Geneva: World Health Organization; 2020 (https://www.who.int/medicines/regulation/benchmarking_tool/en/, accessed 29 January 2021).
6. A framework for evaluating and publicly designating regulatory authorities as WHO-listed authority, Interim list of national regulatory authorities. Geneva: World Health Organization; 2020 (https://www.who.int/medicines/regulation/wla_introduction/en/, accessed 29 January 2021).
7. Pan American Health Organization, Pan American Network for Drug Regulatory Harmonization. Regulatory reliance principles: concept note and recommendations. Ninth Conference of the Pan American Network for Drug Regulatory Harmonization (PANDRH) (San Salvador, 24 to 26 October, 2018. Washington DC: Pan American Health Organization; 2019 (https://iris.paho.org/handle/10665.2/51549, accessed 29 January 2021).
8. The WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce. Geneva: World Health Organization; 2020 (https://www.who.int/teams/regulation-prequalification/pharmacovigilance/certification-scheme, accessed 29 January 2021).
9. History of PIC/S. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme; 2020 (https://picscheme.org/en/history, accessed 29 January 2021).
10. Outcome of WHO survey on reliance. International Pharmaceutical Regulators Programme; 2019 (http://www.iprp.global/news/outcome-who-survey-reliance, accessed 29 January 2021).
11. WHO guideline on the implementation of quality management systems for national regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-fourth report (WHO Technical Report Series, No. 1025). Geneva: World Health Organization; 2020: Annex 13:273–327 (https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 29 January 2021).

Appendix 1

Examples of use of reliance

Regulatory reliance can take many forms and encompasses a wide range of regulatory approaches and practices that involve two or more regulatory authorities. It may be limited to a discrete regulatory process or function or comprise the full scope of regulatory functions throughout the life cycle of a medical product. Many examples around the world illustrate current use of reliance and the diverse ways in which NRAs leverage the work of others. The examples below illustrate the points raised in the GRelP, to show use of reliance in different regulatory functions. The list is not exhaustive but an illustration of current global practices in reliance. It may be replaced in the future by a comprehensive repository of reliance approaches to be established as a part of a toolbox of GRelP.

A1. Clinical trials

Work-sharing in the assessment of clinical trials is being used in some regions, such as the Voluntary Harmonisation Procedure in the European Union (*1*) and the African Vaccine Regulatory Forum (AVAREF) (*2*). By assessing clinical trial applications together, NRAs and, in some cases, ethics committees in different countries can benefit from the assessments performed by the different participating countries with a view to facilitating and ensuring the robustness of the clinical trials application assessment process across countries. The AVAREF platform has been instrumental in building the expertise and capacity of regulators and ethics committees, promoting the use of international standards and expediting clinical trial assessments and decisions for medical products of high public health interest in both emergency and other circumstances. A guideline and a platform for joint assessment of applications for clinical trials as well as guidelines for site inspections for good clinical practices have been set up to facilitate product development, regulatory decision-making and access to promising new medical products (*3*).

A2. Marketing authorization

A2.1 Abridged regulatory pathways with reliance for initial marketing authorization

Several procedures are available through regulatory authorities or the WHO prequalification programme for use of an abridged regulatory pathway by a relying NRA. The European Union Article 58 (also referred to as European

Union Medicines for all) (*4*), the Swissmedic Marketing Authorisation for Global Health Products (*5*) procedures and the WHO collaborative procedure (CRP) for accelerated registration (CRP) (*6*) are three examples of abridged regulatory pathways in which reliance is used to facilitate the registration of medical products.

The European Union Article 58 and the Swissmedic Marketing Authorisation for Global Health Products not only facilitate national registration but also provide an opportunity for experts from NRAs to both observe and participate in assessment and scientific advice procedures, thus building their capacity and establishing confidence in the processes.

The CRP facilitates the assessment and accelerates national registration of WHO-prequalified medical products and medicines approved by a stringent regulatory authority. The CRP provides unredacted reports on the assessment, inspection and performance evaluation (in the case of in-vitro diagnostics) upon request (and with the consent of the manufacturer) to participating NRAs, primarily in low- and middle-income countries. The procedures are detailed in WHO guidelines, which also include guidance on how NRAs can make the most efficient use of the reports in reaching their own decisions, as participating NRAs are expected to reach a decision on marketing authorization within 90 calendar days (regulatory time). The CRP has been successful in both accelerating decisions in countries and building the capacity of regulatory authorities.

The WHO certificate of a pharmaceutical product (CPP) is also used as a reliance tool, in lieu of full or partial assessment for marketing authorization (*7*). NRAs are encouraged to consider use of electronic CPP. These certificates are being used in lieu of a full or partial review, accelerating assessment in many countries such as Benin, Bolivia, Cameroon, Congo, Cuba, Curaçao (Netherlands), Guinea, Haiti, Honduras and Hong Kong (China).

A2.2 Quality information

Many NRAs, and the WHO Prequalification programme, recognize certificates of suitability for monographs in *The European Pharmacopoeia* (*8*) for active pharmaceutical ingredients (APIs) as validation of the quality of a certain API. Some countries also recognize confirmation of API prequalification by the WHO Prequalification programme for APIs (*9*). These two examples provide assured mechanisms of reliance and also reduce the documentation requirements for countries that rely upon or recognize those certificates. When a certificate of suitability for the monographs of *The European Pharmacopoeia* or confirmation of prequalification of an API is issued, the receiving NRA need not duplicate the API assessment but can focus on sections not covered by either document.

A2.3 Work-sharing

The Australia–Canada–Singapore–Switzerland United Kingdom ACCESS Consortium (*10*) was formed in 2007 by "like-minded" medium-sized regulatory authorities to promote work sharing for greater regulatory collaboration and alignment of regulatory requirements. The ACCESS Consortium explores opportunities to share information and work in areas such as biosimilar products, complementary medicines, generic medicines, new prescription medicines, medical devices and information technology. The Consortium capitalizes on each country's strengths, addresses gaps in science, knowledge and expertise and leverages resources to expedite risk assessment, while maintaining or raising quality and safety standards. The Consortium builds on international networks, initiatives and mechanisms to advance work- and information-sharing throughout the life cycles of health products.

A2.4 Joint assessments

Joint assessments can be beneficial to NRAs by spreading the workload, building capacity through broader experience and expertise and helping to build trust in each other's assessments and decision making processes. Similarly, industry can benefit from a common review and a single set of questions, saving both resource and time as compared with separate interactions. In view of these benefits, several joint assessment initiatives have been introduced into regional regulatory networks, sometimes driven by the higher-level priorities of economic blocs seeking to create common markets. Examples of joint assessment initiatives include those in the Regional Economic Communities in Africa (East African Community (*11*)), ZAZIBONA (*12*) in the Southern African Development Community, the Economic Community of West African States/West African Health Organization (*13*)) and the ASEAN Joint Assessment Coordinating Group (*14*).

A2.5 Unilateral recognition

The Mexican Federal Commission for Protection against Sanitary Risk unilaterally recognizes marketing authorizations from certain reference regulatory authorities (*15*).

A2.6 Mutual recognition

The European Union is an example of highly integrated regulatory cooperation, and its many regulatory pathways depend heavily on work-sharing, recognition and other forms of reliance. The approval of medicines is based on a single assessment system, so that an assessment report from any agency in the European Union network can be used as a basis for reliance by other regulators.

In this case, a strong, common legal framework and harmonized regulatory standards shared by all European Union countries has enabled and facilitated reliance and recognition (*16*).

A3. Post-approval changes

In accordance with the same principles as for initial marketing authorization, reliance can also be applied broadly in assessing post-approval changes already approved by NRAs considered to be reference authorities. In the case of CRP, for example, WHO informs the participating NRAs about any variations in prequalified products approved by the WHO Prequalification team (*6*).

The Health Sciences Authority in Singapore applies a verification route with shortened times for approving post-approval changes to quality and product labels, to increase leverage of reference agencies' assessments, minimize duplication of effort and increase efficiency as part of work that includes effective life cycle management of registered therapeutic medicinal products. To qualify, the proposed changes must be identical to those approved by one of the Authority's five reference agencies, with proof of the approval and the approved product label of that reference agency (*17*).

A4. Testing and lot release

A4.1 Network of Official Medicines Control Laboratories

The network of official medicines control laboratories supports regulatory authorities in controlling the quality of medicinal products on the market. Collaboration within the General European Official Medicines Control Laboratories Network (GEON) (*18*) makes the best use of resources by pooling resources and avoids duplication of work and testing. Some of the main goals of the GEON are to ensure mutual recognition among its members of tests conducted by national official medicines control laboratories, coordinate activities among official medicines control laboratories and facilitate sharing of knowledge and work.

A4.2 Lot release and quality monitoring of vaccines and other biological products

Launched in 2017, the WHO National Control Laboratory Network for Biologicals (WHO-NNB) (*19*) brings together national control laboratories and NRAs of vaccine-producing and vaccine recipient countries, WHO contract laboratories, manufacturers' associations, WHO regional offices and other stakeholders, including donors. WHO-NNB ensures effective use of global resources by providing a platform and infrastructure for collaboration and exchange of information on quality and technical aspects. Its main objective

is to facilitate access to and the availability of prequalified vaccines (and other biotherapeutic products) through reliance on batch releases by NRAs and national control laboratories that are members of WHO-NNB, thereby reducing redundant testing and encouraging more cost–effective testing and more effective regulatory oversight.

A5. Pharmacovigilance

Exchanges and sharing of data are critical in pharmacovigilance. More than 100 Member States share data on the safety of medical products in the WHO database of individual case reports of safety, VigiBase, developed and maintained by the Uppsala Monitoring Centre (*20*). Member States use this database (and thereby each other's data) as a single source of pharmacovigilance information to confirm and validate any signals of adverse events associated with medicines and vaccines that they have observed. In Regulation EU No 1235/2010 (*21*), the European Union introduced the concept of a supervisory authority for pharmacovigilance, to be responsible for verifying on behalf of the Union that the marketing authorization holder for a medicinal product satisfies the pharmacovigilance requirements as per European Union legislation.

Countries in the Region of the Americas have been preparing joint assessments of periodic safety updates and risk management plans. Coordinated by Health Canada, pairs of countries have completed evaluation reports for several products. The reports are made available on a regional platform with access restricted to the pharmacovigilance focal points of the NRAs.

A6. Inspections

Governments and NRAs in various regions have made mutual recognition agreements so that they can rely on each other's inspections, avoiding duplication of work and making the best use of resources. These include agreements between the European Union (*22*) and Australia, Canada, Japan, Switzerland and the USA and ASEAN mutual recognition agreements (*23*).

PIC/S is a non-binding, informal cooperative arrangement among regulatory authorities in the field of good manufacturing and good distribution practices of medicinal products for human or veterinary use and, more recently, also in good clinical and good vigilance practices (*24*). Its aim is to facilitate cooperation and networking among competent authorities and regional and international organizations, thus increasing mutual confidence in inspections. PIC/S has issued guidance on inspection reliance, outlining a process for desk-top assessment of compliance with good manufacturing practices (*25*). Reliance is an important aspect of desktop assessments of compliance with relevant good practice guidelines and requirements, as described in WHO guidance (*26*).

The OECD operates a system for mutual acceptance of data in the assessment of chemicals (including pharmaceuticals), in which data generated in any member country in accordance with OECD test guidelines and the principles of good laboratory practice are accepted by any other member country for assessing products for the protection of human health and the environment (*27*).

A7. Examples of medical devices

Reliance is prevalent in the regulation of medical devices, including in-vitro diagnostics. For example, the Medical Device Single Audit Program (*28*) was developed under the auspices of the International Medical Device Regulators Forum (IMDRF). Under this Program, the regulatory authorities of Australia, Brazil, Canada, Japan and the USA have pooled their resources into a robust system of oversight by third party auditing organizations, which, in turn, audit the quality management systems of medical device manufacturers. The Program permits an auditing organization to conduct a single regulatory audit that satisfies the requirements of the regulatory authorities that participate in the Program. The pooled resources are used to establish and maintain oversight of auditing organizations, resulting in more effective use of limited regulatory resources. A single audit programme allows regulatory authorities to leverage resources efficiently and to streamline the regulatory process without compromising public health and to promote better aligned, more consistent regulatory requirements.

The IMDRF has also issued guidance for exchanges of information on the safety of medical devices among participating NRAs (*29*). The system reports incidents that represent a serious threat public health beyond national borders. The IMDRF provides consistent terminology for reporting and coding adverse events for categorized reporting (*30*).

These activities are just two examples of the work of IMDRF in harmonization, convergence and reliance in the area of medical devices. Other examples are optimizing standards for regulatory use (*31*), essential principles of the safety and performance of medical devices (*32*) and requirements for the competence, training and conduct of regulatory reviewers (*33*).

In Singapore, medical devices and in vitro diagnostics that have been authorized through specific pathways in Australia, Canada, Europe, Japan or the USA are eligible for abridged evaluation. To qualify, the proposed intended use must be identical to that approved in the reference country. Typically the documentation includes proof of approval from the reference regulatory authority and summary technical documents to satisfy requirements for supporting documentation (*34*). Additionally, Australia recognizes registrations and certifications from notified bodies designated by the medical device

regulators of Health Canada, European member states, the Pharmaceuticals and Medical Devices Agency of Japan, the US Food and Drug Administration and organizations participating in the Medical Device Single Audit Program (*35*).

A8. Examples of public health emergencies

WHO developed the "emergency use assessment and listing" mechanism as a risk-based procedure for assessing and listing unlicensed vaccines, therapeutics and in-vitro diagnostics for use primarily during public health emergencies of international concern but also in other public health emergencies when appropriate.

PAHO has developed guidance for NRAs and regulatory systems on practical ways of implementing reliance for emergency use of medicines and other health technologies in a pandemic (*36*).

References to Appendix 1

1. Clinical trials facilitation groups. Guidance document for sponsors for a voluntary harmonisation procedure (VHP) for the assessment of multinational clinical trial applications. Heads of Medicines Agencies; 2016 (https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2016_06_CTFG_VHP_guidance_for_sponsor_v4.pdf, accessed 29 January 2021).
2. The African Vaccine Regulatory Forum. Brazzaville: World Health Organization Regional Office for Africa; 2020 (https://www.afro.who.int/health-topics/immunization/avaref, accessed 29 January 2021).
3. GCP inspection guide. Joint review guideline. In: AVAREF tools. Brazzaville: World Health Organization Regional Office for Africa; 2020 (https://www.afro.who.int/publications/avaref-tools, accessed 29 January 2021).
4. Human regulatory. Marketing authorisation. Medicines for use outside the European Union. European Medicines Agency. Amsterdam. European Medicines Agency; 2019 (https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/medicines-use-outside-european-union, accessed 29 January 2021).
5. The Swissmedic Marketing Authorisation for Global Health Product (MAGHP) Procedure. Bern: Swissmedic; 2017 (https://www.swissmedic.ch/swissmedic/en/home/about-us/development-cooperation/marketing-authorisation-for-global-health-products.html, accessed 29 January 2021).
6. Collaborative procedure for accelerated registration. Geneva: World Health Organization, Prequalification of Medical Products; 2020 https://extranet.who.int/prequal/content/collaborative-procedure-accelerated-registration, accessed 29 January 2021 https://www.who.int/teams/regulation-prequalification/pharmacovigilance/certification-scheme/model-certificate-of-a-pharmaceutical-product).
7. Model certificate of a pharmaceutical product. Geneva: World Health Organization; 2020 (, accessed 29 January 2021).

8. Background & legal framework. Certificate of suitability to the monographs of the European Pharmacopoeia. Strasbourg: Council of Europe, European Directorate for the Quality of Medicines & Healthcare; 2020 (https://www.edqm.eu/en/certification-background-77.html, accessed 29 January 2021).
9. Active pharmaceutical ingredients. Geneva: World Health Organization; 2020 (https://extranet.who.int/pqweb/medicines/active-pharmaceutical-ingredients, accessed 29 January 2021).
10. The ACCESS Consortium. Australian Government. Department of Health. Therapeutic Goods Administration (https://www.tga.gov.au/australia-canada-singapore-switzerland-acss-consortium); Government of Canada (https://www.canada.ca/en/health-canada/services/drugs-health-products/international-activities/australia-canada-singapore-switzerland-consortium.html); Health Sciences Authority (https://www.hsa.gov.sg/international-collaboration/therapeutic-products/acss; Swissmedic: https://www.swissmedic.ch/swissmedic/en/home/about-us/international-collaboration/multilateral-co-operation-with-international-organisations---ini/multilateral-co-operation-with-international-organisations---ini.html; , MHRA https://www.gov.uk/government/news/uk-medicines-regulator-joins-up-with-australia-canada-singapore-and-switzerland-regulators; all accessed 29 January 2021.
11. Medicines and Food Safety Unit. Arusha: East African Community; 2020 (https://www.eac.int/health/medicines-and-food-safety-unit, accessed 29 January 2021).
12. Alternative/Expedited process to register medicines via the ZAZIBONA collaborative process. Gaborone: Southern African Development Community; 2015 (http://www.rrfa.co.za/wp-content/uploads/2015/10/ZaZiBoNa-Registration-Pathway_v01_09062015.pdf, accessed 29 January 2021).
13. Regional joint assessment procedure for medicine registration and marketing authorization of medical products. Bobo Dioulasso: West African Health Organization; 2019 (https://www.wahooas.org/web-ooas/sites/default/files/publications/1993/wa-mrh-regional-joint-medicines-assessment-procedure.pdf, accessed 29 January 2021).
14. ASEAN cooperation on standards and conformance to facilitate trade in the region. Jakarta: Association of Southeast Asian Nations; 2020 (https://asean.org/asean-economic-community/sectoral-bodies-under-the-purview-of-aem/standards-and-conformance/, accessed 29 January 2021).
15. Patel P, McAuslane N, Liberti L. R&D briefing 71: Trends in the regulatory landscape for the approval of new medicines in Latin America. London: Centre for Innovation in Regulatory Science; 2019 (http://docplayer.net/146295622-Trends-in-the-regulatory-landscape-for-the-approval-of-new-medicines-in-latin-america.html, accessed 29 January 2021).
16. Medicinal products. EudraLex – EU legislation. EudraBook V1 – May 2015 / EudraLex V30 – January 2015. Brussels: European Commission; 2020 (https://ec.europa.eu/health/documents/eudralex/, accessed 29 January 2021).
17. Therapeutic products guidance. Guidance on therapeutic product registration in Singapore (TPB-GN-005-005). Chapter H. Minor variation (MIV) application submission. Singapore: Health Sciences Authority; 2019 (https://www.hsa.gov.sg/docs/default-source/hprg/therapeutic-products/guidance-documents/guidance-on-therapeutic-product-registration-in-singapore_jan2019.pdf, accessed 29 January 2021).
18. General European OMCL Network (GEON). Strasbourg: Council of Europe, European Directorate for the Quality of Medicines & Healthcare; 2020 (https://www.edqm.eu/en/general-european-omcl-network-geon, accessed 29 January 2021).
19. WHO-National Control Laboratory Network for Biologicals (WHO-NNB). Geneva: World Health Organization; 2016 (https://www.who.int/immunization_standards/vaccine_quality/who_nnb/en/, accessed 29 January 2021).

20. VigiBase. Uppsala: Uppsala Monitoring Centre; 2020 (https://www.who-umc.org/vigibase/vigibase/, accessed 29 January 2021).

21. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products. Off J Eur Union. 2010;L348/1 (https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:348:0001:0016:EN:PDF, accessed 29 January 2021).

22. Mutual recognition agreements (MRA). Amsterdam: European Medicines Agency; 2020 (https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra, accessed 29 January 2021).

23. ASEAN mutual recognition arrangements. Jakarta: Association of Southeast Asian Nations (http://investasean.asean.org/index.php/page/view/asean-free-trade-area-agreements/view/757/newsid/868/asean-mutual-recognition-arrangements.html, accessed 29 January 2021).

24. Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (https://picscheme.org/en/picscheme, accessed 29 January 2021).

25. Guidance on GMP Inspection Reliance. PIC/S; 2018 (https://picscheme.org/docview/2475, accessed 29 January 2021).

26. Guidance on good practices for desk assessment for compliance with good manufacturing practices, good laboratory practices and good clinical practices for marketing authorization of medical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty-second report (WHO Technical Report Series, No. 1010). Geneva: World Health Organization; 2018: Annex 9 (https://www.who.int/docs/default-source/medicines/norms-and-standards/current-projects/trs1010-annex9--desk-assessment.pdf 29 January 2021).

27. Mutual acceptance of data (MAD). Paris: Organisation for Economic Co-operation and Development; 2020 (https://www.oecd.org/chemicalsafety/testing/mutualacceptanceofdatamad.htm, accessed 29 January 2021).

28. Medical device single audit program (MDSAP). Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap, accessed 29 January 2021).

29. Medical devices: post-market surveillance: national competent authority report exchange criteria and report form. Singapore: International Medical Device Regulators Forum; 2017 (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170921-pms-ncar-n14-r2.pdf, accessed 29 January 2021).

30. IMDRF Adverse Event Terminologies Working Group. IMDRF terminologies for categorized adverse event reporting (AER): terms, terminology structure and codes. Singapore: International Medical Device Regulators Forum; 2020 (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-200318-ae-terminologies-n43.pdf, accessed 29 January 2021).

31. IMDRF Standards Working Group. Optimizing standards for regulatory use. Singapore: International Medical Device Regulators Forum; 2018 (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181105-optimizing-standards-n51.pdf, accessed 29 January 2021).

32. IMDRF Good Regulatory Review Practices Group. Essential principles of safety and performance of medical devices and IVD medical devices. Singapore: International Medical Device Regulators Forum; 2018 (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf, accessed 29 January 2021).

33. IMDRF Good Regulatory Review Practices Group. Competence, training, and conduct requirements for regulatory reviewers. Singapore: International Medical Device Regulators Forum; 2017 (http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170316-competence-conduct-reviewers.pdf, accessed 29 January 2021).

34. Overseas reference regulatory agencies. Registration overview of medical devices. Singapore: Health Sciences Authority; 2019 (https://www.hsa.gov.sg/medical-devices/registration/overview#toggle=togglepanel-overseas-reference-regulatory-agencies, accessed 29 January 2021).

35. Comparable overseas regulators for medical device applications. Canberra: Therapeutic Goods Administration, Department of Health; 2019 (https://www.tga.gov.au/comparable-overseas-regulators-medical-device-applications, accessed 29 January 2021).

36. Reliance for emergency use authorization of medicines and other health technologies in a pandemic (e.g. COVID-19). Washington DC: Pan American Health Organization; 2020 (https://iris.paho.org/handle/10665.2/52027, accessed 29 January 2021).

Annex 11

Good regulatory practices in the regulation of medical products

Background

A fundamental role of government is to protect and promote the health and safety of the public, including by delivering health care. A well-functioning health care system requires available, affordable medical products that are safe, effective and of assured quality. As medical products are essential in the prevention, diagnosis and treatment of disease, the consequences of substandard and falsified medical products can be life threatening. This is a concern, as users of medical products are not usually in a position to judge their quality. The interests and safety of the public must therefore be entrusted to a regulatory body or bodies that ensure that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

The regulation of medical products has become increasingly complex with the globalization of product development, production and supply and the rapid pace of technological and social change in the context of limited financial and human resources.The importance of robust regulatory systems was recognized by the Sixty-Seventh World Health Assembly when it endorsed resolution WHA 67.20, Regulatory system strengthening for medical products. The resolution notes 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" (*23*).

A sound system of oversight requires that regulatory authorities be supported by an effective framework of laws, regulations and guidelines and that they have the competence, capacity, resources and scientific knowledge to deliver their mandate in an efficient and transparent manner. The extent to which a regulatory framework fulfils its policy objectives depends on the quality of its development and implementation. GRP are critical to efficient performance of a regulatory system and, consequently, to the public's confidence in the system, while also setting clear requirements for regulated entities. A sound regulatory framework, including international norms and standards, and the recruitment and development of competent staff are necessary but not sufficient conditions to ensure "good oversight". All individuals in regulatory authorities should be guided by GRP in setting appropriate requirements and formulating decisions

that are clear, transparent, consistent, impartial, proportionate, timely and based on sound science. Regulated parties and other stakeholders also play important roles in ensuring a clear, efficient regulatory environment so that quality-assured medical products are available to patients.

Acknowledgements 271

Abbreviations to Annex 11 271

Executive summary 271

1. Introduction 273

2. Purpose 273

3. Scope 273

4. Glossary 274

5. Objectives 276

6. Key considerations 276

7. Overview of a regulatory system for medical products 277

7.1 Components of the regulatory framework 277
7.2 Components of a regulatory system 279

8. Principles of good regulatory practices 282

8.1 Legality 283
8.2 Consistency 284
8.3 Independence 286
8.4 Impartiality 287
8.5 Proportionality 288
8.6 Flexibility 290
8.7 Clarity 292
8.8 Efficiency 294
8.9 Transparency 297

9. Enablers of good regulatory practices 299

9.1 Political and government-wide support 299
9.2 Effective organization and good governance supported by leadership 300
9.3 Inter- and intra-organizational communication, collaboration and coordination 300
9.4 A robust, well-functioning quality management system 300
9.5 Sufficient, sustainable financial resources 300
9.6 Competent human resources 301
9.7 Organizational ethics and values 301
9.8 Science- and data-driven decision-making process 301

10. Implementing good regulatory practices 301

References 302

Acknowledgements

WHO acknowledges all the authors, stakeholders and organizations who contributed to the preparation of this document.

Abbreviations to Annex 11

APEC	Asia–Pacific Economic Cooperation
ASEAN	Association of Southeast Asian Nations
GRP	Good regulatory practices
OECD	Organisation for Economic Co-operation and Development

Executive summary

A fundamental role of government is to protect and promote the health and safety of the public, including providing health care. A well-functioning health care system requires available, affordable medical products that are safe, effective and of consistently assured quality.

The medical products sector is one of the most regulated of all industries, because of the impact of the diverse range of medical products on health, the difficulty in assessing their quality, safety and efficacy or performance[1] and the complexity of their development, production, supply and surveillance. It is therefore essential that the interests and safety of the public be entrusted to a regulatory body responsible for ensuring that only products in legal trade are available and that marketed products are safe, perform as claimed and are of assured quality.

Regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. A coherent legal framework should be established and implemented that provides the required level of oversight while facilitating innovation and access to safe, effective and good-quality medical products. The framework should also have the necessary flexibility and responsiveness, particularly for managing public health emergencies, addressing new technologies and practices and promoting international regulatory cooperation.

Governments incur costs by establishing and maintaining regulatory systems to protect and promote the health of their citizens. Regulated parties incur costs in complying with regulations. Inefficient regulatory systems, however,

[1] Medicines and vaccines: efficacy; medical devices including in-vitro diagnostics: performance

have impacts on the health system, with potentially significant implications for morbidity and mortality, health care costs and the economy.

A sound legal framework, adoption of international norms and standards and recruitment and development of competent staff are necessary but not sufficient conditions to ensure "good regulatory oversight". These measures must be combined with good regulatory practices (GRP) that guide all individuals in organizations entrusted with regulating medical products in formulating decisions that are clear, transparent, consistent, impartial, proportionate, timely and based on sound science and legislation.

GRP can be defined as a set of principles and practices applied to the development, implementation and review of regulatory instruments – laws, regulations and guidelines – to achieve public health policy objectives in the most efficient way. Successful application of GRP is the hallmark of a modern, science-based, responsive regulatory system in which regulations are translated into desired outcomes. GRP provide a means of establishing and implementing sound, affordable, efficient regulation of medical products as an important part of health system performance and sustainability.

This document is intended to present Member States with widely recognized principles of GRP derived from an extensive review of public documents issued by governments and multilateral organizations as well as many consultative workshops, benchmarking exercises and interactions with Member States. The nine principles presented in this document – legality, consistency, independence, impartiality, proportionality, flexibility, clarity, efficiency and transparency – are relevant to all authorities responsible for the regulation of medical products, irrespective of their resources, sophistication or regulatory model. Regulated parties and other stakeholders also have important roles to play in achieving an efficient regulatory environment.

GRP serve as a basis for guidance documents on best regulatory practices. The body of WHO guidance documents is intended to provide regulatory authorities with comprehensive guidance for improving their performance. This document will be supplemented by practical guides and tools designed to facilitate implementation of GRP.

1. Introduction

This document responds to requests from national authorities responsible for regulation of medical products (see 4. Glossary) for guidance in addressing common gaps in regulatory practices identified during benchmarking exercises. The document draws on documents published by multilateral bodies such as the Asia-Pacific Economic Cooperation (APEC) (*10*), the Organisation for Economic Co-operation and Development (OECD) (*11*, *12*), the World Bank (*13*) and the Association of Southeast Asian Nations (ASEAN) (*14*), as well as guides published by a number of governments. The document also takes account of earlier WHO documents that touch on aspects of GRP (*15–22*) and of WHO experience in applying the WHO Global Benchmarking Tool (GBT) and promoting the principles of good regulatory practices (GRP). Proper implementation of GRP through GRP enablers across the regulatory system (see 4. Glossary) can result in desired regulatory outcomes and impact.

2. Purpose

This document presents the high-level principles of GRP. They are intended to serve as benchmarks and thereby guide Member States in applying good practices in regulation of medical products. This document is also meant to guide Member States in prioritizing the functions of their regulatory system according to their resources, national goals, public health policies, medical products policies and the medical product environment. This "principles-based" document will be supplemented by practical guides and tools to facilitate implementation of GRP by organizations responsible for the regulation of medical products. This basic document is complemented by related guidance on best regulatory practices, including good governance practices (*24*), good reliance practices (*25*), good review practices (*26*) and quality management systems (see 4. Glossary) for national regulatory authorities (NRAs) (*27*). The group of documents is intended to provide regulatory authorities with comprehensive guidance on improving performance.

3. Scope

This document presents principles and considerations in the development and use of the regulatory instruments that underpin regulatory activities. Broader practices and attributes are presented that define well-performing regulatory systems for medical products.

The document is relevant to all regulatory authorities, irrespective of their resources, maturity or regulatory model. High-level GRP principles are

equally applicable to supranational (e.g. regional), national and subnational regulatory systems, and systems in which several institutions are charged with regulating certain products or activities in a country or jurisdiction. The document is also intended for a number of related audiences: institutions and policy-makers responsible for formulating health policies, laws, regulations and guidelines; institutions that, together, form national or supranational systems for regulation of medical products; and regulatory networks and parties affected by or otherwise interested in regulatory frameworks, such as industry or other developers of medical products.

4. Glossary

The definitions given below apply to the terms as used in this document. They may have different meanings in other contexts. Readers are also encouraged to consult related WHO guidance for more complete definitions relevant to best regulatory practices (see References).

Co-regulation. A system of shared regulatory responsibilities in which an industry association or professional group assumes some regulatory functions, such as surveillance and enforcement or setting regulatory standards.

International standards and guidelines. For the purpose of this document, the term includes relevant WHO standards and guidelines and any other relevant, internationally recognized standards (e.g. International Organization for Standardization or pharmacopoeial standards) and guidelines (e.g. the International Council on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use or guidelines of the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme).

Medical product. For the purpose of this document, the term includes medicines, vaccines, blood and blood products and medical devices, including in-vitro diagnostics.

Public health emergency. The condition that requires a governor to declare a state of public health emergency, defined as

> an occurrence or imminent threat of an illness or health condition, caused by bioterrorism, epidemic or pandemic disease, or (a) novel and highly fatal infectious agent or biological toxin that poses a substantial risk of a significant number of human fatalities or incidents or permanent or long-term disability.

The declaration of a state of public health emergency permits a governor to suspend state regulations and change the functions of state agencies (*1*).

Quality management system. An appropriate infrastructure comprising 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.

Recognition. Acceptance of the regulatory decision of another regulator or other trusted institution. Recognition should be based on evidence that the regulatory requirements of the reference regulatory authority are sufficient to meet the regulatory requirements of the relying authority. Recognition may be unilateral or mutual and may, in the latter case, be the subject of a mutual recognition agreement.

Regulatory convergence. A voluntary process whereby the regulatory requirements in different countries or regions become more similar or "aligned" over time. Convergence results from gradual adoption of internationally recognized technical guideline documents, standards and scientific principles, common or similar practices and procedures or the establishment of appropriate domestic regulatory mechanisms that align with shared principles to achieve a common public health goal (*2*).

Regulatory cooperation. A practice among regulatory authorities for efficient and effective regulation of medical products. May be practised by an agency, an institution or a government. The formal mechanisms include creation of joint institutions, treaties and conventions such as mutual recognition agreements, while less formal mechanisms include sharing information, scientific collaboration, common risk assessment, joint reviews and inspections and joint development of standards. May also include work with international counterparts to build regulatory capacity or provide technical assistance, thus contributing to improvement of international regulatory governance practices (*3*–*6*).

Regulatory harmonization. A process whereby the technical guidelines of participating authorities in several countries are made uniform (*7*).

Regulatory impact analysis. Process of examining the probable impacts of a proposed regulation and of alternative policies to assist the policy development process (*8*).

Regulatory stock. Collection or inventory of accumulated regulations.

Regulatory system. The combination of institutions, processes and the regulatory framework with which a government controls particular aspects of an activity (*9*).

Reliance. The act whereby a regulatory authority in one jurisdiction takes into account and gives significant weight to assessments by another regulatory

authority or trusted institution or to any other authoritative information in reaching its own decision. The relying authority remains independent, responsible and accountable for the decisions taken, even when it relies on the decisions, assessments and information of others.

5. Objectives

GRP ensure sound, effective regulation of medical products as an important part of health system performance and sustainability. If they are implemented consistently and effectively, they can result in higher-quality regulation, better regulatory decision-making and compliance, more efficient regulatory systems and better public health outcomes. They help to ensure that regulatory systems remain up to date as the technologies and systems in which they are used continue to evolve. In an increasingly complex, interconnected regulatory environment, GRP also promote trust among regulatory authorities and other stakeholders, such as industry, academia, research centres and health care professionals and thereby facilitate international cooperation and the adoption of more effective and efficient approaches to ensuring the quality, safety and efficacy or performance of medical products in the global regulatory community. The ultimate aim of GRP is to serve and protect public health and patients' interests, with respect for all applicable ethical principles.

6. Key considerations

The medical products sector is one of the most regulated of all industries because of the impact that the diverse range of medical products can have on health and society, the difficulty in assessing their quality, efficacy or performance and safety, lessons learnt from public health tragedies and the complexity of developing, producing, supplying and monitoring medical products to ensure that they consistently perform as intended. Many countries therefore have increasingly sophisticated sets of laws, regulations and guidelines to control all aspects of the life cycle of medical products.

In providing the necessary regulations and tools for fulfilling publicly entrusted mandates, regulatory authorities have a duty to ensure that they regulate in a manner that achieves public policy objectives. They must therefore establish and implement a coherent regulatory framework to provide the required level of oversight and control while facilitating innovation and access to safe, effective and high-quality medical products. They must also build the necessary flexibility and responsiveness into the regulatory framework, particularly for managing public health emergencies (see 4. Glossary), addressing new technologies and best practices and promoting international regulatory cooperation (see 4. Glossary).

Increasingly, policy-makers and regulatory authorities are adopting modern models of regulation that are responsive to resource constraints while meeting the challenges posed by scientific development, globalization, rising public expectations and public health emergencies. Weak or inefficient regulatory systems can limit access to safe, effective and, high quality medical products and pose a threat to public health. As countries strengthen their regulatory capacity, they must ensure that their regulatory systems are science-based, that they adhere to international standards and guidelines and that their approach leverages the work of other, trusted regulatory authorities and institutions when possible. To this end, countries are encouraged to formulate and implement policies and strategies that promote international collaboration (*23*), convergence, harmonization, information- and work-sharing and reliance (see 4. Glossary) as part of GRP (*25*). WHO is establishing a framework for evaluating NRAs and regional regulatory systems and for designating those that meet the requirements of WHO listed authorities (*28*).

Regulatory control of medical products to protect public health is fully acknowledged, as noted above. The issue is how to regulate effectively, efficiently and transparently, such that the interests of the health care system are served. Consistent application of GRP in all aspects of oversight is essential in ensuring that those interests are served and in providing the foundation for a well-performing, respected regulatory system. GRP are principles and practices applied to the development, implementation and review of regulatory instruments – laws, regulations and guidelines – in order to achieve public health policy objectives in the most efficient way. GRP instil a culture of best practices among institutions responsible for regulatory oversight to ensure that regulation is fairly, consistently and effectively applied.

7. Overview of a regulatory system for medical products

Definitions are essential for a common understanding of concepts. While more terms are defined in the Glossary, the terms "regulatory framework", "legal framework", "regulatory authority", "regulatory system" and "regulatory outputs" are explained below to ensure proper understanding of their use in this document.

7.1 Components of the regulatory framework

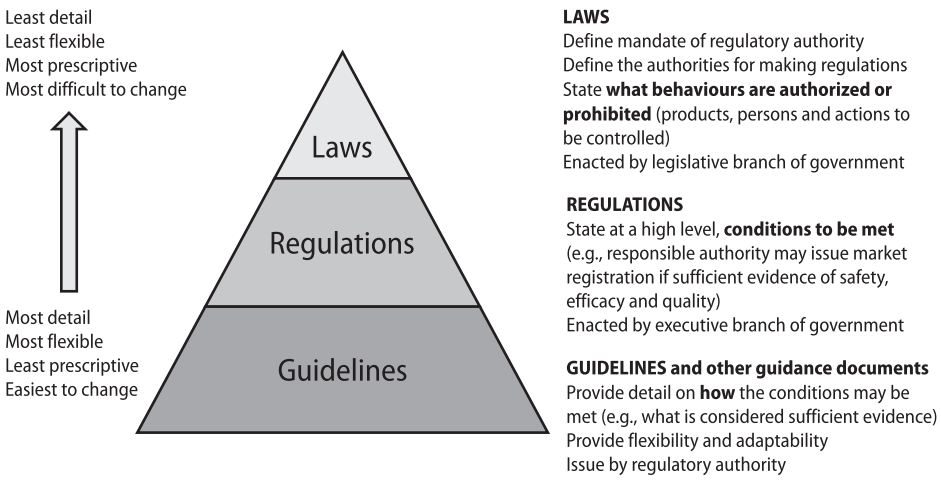
In this document, the terms "law" and "regulation" are used to describe the components of the legal framework (binding legislation). Other terms may be used in some jurisdictions, such as "act" instead of "law" or "ordinance" instead of "regulation".

Laws generally define the roles and responsibilities of institutions, in this case, a regulatory authority, ministry of health or other relevant organizations. They define the products, persons and activities that are to be regulated and state what is permitted and what is not. More importantly, laws authorize an institution to make lower-level (or subordinate) regulations.

Regulations are a diverse set of instruments by which governments place requirements on enterprises and citizens. Regulations usually state at high level the conditions to be met and the requirements defined in laws. For instance, a law may prohibit the manufacture, importation or sale of a medical product in the absence of specific authorization, while regulations would set out the conditions for obtaining authorization, such as the provision of certain types of information (the results of non clinical testing and clinical trials, data on manufacturing and control) that allow the regulatory authority to establish the quality, safety and efficacy or performance of a medical product.

Guidelines (and other guidance documents) provide further detail on how the regulated stakeholders can comply with laws and regulations. Guidelines may also provide details of the processes of enforcement of the respective legislation (laws and regulations). Within a regulatory framework for medical products, such documents are usually non-binding and are generally more detailed and scientific in nature. They are thus appropriate for describing the approaches that are generally considered suitable for satisfying regulatory requirements but unsuitable for inclusion in legislation.

Fig. 1
Architecture of a regulatory framework



7.2 Components of a regulatory system

A *regulatory authority* is a public institution(s) or governmental body or bodies authorized by law to exercise independent regulatory oversight over the development, production, marketing and surveillance of medical products. Although the term implies that a single organization is responsible for all regulatory functions, these functions may be undertaken by one or more institutions that report to the same or a different senior official. The regulatory authority plays a critical role in ensuring the quality, safety, efficacy and performance of medical products and also the relevance and accuracy of product information.

The *regulatory framework* is the collection of laws, regulations, guidelines, guidance documents and other regulatory instruments through which a government and a regulatory authority control particular aspects of a specific activity.

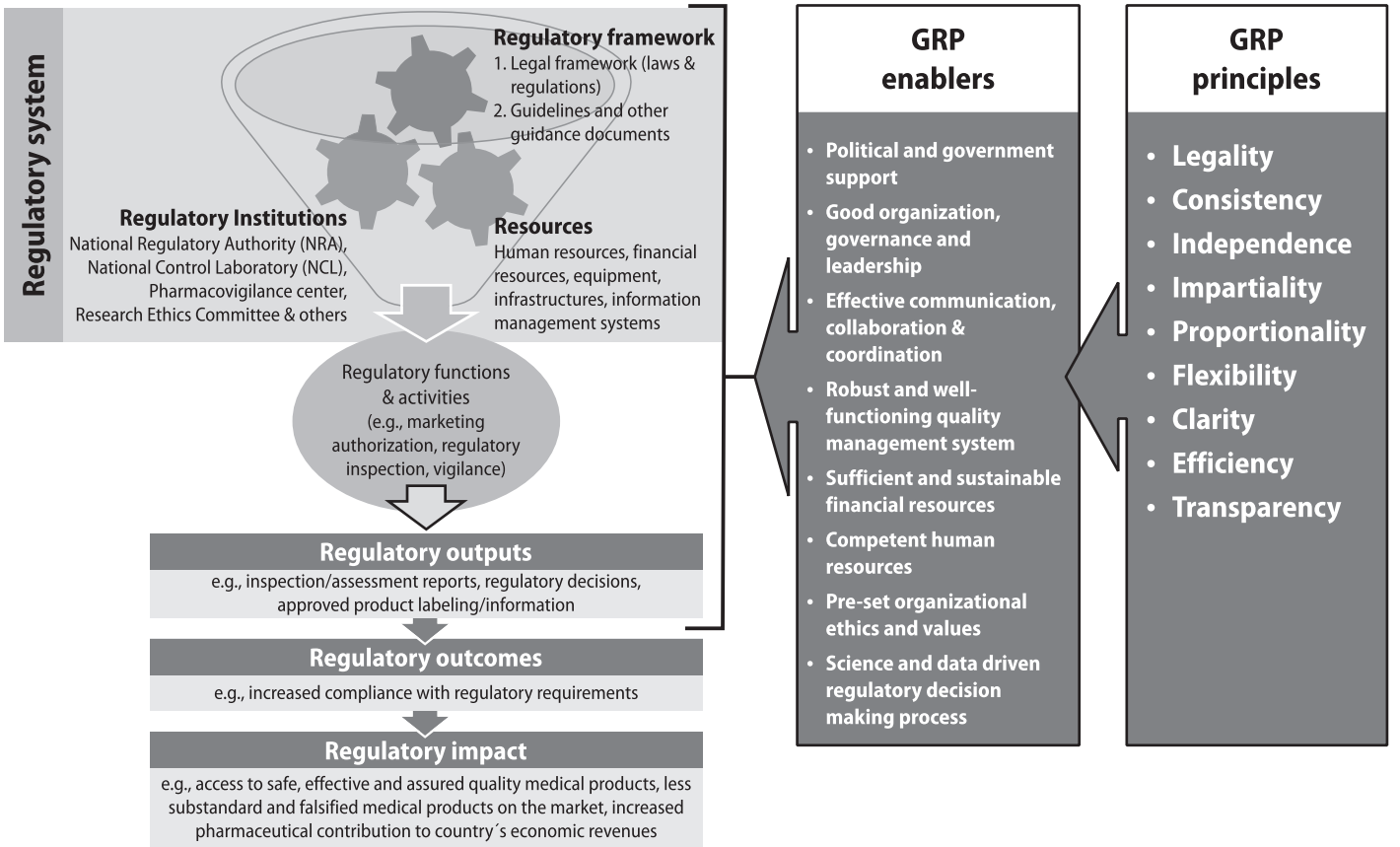
The *legal framework* is the part of the regulatory framework that contains binding pieces of legislation, such as laws and regulations.

Regulatory outputs are the results or products of the regulatory authority, such as reports of inspections and assessments, decisions and product labels.

The term *regulatory system* is used to describe the combination of institutions, processes, regulatory framework and resources which, taken together, are integral to effective regulation of medical products in a country or multi country jurisdiction. GRP should be considered and applied to the whole regulatory system.

Fig. 2 illustrates the principles and enablers of GRP and the components of a regulatory system.

Fig. 2
Principles and enablers of good regulatory practices (GRP) and components of a regulatory system



In the overall regulatory system, three components (inputs) contribute most to regulatory functions and activities: (i) the regulatory framework, composed of the legal framework (laws and regulations), guidelines and other guidance documents; (ii) regulatory institutions, which may be represented by one or more entities, including the NRA, the national control laboratory, pharmacovigilance centres and research ethics committees; and (iii) all types of resources, including human and financial, infrastructure and equipment and information management systems. The regulatory outputs depend on the functions and activities concerned (e.g. regulatory and marketing authorization, inspection and assessment reports). The concepts and principles of GRP apply to the overall regulatory system, as explained above. For application and implementation of GRP, several enablers are essential (see section 9. Enablers for Good Regulatory Practices). When the principles of GRP are properly implemented through the enablers, the desired regulatory outcome and impact can be achieved.

WHO classifies the spectrum of regulatory activities for medical products into seven common regulatory functions, which are applicable to all medical products: clinical trials oversight, marketing authorization, vigilance, market surveillance and control, licensing of establishments, regulatory inspection and laboratory testing (*29*). In addition, a number of non common functions apply to certain medical products, such as official lot release of vaccines and other biologicals.

The term *regulatory authority* implies that a single organization is mandated to perform all regulatory functions. This is not always the case. For example, different organizations may be legally responsible for regulating medicines and vaccines and for medical devices. Even when one body is responsible for all regulatory functions, aspects critical to certain functions may lie outside its authority, such as those performed by surveillance or vigilance centres that have formal relations with the authority; these include activities such as collecting reports on adverse events, surveillance for substandard and falsified medical products and monitoring advertising. Certain regulatory functions may be undertaken by third parties, as in the case of auditing organizations for medical devices. In order to ensure a comprehensive and efficient regulatory system, clear roles, responsibilities, processes and communication channels must be established among the different organizations responsible for performing regulatory functions.

Regulatory activities may also be undertaken at supranational (e.g. regional), national or subnational level. Examples include supranational evaluation of certain products for the purpose of granting marketing authorization that is valid for several countries or inspections of certain manufacturing sites for medical products for good manufacturing practices at national level.

8. Principles of good regulatory practices

There is no universal model for regulation of medical products. Each approach reflects national health policies and priorities, national socioeconomic development, the availability of resources and infrastructure, the health system, the national legal system, research and development capacity and local production capacity. Nonetheless, as in other regulated sectors, there is growing international consensus on best practices to be applied in regulation of medical products.

A review of public documents on GRP (*10*, *13*, *14*, *30*) reveals common practices that should be adopted by all institutions responsible for or involved in regulation of medical products. These principles apply equally to the development and implementation of regulatory oversight and to daily regulatory business. GRP are guided by overarching principles. Nine principles are listed in Table 1 and described below, with considerations relevant to regulation of medical products. The principles, practices and examples will be further elaborated in supplementary guidance that will complement this document.

Table 1
Principles of good regulatory practices

Legality	Regulatory systems and the decisions that flow from them must have a sound legal basis.
Consistency	Regulatory oversight of medical products should be consistent with existing government policies and legislation and be applied in a consistent and predictable manner.
Independence	Institutions that execute regulation of medical products should be independent.
Impartiality	All regulated parties should be treated equitably, fairly and without bias.
Proportionality	Regulation and regulatory decisions should be proportional to risk and to the regulator's capacity to implement and enforce them.
Flexibility	Regulatory oversight should not be prescriptive but rather be flexible in responding to a changing environment and unforeseen circumstances. Timely responsiveness to a specific need and in particular to public health emergencies should be built into the regulatory system.
Clarity	Regulatory requirements should be accessible to and understood by users.

Table 1 *continued*

Efficiency	Regulatory systems should achieve their goals within the required time and at reasonable effort and cost. International collaboration promotes efficiency by ensuring the best use of resources.
Transparency	Regulatory systems should be transparent; requirements and decisions should be made known, and input should be sought on regulatory proposals.

8.1 Legality

Regulatory systems and the decisions that flow from them must have a sound legal basis.

Key elements:

- The regulatory framework should provide the necessary authority, scope and flexibility to safeguard and promote health.
- Delegation of power and responsibilities to various levels of the regulatory system should be clear and explicit.
- Regulatory frameworks should support and empower regulatory authorities to contribute to and benefit from international cooperation.
- Systems should be in place to ensure that regulatory decisions and sanctions can be reviewed.
- The regulatory framework should clearly define the scope and lines of authority of the institutions that form the regulatory system to ensure its integrity.
- The regulatory authority must be held accountable for its actions and decisions to the public, those regulated and the government within a legal framework.

The principle of legality requires that a regulatory system be structured such that all regulatory actions and decisions are based on clear legal authority, thus respecting the "rule of law".

A regulatory body exists to achieve objectives deemed by the government to be in the public interest. It must operate within and in accordance with the powers conferred by the legal framework (*31*). The law or act that establishes the regulatory authority should clearly state the objectives of the enabling legislation, the powers of the authority, the scope of the products and general activities that the authority is mandated to regulate and the provisions for making regulations.

Delegation of power and responsibilities to different levels of the regulatory system should be explicit and clear. When more than one institution or level of government is involved in regulating medical products, the functions and responsibilities of each should be clear and complementary, and the processes for communication and coordination among them should be defined (see section 8.2 Consistency).

As cooperation among regulatory authorities is essential to manage increasingly complex and cross jurisdictional issues, a modern legal framework for medical products must support and encourage all forms of cooperation, including convergence, harmonization, information- and work-sharing, reliance and recognition (see 4. Glossary). Ideally, this is stated explicitly in provisions of laws and/or regulations, with operational detail provided in policies and procedural guidance. A legal framework should at least not prohibit all forms of regulatory cooperation, such as the use of assessments and decisions of other trusted regulatory authorities and institutions in conducting its own work. Cooperation does not alter the sovereign responsibility and accountability of each regulatory authority to protect the health and safety of its citizens but allows the exchange of good practices and may save resources and avoid duplication.

Legislation must be in place to control and perform all the required regulatory activities under common and non-common regulatory functions. Policies, guidelines and procedures cannot compensate for the absence of legislation. A legal framework should ensure the integrity of the regulatory system by providing clear authority, scope, power, roles and responsibilities to the institutions that form the system. Conflict in organizational authority or responsibilities should be avoided.

All regulatory authorities must be accountable to the public, the bodies they regulate and the government for their actions and decisions as part of good governance and accountability. In the context of GRP, regulatory authorities are accountable when they are: (i) responsible for acting according to certain standards and commitments, (ii) answerable for their actions and (iii) willing to face the consequences when standards or commitments are not met.

Regulatory actions and decisions should be consistent with the authority and controls provided for by the legal framework. Processes should therefore be in place for review of regulatory decisions, including internal appeals and judicial appeal of the decisions of regulators, such as on the grounds of procedural fairness and due process, in addition to scientific and administrative grounds.

8.2 Consistency

Regulation of medical products should be consistent with government policies and legislation and be applied consistently and predictably.

Key elements:

- The regulatory framework for medical products should fit coherently into the national legal and policy framework.
- New regulations should complement, and not conflict with, existing regulatory instruments.
- Regulatory requirements should be implemented and enforced consistently for all medical product sectors and stakeholders.

Regulation of medical products must be performed in the context of and in ways coherent with the national legal framework, general government policies and public health policy objectives. It should also be coherent with any treaties, conventions and regional or international agreements to which the country is a party as well as any supranational legislation that affects constituent member states.

Any overlap or conflict with existing laws and regulations should be avoided, as this causes confusion, duplication of mandates and unnecessary regulatory work and increases the likelihood of noncompliance. Manufacturers (for the purpose of this document, manufacturers also means marketing authorization holders), importers, distributors and other stakeholders should be able consistently to identify the responsible authority in laws and regulations. Consistency is particularly important when regulation of medical products is decentralized, for instance, with central and state or provincial authorities. Effective systems should be in place for consultation, cooperation and coordination among the different levels of government to promote national uniformity of regulatory requirements while respecting local responsibilities. All regulatory functions and activities should be efficiently integrated to ensure the uniformity of the regulatory system. Similar considerations apply when more than one institution or department at the same level of government is responsible for different, or the same, regulatory functions and products – a situation that is not uncommon. Unclear or conflicting mandates and requirements create complex regulatory systems and challenge effective communication and coordination. In all instances, formal mechanisms for proper coordination should be established during the drafting and execution of regulatory instruments and the operations of bodies charged with the regulation of medical products.

Consistency in regulatory actions and decisions is ensured when the same or similar circumstances lead to the same or a similar outcome. It is therefore important that the regulatory system build an institutional memory, by recording decisions, to ensure similar, fair treatment in future situations.

Regardless of differences in technology, the level of regulatory oversight in relation to the risk posed by different types of medical products and regulated entities (manufacturers, importers and distributors) must be consistent. Consistency is upheld when the regulatory framework provides for impartial appeal of regulatory decisions. The enforcement of such appeals and corrective measures should also be consistent among sectors.

Consistency is also ensured by sufficient, clear regulatory guidance, based, when possible, on international guidelines; orientation and training programmes for staff; and regular, transparent interactions with regulated parties and other stakeholders (e.g. industry associations, patients, health care professionals associations and other relevant government institutions). These are mechanisms for improving process and for the identification and resolution of issues.

Application of a well-functioning quality management system that covers all regulatory activities (*33*) is critical for regulatory consistency. This includes adoption of a process approach, involving systematic definition and management of regulatory processes and their interactions to achieve the intended results in accordance with the quality policy and strategic direction of the organization.

Performance-based indicators, internal reviews and external audits may also be important in ensuring consistency in the application of regulations and regulatory operations.

8.3 Independence

Institutions responsible for regulation of medical products should be independent.

Key elements:

- The regulatory system must operate, and be seen to operate, in an independent and authoritative manner, discharging its duties independently from politicians, government and regulated entities.
- Regulatory activities and decisions should be free of improper and undue influence of stakeholders.
- Appropriate funding and clear funding processes are essential.
- The independence of the leadership should be established to ensure independent behaviour during and after employment.

According to an OECD publication entitled *Creating a culture of independence* (*32*):

> Regulatory agencies (authorities) often find themselves under various pressures from different stakeholders and interest groups which can subject them to different forms of influence. To ensure they conduct their activities correctly and achieve the right policy outcomes they must take on board legitimate interests and protect themselves from inappropriate or undue influence.

Good governance and anti-corruption measures (*24*) should be built into the regulatory framework to obviate actual or perceived conflicts of interest, unfounded bias or improper influence by stakeholders (also known as "regulatory capture"). To maintain public confidence, the regulatory authority must operate, and be seen to operate, independently, authoritatively and impartially and to discharge its duties independently of the regulated entities (e.g. researchers and industries).

When regulators are funded by fees, an appropriate cost-recovery mechanism is essential to set the "right" fee and to avoid a regulator that is under-funded, captured by industry or undermined by the executive. It may be easy to influence a regulator that is funded from general government revenues by reducing its resources. Annual appropriations make it easier to influence a regulator than multi annual appropriations, which are less susceptible to short-term shocks, such as political or electoral imperatives. Adequate safeguards can protect the budget from being used to unduly direct the regulator.

The nomination and appointment of the regulator's leadership should be based on transparent and accountable processes. Clear rules to avoid conflicts of interest should be in place to ensure independent behaviour during and after employment.

8.4 Impartiality

All regulated parties should be treated equitably, fairly and without bias.

Key elements:

- Regulatory activities and decisions should be free of conflicts of interest or unfounded bias.
- The regulatory system must operate impartially.
- The regulatory authority should not be engaged in the activities it regulates nor be hierarchically subordinate to the institutions that perform the regulated activities.
- Regulatory decisions should be based on science and evidence, and the decision-making process should be robust, according to defined criteria.

Regulatory instruments must be written such that the regulatory activities and decisions made on the basis of such instruments are legitimate, evidence-based and ethical. Public and private bodies and domestic and foreign entities should be regulated equitably, with the same principles and framework, to ensure competitive neutrality.

The regulatory authority must operate impartially, discharging its duties independently of the regulated entities (see section 8.3 Independence). This principle extends to researchers and other experts sitting on scientific and advisory committees that make recommendations to the regulatory authority on regulatory policy or the authorization of medical products. Declarations of interest must be completed and reviewed, and rules for withdrawal should be defined before discussions in order to maintain the integrity and impartiality of the committee and its recommendations.

The regulatory authority should not be engaged in the activities it regulates nor be hierarchically subordinate to the institutions that perform the regulated activities, including the procurement of medical products by a ministry of health or other government institution.

Regulatory activities and decisions should be based on science and evidence and be predictable. While good regulatory judgement and discretion are necessary in enforcement, actions and decisions should be based on regulatory requirements and on the evidence for or the circumstances of the situation (see also sections 8.2 Consistency and 8.6 Flexibility).

Regulators should avoid actual or perceived influence and be open and transparent about their decisions and decision-making process. The scientific and technical basis for regulatory oversight should be objective and accessible. Public consultation and transparency throughout decision making should ensure impartiality, better regulatory outcomes and greater public confidence in the use of regulated products.

8.5 Proportionality

Regulatory oversight and regulatory decisions should be proportional to the risk and to the regulator's capacity to implement and enforce the decisions.

Key elements:

- Regulatory oversight should be adequate to achieve the objectives without being excessive.
- Regulatory measures should be proportionate to the risk of the product or activity or service.

Box *continued*

- Regulations should not exceed the national capacity to implement and enforce them.
- Assessment of medical products should be based on a benefit–risk evaluation and continuous monitoring of the benefit–risk profile in a robust vigilance system.

The principle of proportionality demands that an action not exceed what is necessary to achieve the intended objective. This principle should be applied to all elements of a regulatory system. Regulation should be created only when necessary and should be adequate for the aim and not excessive. The content and form of regulation should be appropriate to both the issue being addressed and the risk it poses. For instance, extensive pre-clinical and clinical studies are necessary to ensure the safety and efficacy of a new medicine for marketing authorization, whereas studies such as of in-vivo bioequivalence or, when appropriate, in-vitro studies are sufficient for generic medicines.

Regulatory enforcement and inspection regimes should also be proportionate to the risk and severity of an infraction in order to reduce or mitigate the health risk posed by the infraction. A proportionate, risk-based approach allows the regulator to allocate resources where the need is greater. It also ensures that the cost of complying with a regulation is proportionate to the nature of the risk. For instance, the frequency of inspections could be determined in part by a manufacturer's history of compliance.

The principle of proportionality also applies to the policies and processes by which regulations are made. Regulation-making should be flexible and proportionate to the complexity and/or impact of the problem that it is to address. For instance, a rigorous cost–impact analysis may be required for a new, complex regulatory framework, whereas a more pragmatic approach could be used for simple regulations or when the policy alternatives are limited.

Regulation should not exceed national capacity to implement and enforce it.

> If there are no strategies, facilities and resources for implementation and enforcement, legislation on its own will achieve nothing. A law with modest aims and objectives that is properly enforced is preferable to a more comprehensive one that cannot be implemented (*21*).

Furthermore, lack of resources or ability to implement and enforce represent a liability for governments.

Assessment of medical products should be based on a benefit–risk evaluation based on the evidence submitted on the quality, safety and efficacy

or performance of the product. All the demonstrated benefits of the medical products should be weighed against the identified risks. Regulatory systems should include appropriate surveillance or vigilance to monitor the benefit–risk profile and to take any actions required.

8.6 Flexibility

Regulatory oversight should be flexible in order to respond to a changing environment and unforeseen circumstances.

Key elements:

- The regulatory system, including its frameworks, should provide sufficient flexibility to reflect or respond to changes in the regulated environment, such as evolving science and technology.
- The regulatory system should be prepared to provide timely responses to urgent situations such as public health emergencies and shortages of medical products.
- The language of regulation should reflect performance when possible, allowing for alternative approaches to achieve the same result.
- The regulatory system should provide the flexibility for applying good judgement.

Flexibility is essential to ensure that regulatory frameworks and regulatory systems remain "fit for purpose". The design and use of regulatory instruments must therefore be appropriate. A meaningful, understandable, enforceable regulatory framework should contain sufficient detail to ensure clarity. It should also allow flexibility to respond to new technologies and innovation and to changes in the regulated environment and to ensure a timely response to unforeseen public health threats. Flexibility in regulatory oversight should be risk-based and should not compromise the quality, safety, efficacy or performance of a product (*28*).

Responsiveness is an extended principle of flexibility. It represents the possibility of responding more rapidly than usual in certain circumstances. For example, an expedited response or review might be necessary in a public health emergency.

Responsiveness is time-bound and temporary, as it is necessary in urgent situations such as a public health emergency, serious shortages of a medical product with no alternative, an unmet medical need or rare disorder and medical products for compassionate use or donation. Regulatory systems should be well prepared and have the necessary regulatory instruments to respond to and manage such situations. The NRA should have flexible and

expedited development programmes or review processes to accelerate the access to patients by approval of innovative products for serious, life threatening and rare diseases and to address unmet medical needs. Flexible and responsive provisions are critical for ensuring that the authority can make decisions based on the best available science and on benefit–risk considerations, often in the face of less than complete information (e.g. compassionate use, emergency use authorization or listing). Lack of the necessary regulatory tools and flexibility can be a real, significant impediment to ensuring public safety, particularly during public health emergencies.

When regulatory responsiveness is essential, a regulatory authority should consider prioritizing its activities through a risk-based approach. The involvement of policy- and decision makers and regulatory collaboration and coordination within the international regulatory community significantly contribute to regulatory responsiveness.

The aim of flexibility and responsiveness in regulatory frameworks should be to accommodate the evolution of science and technology. The language of the regulations that support laws is usually based on performance rather than being prescriptive (*15*), thus allowing regulated parties to use alternative approaches to achieve the same outcome.

Guidelines and other guidance documents are the most detailed, most flexible and most amendable regulatory instruments. These attributes ensure that the regulatory framework can respond to new risks in a timely manner and allow for possible use of advances in regulatory science and technology for a future medical product. Unlike laws and regulations, guidelines in themselves usually do not have the force of law; however, guidelines are very effective if appropriately anchored in the regulation and used to describe how compliance with the regulation may be achieved. They should also allow for other, justified approaches to compliance. Alternative approaches to the principles and practices described in guidance may be acceptable, provided they are adequately justified. The flexibility and amendable attributes of guidelines are lost if such detailed texts become part of regulation.

For science that is evolving rapidly but not sufficiently mature to justify regulatory guidelines, lists of "points to consider" can provide useful principles-based guidance and definitions for promoting best practices, a common regulatory understanding and international convergence and prepare the ground for eventual guidelines. International guidelines and standards should always be considered in developing new guidance documents, and regulators should support international harmonization and convergence. National requirements beyond international standards should be well justified.

The regulation of medical products is complex and evolving. New technologies and practices will continue to pose challenges to regulatory systems and redefine the boundaries of what can and should be regulated. Before

developing regulations to address new technologies or address certain practices, regulators should have the necessary regulatory flexibility to interpret existing legislation and regulations appropriately. It should be possible to revise or withdraw a regulation or guideline when it is no longer required.

8.7 Clarity

Regulatory requirements should be accessible to and understood by users.

Key elements:

- Regulatory instruments should be written in language that is understood by users.
- The terminology should be defined and consistent with international norms when possible.
- Consultation, education and training in new requirements contribute to clarification and compliance.
- Guidelines and good guidance practices are instrumental to proper interpretation of regulations.
- The process and basis for taking regulatory decisions and enforcement actions should be clear.

Compliance with and consistent application of regulatory requirements and processes require a clear understanding of what is expected. Both the regulator and the regulated party should understand the conduct that is expected and the consequences of non-compliance.

Proposed regulatory instruments should be written in language that can be understood by the intended users. This will require collaboration with legal personnel in considering the objectives of the legal instrument, the intended audience, other stakeholders who may be impacted and feedback from internal and external consultations, including subject matter experts. Drafting of instruments in clear, unambiguous, precise language in a form consistent with other laws and regulations reduces possible disputes or misinterpretation and promotes compliance. Meetings between NRAs and regulated entities can be helpful in clarifying the application of guidance and cases in which there is no guidance.

As an initial step, an authority that is drafting medical product regulations should conduct a review to identify unclear areas and resolve any inconsistencies in the regulation itself or with other regulations. This step also provides an opportunity to review the "regulatory stock" – the accumulated body of applicable regulations (see 4. Glossary) – to identify whether updating

and better integration of regulatory requirements are necessary to eliminate inconsistencies, redundancy and complexity or to adapt to new requirements.

Interested parties, including the public, should be informed of and contribute to regulatory development and regulatory impact analysis (see 4. Glossary) in order to improve the quality and language of a regulatory instrument, ensuring clear understanding of what is intended and increasing the likelihood of buy-in and future compliance. The means by which interested parties can contribute should be made clear.

Regulatory impact analysis is valuable for systematic assessment of the expected effects of regulatory proposals. It is usually undertaken by policy analysts in the regulatory departments, agencies or ministries that are sponsoring the proposal, primarily to assist decision-makers in considering a proposal. The product of a regulatory impact analysis is a document that summarizes the regulatory proposal, possible alternatives and the aspects and impacts of implementing the proposal.

Terms should be defined in order to avoid ambiguity or misinterpretation. When possible, they should be consistent with established international norms, standards and harmonized guidelines. As noted previously, international standards and guidelines (see 4. Glossary) are particularly important vehicles for promoting common regulatory language, convergence and international cooperation.

The principle of clarity is also applicable to regulatory and administrative guidelines, which are instrumental for interpreting and providing operational clarity to regulations. Guidelines should be developed according to good guidance practice to ensure that they are written clearly and concisely and are consistent with other guidelines and the underlying regulations. Standard templates and formats, style guides, editors, experts in the regulatory framework and users' feedback obtained with established tools (e.g. forms, webinars, institutional polls) should be used.

Draft guidelines, like regulations, should be submitted for internal and external consultation to confirm that the language is clear or requires revision to improve comprehension. Plain language and simple sentence structure should be the goals, with illustrative examples when possible. Education, awareness sessions and training, with clear timelines for adoption of new regulations and guidelines, should be considered for ensuring clarity and compliance when introducing or amending regulations and guidelines, particularly when they are complex.

Regulations and supporting guidelines should be reviewed periodically to ensure that they reflect the authority's current practices and expectations, are adapted to scientific and technological developments and are aligned with current international standards and guidelines, when applicable. Review and revision of a guideline should include consideration of the consequential changes in other guidelines, which should be revised simultaneously.

The process and basis for taking regulatory decisions and enforcing them should be clear and accessible to those directly impacted or otherwise affected (see section 8.9 Transparency).

In summary, clarity is essential in all aspects of regulatory oversight (requirements, procedures, decisions and communications) if regulatory programmes are to have the desired effect.

8.8 Efficiency

Regulatory systems should achieve the intended results within the required time and at reasonable effort and cost.

Key elements:

- Efficient regulatory systems achieve the intended public health goals.
- A sound regulatory framework, competent staff and effective use of resources and information from other authorities are the key elements of an efficient regulatory system.
- Policy-makers should seek the most efficient, least burdensome means of achieving their regulatory purposes and confirm effectiveness after implementation.
- The total burden and resources required for cumulative regulation should be evaluated.
- Regulatory authorities should continually explore ways of improving efficiency in fulfilling their mandate.
- Alignment of regulatory requirements with those of other countries and international collaboration promote efficiency.
- Regulated entities contribute critically to the efficiency of regulatory systems.
- The efficiency of regulatory instruments and regulatory operations should be assessed with performance-based indicators.

An efficient regulatory system must be based on science and evidence and the principles of risk assessment and management and embed a strategy of international regulatory cooperation into daily business. A regulatory system in which sound decisions cannot be made in a timely, consistent fashion is not effective. Its efficiency depends not only on sufficient resources but also on the type of resources and their effective use, irrespective of size. In this context, lack of integrity in the overall regulatory system is a barrier to regulatory efficiency.

Regulatory systems with fewer resources can be as effective as those with more resources if they use a risk-based approach, take advantage of the

work and decisions of other regulatory authorities and focus their resources on essential, value-added activities that can be provided only by the regulatory authority (*26*).

Regulatory oversight cannot be considered efficient if it creates unjustified barriers to access, trade or international regulatory cooperation. Successful establishment of effective regulatory control on medical products depends on a number of factors, as previously described, including:

- analysis of options, including the results of consultations with stakeholders, as regulations are more likely to be effective if those who are impacted have provided input;
- regulations that are proportional to the perceived risk, encourage innovation and pose no unnecessary barriers to trade (e.g. sample testing at import); and
- early planning for implementation and for the practicalities of future enforcement. Application and enforcement should not be after-thoughts.

In developing new regulatory instruments and analysing their impact, the regulatory authority should develop "strategies for education, assistance, persuasion, promotion, economic incentives, monitoring, enforcement, and sanctions" (*34*). The authority should decide which compliance strategies to establish and whether consumer awareness and market forces can reasonably be used, in addition to the threat of penalties. The role of civil society in monitoring adherence to regulation should also be considered. Co-regulation (see 4. Glossary) may be considered in certain circumstances. In such situations, a government issues regulations and enters into a non-statutory agreement with a body (e.g. industry or professional health care association) to develop and administer a compliance programme. When a government works with and through such a body in regulating the activity, it does not delegate its oversight of the activity.

Regulatory authorities may also consider use of third parties to conduct their activities. This model is prevalent in the regulation of medical devices, such as use of recognized auditing organizations to audit manufacturers' quality management systems to ensure that they are of an international standard and respect applicable regulatory requirements. Regulatory resources are used to establish and maintain oversight of audit organizations, resulting in more effective use of limited resources (*35*).

A government incurs costs by establishing and maintaining regulatory systems. Industry and other regulated parties incur costs in complying with regulations, such as undertaking studies, preparing application dossiers, maintaining records and paying fees – the cost of doing business. Additional

costs accrue in inefficient regulatory systems. If the cost of complying with a regulation is disproportionately high, companies may decide not to develop a product and/or commercialize it in a particular market. For instance, a mandatory requirement to conduct local clinical trials as a condition for marketing authorization could be a disincentive to entering that market, particularly if trials conducted elsewhere reflect the patient profiles of the intended market and demonstrate the safety and efficacy of the product. Similarly, long and/or unpredictable times for product review result in lost revenue and unnecessary delays in the availability of products for patients, with potentially significant negative implications for morbidity, mortality, health care costs and the economy. Healthy economies require healthy people.

Inefficiency also results in a negative impact on a regulatory authority's resources, reputation and job satisfaction and increases the time spent addressing complaints about performance. Regulatory frameworks that reflect the principles of proportionality, flexibility and consistency are more likely to be efficient, as they allow resources to be allocated to the regulatory activities that most need them.

International collaboration. Regulatory frameworks that are consistent and aligned with those of other countries and regions encourage the necessary investment to bring appropriate, affordable products to that market. Internationally consistent frameworks also enable the regulatory authority to participate in work sharing networks and other forms of regulatory cooperation (including convergence, harmonization, information- and work-sharing, reliance and recognition). When properly anchored in the regulatory framework, reliance on the work of other authorities eliminates or reduces inefficient duplication of regulatory evaluations of medical products and inspection or audit of facilities. International collaboration thus facilitates access to medical products for all.

Regulatory authorities should continually explore means of improving their efficiency while maintaining standards for evaluating the quality, safety and efficacy or performance of medical products. This could include introduction or refinement of good review practices (*28*) and a quality management system (*28*); greater, more effective use of information technology; consultations with industry, health care professionals and patients on common deficiencies and how best to address them; risk-based criteria for scheduling and conducting inspections; addressing gaps in guidance; performance measurement; and – as noted above – regulatory cooperation and reliance (*26*).

Industry also contributes critically to the efficiency of regulatory systems. For example, high-quality applications for marketing authorization

reduce the overall review time by reducing the number of review cycles. Similarly, a manufacturer with a good compliance record should not require the same frequency or depth of inspection as a poorly performing manufacturer. Consultations and training can effectively complement enforcement in achieving the desired level of compliance.

In a regulatory impact analysis, policy-makers should seek the most efficient, least burdensome means of achieving their regulatory purposes at a minimum reasonable cost. A regulatory approach should include consideration of the total burden and resources required for cumulative regulation.

Periodic performance assessments should be conducted to evaluate the actual efficiency of regulatory instruments to ensure that the foreseen benefits are realized and, if so, the direct and indirect costs.

8.9 Transparency

Transparency is the hallmark of a well-functioning regulatory system and is essential for building public trust and enabling international cooperation.

Key elements:

- Transparency requires investment and a culture of openness, supported by government policy, commitment and action.
- Stakeholders should be consulted in the development of new or revised regulatory instruments.
- Regulatory requirements, processes, fees, assessments, decisions and actions should be as accessible as possible.
- The policies of the regulatory authority with respect to disclosure should be consistent with national laws on access to information.

The WHO Constitution states "Informed opinion and active co-operation on the part of the public are of the utmost importance in the improvement of the health of the people." Transparency is in the interests of patients, consumers, governments, health care workers and manufacturers, as it increases public trust and confidence in the regulation of medical products. Transparency in regulatory requirements and actions results in better informed decisions about investment in the public and private sectors and discourages discriminatory, corrupt or abusive practices.

With transparency, all affected and potentially interested parties – domestic, foreign, public and private – have a meaningful opportunity to be informed of new or amended regulations and guidelines and to make their

views known before they are enacted. With transparency, once medical product regulations and guidelines are adopted, they are readily available and accessible to stakeholders and the general public. Relevant laws, regulations and guideline documents should be posted on the authority's website. Additionally, national industry and professional associations often work with regulatory authorities to disseminate new regulatory texts or to provide opportunities for exchanges of relevant information.

The assessments (positive and, when possible, negative), decisions and actions of the regulatory authority should be documented and made publicly available, with the rationale for the decisions, ideally by issuing a public assessment report. This information is important to a range of stakeholders, including industry, researchers, health professionals, patients and consumers, who use the information for various purposes. It is also essential for building trust and confidence in the regulatory system.

Regulated parties should be able to access the full reports of a product assessment or site inspection that pertains to them. This not only provides insight into the basis for comments and decisions but is also educational, helping to improve regulatory compliance and the quality of future submissions. This practice can also be beneficial to the regulatory authority by fostering a culture of transparency and accountability at operational and management levels. Furthermore, it can lead to higher-quality reports by ensuring that they clearly explain how such assessments led to decisions. The manufacturer should be given the opportunity to redact any trade secret or confidential personal or commercial information before publication.

Transparency requires investment and a culture of openness, which, in turn, should be supported by government policy, commitment and action. While not all regulatory authorities may be able to implement the full range of measures for an optimally transparent regulatory system, a step wise approach can be adopted. Given the prevalence of smart devices and the Internet, an up-to-date, searchable public website could be established and maintained that contains basic information such as:

- the roles, responsibilities, organization and contact information of the regulatory authority;
- access to the laws, regulations, guidelines and procedures necessary to satisfy regulatory requirements and improve the efficacy, safety and quality of medical products;
- a searchable registry of approved, suspended and withdrawn products;
- product information for health care professionals and patients;
- the licensing status of manufacturing sites;

- health advisories, safety information, alerts on quality or on substandard or falsified medical products, advisory notices, recalls and other time-sensitive information of public health interest;
- performance targets and results and annual reports;
- proposed new regulatory instruments, including periods for comment and how to provide input; and
- public assessment reports and reports of facility audits or inspections.

The findings of all audits or oversight reviews of the performance and functioning of the regulatory authority should be made public. Such reviews are important elements of public accountability, as are reports of performance against targets and annual reports.

In fulfilling their responsibilities, regulatory authorities will create or access proprietary or confidential information. Examples include identifiable personal information from clinical trials or reports of adverse events, trade secrets or confidential commercial information such as specifications of medical product compounds or materials or manufacturing processes. Measures should be established to prevent the disclosure of such information, with a mechanism to address disputes about the proprietary nature or confidentiality of information.

In general, national laws and regulations should favour transparency and public access to both the process and the criteria of regulatory decision-making. The disclosure policies of a regulatory authority should be consistent with national laws on public access to government information or "freedom of information". Procedures and contact points for obtaining information held by a regulatory authority should be accessible and clear.

Transparency enables adoption of new, more efficient ways of conducting regulatory operations. It is incumbent upon regulators to practise transparency in regulatory operations and decisions, not only as a fundamental principle of GRP but also to build trust and maximize opportunities for cooperation and reliance as part of the shared responsibility of the regulatory community.

9. Enablers of good regulatory practices

An enabling environment facilitates successful implementation of GRP. Some elements are described below.

9.1 Political and government-wide support

Sustained support at the highest political and government levels, including policy-makers, is essential for proper implementation of the concept and principles of GRP. GRP should form an integral part of all government policies on regulatory systems and be backed by strong political support.

9.2 Effective organization and good governance supported by leadership

The structure and line of authority among and within all institutions in the regulatory system should be well defined. The integrity of the overall regulatory system is critical to the efficient performance of each of its constituent institutions. If more than one institution is involved in the regulatory system, the legislation or institutional regulation should provide for clear coordination and no overlap of regulatory activities. Leadership is critical for setting and realizing the organizational vision, mission, policies and strategies, which in turn significantly contribute to organizational efficiency.

9.3 Inter- and intra-organizational communication, collaboration and coordination

Adequate, effective communication plays a fundamental role in the exchange of information within and outside the institutions that form the regulatory system. When regulatory authorities communicate regularly, both internally and externally, they remain more transparent and accountable. Communication of correct information prevents potential misunderstandings and dissemination of misleading information to patients and the public. Communication is a powerful tool for collaboration and coordination with relevant national and international stakeholders, which leads in turn to efficient use of resources and better regulatory outcomes.

In view of their responsibilities, regulatory authorities should have the personnel, infrastructure and technical tools adequate for the performance of their tasks. Coordination may be facilitated by communication technologies and efficient, rapid information-sharing, which will result in fewer gaps and less duplication of effort.

9.4 A robust, well-functioning quality management system

A quality management system (*28*), which includes application of quality risk management principles, makes the decisions of regulatory authorities more credible and their operations more stable and consistent. A quality management system contributes to systematic planning, control and improved quality in all processes in regulatory functions and ensures a comprehensive approach.

9.5 Sufficient, sustainable financial resources

Investment in a regulatory system is critical to a well-functioning health care system. Adequate financial resources to fulfil its regulatory mandate effectively and to improve the performance of regulatory activities continuously are essential

for the independence, impartiality, consistency and efficiency of a regulatory system. The financial resources of all institutions of the regulatory system should be sustainable, apart from donations from donors or philanthropic entities.

9.6 Competent human resources

An array of technical and scientific knowledge and skills of regulatory staff contribute to the development, implementation and maintenance of an effective regulatory system for medical products. Policies and measures for personal and career development (e.g. training programmes, competitive remuneration schemes) are critical for regulatory authorities to attract competent staff and retain them in the service.

9.7 Organizational ethics and values

Regulatory personnel should abide by organizational ethical principles and values and show professionalism. All regulatory staff should be made aware of and be trained in the ethical principles and values of the regulatory authority (e.g. a code of conduct). A system should be established, within or outside the regulatory system, for managing departures from organizational ethics and values.

9.8 Science- and data-driven decision-making process

Regulatory decisions and decision-making should be based on scientific foundations and accurate data rather than intuition or arbitrariness. Science-based decisions provide for consistent, predictable regulatory outcomes. Adherence to international standards and guidelines is a key enabler of science based regulatory decision-making.

The enablers listed above are not effective when present individually. Rather, they work in harmony in the application and implementation of GRP. For example, sufficient, sustainable financial resources contribute to the recruitment, development and maintenance of competent human resources. Similarly, financial resources should be managed according to good governance practices.

10. Implementing good regulatory practices

WHO Member States are encouraged to implement GRP in their regulatory systems with due consideration of the realities of their legal and regulatory systems. Transparent, predictable processes should be used to ensure high-quality regulatory oversight that achieves the intended objectives while minimizing negative impacts and costs. At the same time, regulatory systems should be sufficiently flexible for the processes to be applied proportionately

to the scope, magnitude and complexity of the issue. Sustained support at the highest levels, with adequate resources, is essential.

Further guidance will be issued to assist Member States both in establishing new regulatory systems for medical products and in updating existing ones.

References

1. WHO definitions: emergencies. Geneva: World Health Organization; 2020 (https://www.who.int/hac/about/definitions/en/, accessed 29 January 2021).
2. Regulatory harmonization. Geneva: World Health Organization; 2014. WHO Drug Inf. 2014;28(1):3–10. (http://www.who.int/medicines/publications/druginformation/issues/DrugInformation2014_Vol28-1/en/, accessed 29 January 2021).
3. International regulatory co-operation: addressing global challenges. Paris: Organisation for Economic Co-operation and Development; 2013 (http://dx.doi.org/10.1787/9789264200463-en, accessed 29 January 2021).
4. Guidelines on international regulatory obligations and cooperation. Ottawa: Treasury Board of Canada Secretariat; 2007 (http://www.tbs-sct.gc.ca/hgw-cgf/priorities-priorites/rtrap-parfa/guides/iroc-cori/iroc-cori-eng.pdf, accessed 29 January 2021).
5. International regulatory cooperation – better rules for globalization. Paris: Organisation for Economic Co-operation and Development; 2013 (http://www.oecd.org/gov/regulatory-policy/irc.htm, accessed 29 January 2021).
6. Recommendation of the Council on Regulatory Policy and Governance. Paris: Organisation for Economic Co-operation and Development; 2012 (http://www.oecd.org/gov/regulatory-policy/2012-recommendation.htm, accessed 29 January 2021).
7. Regulatory harmonization and convergence. Silver Spring (MD): US Food and Drug Administration; 2015. (http://www.fda.gov/BiologicsBloodVaccines/InternationalActivities/ucm271079.htm, accessed 29 January 2021).
8. Best practice regulation handbook. Canberra: Australian Government; 2007 (http://regulationbodyofknowledge.org/wp-content/uploads/2013/03/AustralianGovernment_Best_Practice_Regulation.pdf, accessed 29 January 2021).
9. Evaluating the effectiveness of infrastructure regulatory systems. Washington DC: The World Bank; 2006:17 (https://ppp.worldbank.org/public-private-partnership/sites/ppp.worldbank.org/files/documents/world_bank-_ppiaf-_handbook_for_evaluating_infrastructure_regulatory_systems_2006_english.pdf, accessed 29 January 2021).
10. APEC–OECD Co-operative Initiative on Regulatory Reform. APEC–OECD integrated checklist on regulatory reform. Paris: Organisation for Economic Co-operation and Development; 2005 (http://www.oecd.org/regreform/34989455.pdf, accessed 29 January 2021).
11. The OECD report on regulatory reform. Paris: Organisation for Economic Co-operation and Development; 1997 (http://www.oecd.org/gov/regulatory-policy/2391768.pdf, accessed 29 January 2021).
12. OECD guiding principles for regulatory quality and performance. Paris: Organisation for Economic Co-operation and Development; 2005 (www.oecd.org/fr/reformereg/34976533.pdf, accessed 29 January 2021).

13. Better regulation for growth. Governance frameworks and tools for effective regulatory reform. Washington DC: The World Bank; 2007 (http://documents1.worldbank.org/curated/en/955811468330978599/pdf/556350WP0Box0310Governance01PUBLIC1.pdf, accessed 29 January 2021).

14. ASEAN good regulatory practice (GRP) guide. Bangkok: Association of Southeast Asian Nations; 2009 (http://regulatoryreform.com/wp-content/uploads/2015/08/ASEAN-Good-Regulatory-Practice-GRP-Guide-2009.pdf, accessed 29 January 2021).

15. The "blue book". Marketing authorization of pharmaceutical products with special reference to multisource (generic) products, a manual for national medicines regulatory authorities (NMRAs). Second edition. Geneva: World Health Organization; 2011 (https://apps.who.int/iris/bitstream/handle/10665/44576/9789241501453_eng.pdf;jsessionid=52D37F5BD27B9BB5055CF9DA79453B5B?sequence=1, accessed 29 January 2021).

16. National drug regulatory legislation: guiding principles for small drug regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: thirty-fifth report (WHO Technical Report Series, No. 885). Geneva: World Health Organization; 1999: Annex 8 (https://www.who.int/medicines/technical_briefing/tbs/National_drug_regulatory_legislation_Annex8TRS885_en.pdf), accessed 29 January 2021).

17. Regulation of vaccines: building on existing drug regulatory authorities. Geneva: World Health Organization; 1999 (document WHO/V&B/99.10) (http://apps.who.int/iris/bitstream/10665/65968/1/WHO_V-B_99.10_eng.pdf, accessed 29 January 2021).

18. Effective drug regulation: a multi-country study. Geneva: World Health Organization; 2002 (https://apps.who.int/iris/bitstream/handle/10665/42470/9241562064.pdf?sequence=1&isAllowed=y, accessed 29 January 2021).

19. Medical device regulations: global overview and guiding principles. Geneva: World Health Organization; 2003 (http://www.who.int/medical_devices/publications/en/MD_Regulations.pdf, accessed 29 January 2021).

20. A model regulatory programme for medical devices: an international guide. Washington DC: Pan American Health Organization; 2001 (http://new.paho.org/hq/dmdocuments/2009/AmodelRegulatoryProgramforMedicalDevices_AnInternalGuide.pdf?ua=1, accessed 29 January 2021).

21. How to develop and implement a national drug policy, second edition. Geneva: World Health Organization; 2001 (http://www.who.int/medicines/areas/policy/emp_ndp2nd/en/, accessed 29 January 2021).

22. Global model regulatory framework for medical devices including IVDs. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/255177/9789241512350-eng.pdf?sequence=1, accessed 29 January 2021).

23. Resolution WHA67.20. Regulatory system strengthening for medical products. In: Sixty-seventh World Health Assembly, Geneva, 19–24 May 2014. Resolutions and decisions: resolutions. Geneva: World Health Organization; 2014 (http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R20-en.pdf, accessed 29 January 2021).

24. Good Governance for Medicines: Model Framework, Geneva: World Health Organization; 2014 (http://www.who.int/medicines/areas/governance/ggm_modelframe_updated/en/, accessed 29 January 2021).

25. Good Reliance Practices: Good reliance practices in regulatory decision-making: 6 high-level principles and recommendations 8 Draft. Geneva: World Health Organization; 2020 (working document QAS/20.851 (https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS20_851_good_reliance_practices.pdf?ua=1, accessed 29 January 2021).

26. Good review practices: guidelines for national and regional regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-ninth report. Geneva: World Health Organization; 2015: Annex 9 (WHO Technical Report Series, No. 992; http://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex9-TRS992.pdf?ua=1, accessed 29 January 2021).

27. WHO guideline on the implementation of quality management systems for national regulatory authorities. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: fifty fourth report. Geneva: World Health Organization; 2020: Annex 13 (WHO Technical Report Series, No. 1025, https://www.who.int/publications/i/item/978-92-4-000182-4, accessed 29 January 2021).

28. Policy evaluating and publicly designating regulatory authorities as WHO-listed authorities. Draft. Geneva: World Health Organization; 2019 (working document QAS/19.828; https://www.who.int/medicines/areas/quality_safety/quality_assurance/QAS19_828_Policy_on_WHO_Listed_Authorities.pdf?ua=1, accessed 29 January 2021).

29. WHO Global Benchmarking Tool (GBT) for evaluation of national regulatory systems (https://www.who.int/medicines/regulation/benchmarking_tool/en/, accessed 29 January 2021).

30. APEC Sub-committee on Standards and Conformance. Information notes on good practice for technical regulation. Singapore: Asia-Pacific Economic Cooperation; 2000 (http://www.inmetro.gov.br/qualidade/comites/pdf/docAPEC.pdf, accessed 29 January 2021).

31. Improving regulation and regulatory review. Executive Order 13563. Executive Office of the President. Federal Register: the Daily Journal of the United States Government, 21 January 2011 (https://federalregister.gov/a/2011-1385, accessed 29 January 2021).

32. The governance of regulators. Creating a culture of independence. Practical guidance against undue influence. Paris: Organisation for Economic Co-operation and Development; 2017 (https://www.oecd.org/gov/creating-a-culture-of-independence-9789264274198-en.htm, accessed 29 January 2021).

33. Recommendation of the Council of the OECD on improving the quality of government regulation, including the OECD reference checklist for regulatory decision-making and background note. Paris: Organisation for Economic Co-operation and Development; 1995 (https://legalinstruments.oecd.org/public/doc/128/128.en.pdf, accessed 29 January 2021).

34. Medical device single audit program (MDSAP). Silver Spring (MD): Food and Drug Administration; 2020 (https://www.fda.gov/medical-devices/cdrh-international-programs/medical-device-single-audit-program-mdsap, accessed 29 January 2021).

SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The International Pharmacopoeia, tenth edition.
2021 (online)

WHO Expert Committee on Specifications for Pharmaceutical Preparations
Fifty-fourth report.
WHO Technical Report Series, No. 1025, 2020 (xiv + 325 pages)

International Nonproprietary Names (INN) for pharmaceutical substances
Cumulative List No. 17 2018 (available on CD-ROM only) and Cumulative List No. 18 2021 (available as searchable pdf – in preparation)

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
Seventy-first report
WHO Technical Report Series, No. 1028, 2020 (xi + 101 pages)

Further information on these and other WHO publications can be obtained from
WHO Press, World Health Organization, 1211 Geneva 27, Switzerland
www.who.int/bookorders
tel.: +41 22 791 3264; fax: +41 22 791 4857; email: bookorders@who.int

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 guidance texts were adopted and recommended for use:

Guidelines and guidance texts adopted by the Expert Committee on Specifications for Pharmaceutical Preparations; Points to consider when including Health Based Exposure Limits (HBELs) in cleaning validation; Good manufacturing practices: water for pharmaceutical use; Guideline on data integrity; WHO/United Nations Population Fund recommendations for condom storage and shipping temperatures; WHO/United Nations Population Fund guidance on testing of male latex condoms; WHO/United Nations Population Fund guidance on conducting post-market surveillance of condoms; WHO "Biowaiver List": proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms; WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce; Good reliance practices in the regulation of medical products: high-level principles and considerations; and Good regulatory practices in the regulations of medical products.

All of the above are included in this report and recommended for implementation.

ISBN 9789240020900