

# Norms and standards

## 70 years of WHO standards on medicines quality

Expert Committee on Specifications for Pharmaceutical Preparations, 1947-2017:  
Addressing changing public health challenges

**The Expert Committee on Specifications for Pharmaceutical Preparations advises the WHO Director-General and Member States on matters of medicines quality assurance. When it started its work in 1947 it focused on maintaining *The International Pharmacopoeia*. Its scope of work broadened and deepened over the years, reflecting the emergence of new approaches to quality management in pharmaceutical production and regulation. This article highlights the Committee's main areas of work. A list of current guidelines and work in progress is provided in the Appendix.**

### Background

Expert Committees advise the WHO Director-General and Member States in technical areas related to public health. Their members are recruited from WHO's Expert Advisory Panels. Stringent procedures are in place for their selection and for the management of conflicts of interest. The technical guidance adopted by the Committees is developed through a public consultation process. Once adopted, the guidelines are published as annexes to the Committees' meeting reports in the WHO Technical Report Series (TRS).

The Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) is one of the WHO Expert Committees that meet regularly<sup>1</sup>. It advises the WHO

Director-General and Member States on quality assurance during the life cycle of medicines and in their regulation. In 2017 it looks back on seventy years of standard-setting work.

### History

The ECSPP was established as "Expert Committee on the Unification of Pharmacopoeias". It met for the first time in 1947 (1), and the report of its fourth session was published in 1950 in the very first WHO Technical Report Series (2). At that time many of today's WHO Member States were not yet part of WHO. Modern concepts of medicines quality assurance were only starting to emerge, often in response to unfortunate incidents with medicines that caused serious harm (Box 1).

The decades that followed saw the development of scientific approaches to ensure the quality, safety and efficacy of pharmaceutical products. However, many developing countries did not have the

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<sup>1</sup> See [www.who.int/about/collaborations/expert\\_panels/en/](http://www.who.int/about/collaborations/expert_panels/en/). Others are the WHO Expert Committee on Biological Standardization (ECBS), the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the WHO Expert Committee on Selection and Use of Essential Medicines and the WHO Expert Committee on Drug Dependence.

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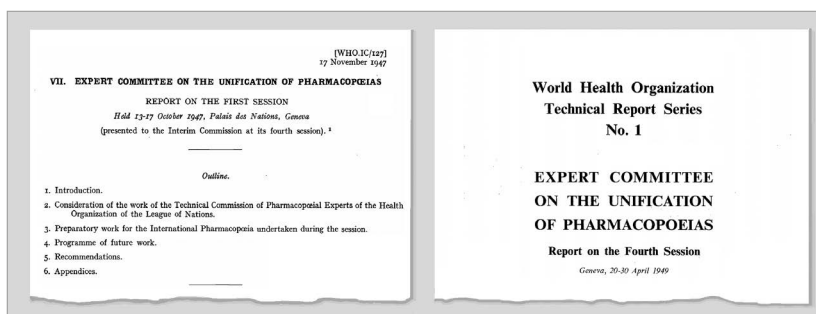
resources to establish medicines regulatory authorities that could effectively protect the health of their populations.

The operations of the pharmaceutical industry are guided by the legal requirements in force in the target markets. In a globalized marketplace this often

means that high quality medicines are being produced for use in stringently regulated environments, while fewer requirements and lower standards are applied for medicines used elsewhere. Moreover, as starting materials and services are sourced from across the globe, local weaknesses in

**Box 1: Medicines quality assurance: a timeline**

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| <p>1937 Over 100 people in the U.S. die following the use of an elixir which used diethylene glycol as a solvent without any safety testing</p> <p>1937 League of Nations sets up a Technical Commission of Pharmacopoeial Experts</p> <p>1938 U.S. Federal Food, Drug and Cosmetic Act introduced, with a premarket notification requirement for new drugs</p> <p><b>1947</b> WHO Interim Commission takes over the work on pharmacopoeias from the League of Nations and reports on its first session</p> <p>1948 First World Health Assembly establishes the "Expert Committee on the Unification of Pharmacopoeias" (renamed twice thereafter)</p> <p>1956–60 Thalidomide marketed in 46 countries worldwide, leading to an estimated 10 000 babies being born with deformities</p> <p>1962 New U.S. legislation requires proof of safety and efficacy before approval of new drug applications for the first time. FDA authorized to require compliance with current Good Manufacturing Practices (GMP)</p> <p>1963 World Health Assembly adopts Resolution WHA16.36 on Clinical and pharmacological Evaluation of Drugs. U.K. Committee of Drug Safety established</p> <p>1969 First WHO guidance on <i>Good practices in the manufacture and quality control of drugs</i> published with World Health Assembly Resolution WHA22.50, (following up on Resolutions WHA20.34 of 1967 and WHA21.37 of 1968)</p> <p>1970 Pharmaceutical Inspection Convention (now: Pharmaceutical Inspection Cooperation Scheme, PIC/S) established, with GMP guidelines based on those of WHO</p> <p>1975 Multistate procedure for medicines registration introduced in Europe, starting harmonization of medicines regulation</p> | <p>1984 U.S. legislation introduces bioequivalence studies for generic medicines in lieu of clinical efficacy and safety studies</p> <p>1985 First international conference on essential medicines policies held in Nairobi, leading to the adoption of the WHO revised drug strategy</p> <p>1989 At the Fifth International Conference of Drug Regulatory Authorities (ICDRA) Europe, Japan and U.S agree on action plans for harmonization. Pharmacopoeial Discussion Group formed</p> <p>1990 International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) established</p> <p>1990 First WHO <i>Guiding principles for small national drug regulatory authorities</i> published</p> <p>2001 UN Secretary General Kofi Annan calls for a Global Fund to fight HIV, tuberculosis and other infectious diseases</p> <p>2001 WHO prequalification of medicines launched to assess key medicines against WHO norms and standards</p> <p>2005 WHO guideline on assessing bioequivalence of fixed-dose combinations published, supporting a global scale-up of antiretrovirals</p> <p>2006 WHO <i>Model Quality Assurance System for procurement agencies</i> published, required for all Global Fund-financed health products</p> <p>2008 WHO biowaiver procedure proposed</p> <p>2010 WHO introduces joint assessments with East African Community and joint inspections</p> <p>2014 World Health Assembly Resolution WHA67.20 makes the first-ever global-level call for Regulatory capacity-building</p> <p>2015 EMA suspends over 700 products over concerns with their bioequivalence data</p> <p>2016 WHO guideline on <i>Good data and record management practices</i> published</p> |
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**Figure 1:** The titles of the first (1) and fourth (2) reports of the WHO Expert Committee tasked with providing standards and specifications for medicines. The Committee was renamed “Expert Committee on International Pharmacopoeia” in 1951 and received its current name, “Expert Committee on Specifications of Pharmaceutical Preparations”, in 1959.

regulatory control can have global impact. Today all the world’s regulatory authorities – including the well-established ones – are calling for cooperation and convergence of standards to close the regulatory gaps.

These developments have been shaping the need for comprehensive WHO guidance on medicines quality assurance that can be implemented in all Member States.

### WHO technical guidance

In the 70 years of its history the ECSPP has broadened its scope of work to cater for the changing needs. It has come to provide unified international norms and standards for all aspects of quality assurance in a medicine’s life cycle, supporting the global move towards convergence, collaboration and reliance among regulatory authorities. The current guidelines are listed in *Appendix 1*. An overview of the ECSPP’s work in the different areas is provided below.

#### *Pharmacopoeial standards*

Maintaining pharmacopoeial standards was the initial mandate of ECSPP. The first volume of *The International Pharmacopoeia* was published in 1951. The current Sixth Edition includes monographs for 439

pharmaceutical substances, 142 dosage forms and 27 radiopharmaceuticals, 174 infrared reference spectra, as well as monographs on general dosage forms, analytical methods and other supplementary texts. By providing publicly available standards for testing of commonly used medicines, many which are not included in any other pharmacopoeia, *The International Pharmacopoeia* fulfils a unique public health role.

Although “unification of pharmacopoeias” has been a goal since the Committee took up its work, the world’s pharmacopoeias have evolved separately. The WHO Index of World Pharmacopoeias<sup>2</sup> lists pharmacopoeial authorities of 53 countries and two regions.

In 2012, WHO convened representatives of pharmacopoeias from 23 countries for the first time to discuss options for convergence of standards. The WHO international meetings of world pharmacopoeias became a regular event and have served as a forum to develop a guideline on Good Pharmacopoeial Practices (GPhP), published in 2016. By promoting collaboration among pharmacopoeias this

<sup>2</sup> Available on the WHO webpage on Medicines quality assurance, [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/en/)

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guidance is expected to lead to a prospective harmonization of standards, with significant potential benefits for manufacturers and regulatory authorities.

#### *Quality control*

In the early days of the ECSPP's history quality control testing was the mainstay of medicines control. While the emphasis has shifted away from pre-market testing towards an ongoing control whether batches supplied meet the agreed specifications, quality control testing remains an important regulatory function. At a time when shortages of various types of medicines are a persistent concern, efficient quality monitoring is critical for continued supply of products.

WHO provides detailed guidance on all aspects of laboratory testing. In 1984 the Committee recommended that countries should set up national pharmaceutical quality control laboratories, and provided guidance on organization and staffing. The first text on good laboratory practice (GLP) followed in 1987 – last revised in 2010 – and a specific text for pharmaceutical microbiology laboratories was added in 2011. WHO prequalification of quality control laboratories was introduced in 2006 and is based on the standards adopted by the ECSPP.

#### *Production and inspections*

When modern medicines regulation started to develop in the 1960s it was recognized that quality cannot be “tested into a product”. Instead it must be built into a product at every step of development and production. The regulatory paradigm has shifted from quality control of the finished product to control of the manufacturing processes, as verified in inspections.

Accordingly, the ECSPP took on the development of norms and standards for the manufacture of finished pharmaceutical

products and their active pharmaceutical ingredients (APIs). The first WHO guideline on good manufacturing practice (GMP) was published in 1969 (3) and formed the basis for the GMP text of the Pharmaceutical Inspection Convention (PIC) upon its establishment in 1970.

The WHO GMP guidance has been continuously updated and supplemented by guidance on specific aspects and for specific product types. The current texts reflect today's focus on quality management systems with effective mechanisms to identify, quantify and manage risks throughout the entire life cycle of a medicine.

Guidance on GMP inspections and classification of deficiencies has also been updated to support collaboration and reliance, reducing the burden of inspections on both manufacturers and regulators. A text on desk reviews of inspection information is in preparation.

#### *Distribution*

As pharmaceutical operations have become globalized, active ingredients and finished products cross many borders before they reach the end users. Joint global efforts are needed to safeguard the quality of pharmaceuticals in the supply chains. WHO has provided guidelines on good practices for trade and distribution both for medicines and starting materials as well as good storage practices including for time- and temperature-sensitive products.

Procurement agencies play a crucial role in assuring the quality of medicines that they delivered. The WHO *Model Quality Assurance System for procurement agencies* (MQAS) was first adopted in 2006. It provides a comprehensive toolkit for procurement organizations to safeguard the quality of medicines at all stages, from the qualification of suppliers throughout purchasing, storage

and distribution of the products. The MQAS was updated in 2014 with input from the major international organizations that procure and/or fund medicines.

Quality surveys through testing of samples provide information about the quality of medicines circulating on the market at a given time. They are useful to verify the effectiveness of other regulatory measures such as marketing authorization, inspections and post-marketing surveillance activities. The 2016 *Guidelines on the conduct of surveys of the quality of medicines* outline the steps to consider when preparing and conducting a sample testing survey.

Special methods are required to detect and test products that have been introduced into the supply chains with fraudulent intent. Responding to a need expressed by quality control laboratories in a survey, WHO proposes a new guidance on testing of suspected spurious, falsely-labelled, falsified and counterfeit medicines. This technical guidance complements the work of the Member State Mechanism on substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products, which was established in 2012<sup>3</sup>.

### *Good pharmacy practice*

Pharmacists play an important role in delivering medicines to patients. WHO and the International Pharmaceutical Federation (FIP) have a long history of collaboration in providing guidelines on good pharmacy practice. The most recent addition is a “points to consider” document on preparing children-specific medicines that are not available as authorized products.

### *Regulation and prequalification*

Work on the first WHO *Guidelines for small drug regulatory authorities* started in 1985 as a component of the Organization’s Revised Drug Strategy (4). The regulatory guidance adopted by the ECSPP has been completed and updated in line with evolving regulatory concepts. Unlike national and regional regulations, the WHO guidelines reflect global perspectives on issues such as stability of medicines across climatic zones, or the selection of comparator products when demonstrating bioequivalence of generics.

Comprehensive guidance has been generated by the Committee to underpin WHO prequalification of medicines. Established in 2001, when HIV treatment was unaffordable in the public sector of most WHO Member States, this programme has increased global access to affordable key medicines of assured quality. The WHO guidance on assessing bioequivalence of fixed-dose combinations, which was published in 2005, contributed significantly to scaling up global access to ARV therapy (5). Prequalification was subsequently extended to additional medicines categories. A procedure to prequalify APIs in their own right was introduced in 2009. Since 2013 WHO offers a collaborative registration procedure for WHO-prequalified medicines in participating countries, which accelerates the review process while ensuring that the stringent quality standards used in prequalification are maintained.

The WHO prequalification team provides important input to the ECSPP’s work from its experience with implementing stringent standards in a wide variety of settings. Several prequalification guidelines have been subsequently adapted for use by regulatory authorities.

With increasing globalization, digitalization and outsourcing of services,

<sup>3</sup> WHO Essential medicines and health products. WHO Member State Mechanism. [www.who.int/medicines/regulation/ssffc/mechanism/en/](http://www.who.int/medicines/regulation/ssffc/mechanism/en/)

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new issues are emerging. An example are the recurring concerns about data integrity at contract research organizations that perform bioequivalence studies. The 2016 WHO *Guideline on good data and record management practices* is the first text of its kind globally to bring together the relevant information in one place, completing the existing good practice guidelines in the various areas (GXP).

Today, no regulatory authority can achieve its mandate without using smart ways of reviewing data and making decisions. 2015 saw the publication of the *WHO guidelines on Good review practices* intended to support Member States, including those with less mature regulatory systems. A more comprehensive, high level framework document on all aspects of *Good regulatory practices* is under development.

Reliance on the decisions of stringent regulatory authorities (SRA), defined as members or associates of ICH, is provided for in several WHO guidelines. As ICH is evolving to become a global organization, this definition need revisiting. At its 51<sup>st</sup> Meeting the ECSPP adopted an interim revised definition and noted the work being done towards new assessment approaches that will enable collaboration and reliance on regulatory authorities with proven efficiency in specific fields.

Regulatory capacity needs to be strengthened in additional areas, notably for medical devices, including diagnostics. This complex and growing product group is increasingly important for public health, yet few Member States regulate it fully. The 2016 WHO global model regulatory framework for medical devices comes at a time when there is significant scope for the introduction of unified standards in this area.

## Conclusion

WHO is the only organization with a mandate to protect global health. The development, establishment and promotion of international standards for pharmaceuticals are among the functions laid down in its constitution. Its technical guidance on medicines quality is designed to serve regulatory authorities of all Member States, as well United Nations agencies and other major international bodies. It provides a technical platform for convergence as recommended by the 17<sup>th</sup> International Conference of Drug Regulatory Authorities (ICDRA) (6). At a time when access to essential medicines is a pressing issue on the sustainable development agenda, the ECSPP's standard-setting work makes a unique and critical contribution towards more equitable access to needed medicines of assured quality.

## References

- 1 WHO. Expert Committee on the Unification of Pharmacopoeias: Report on the first session, held 13-17 October 1947, Palais des Nations, Geneva. WHO; 1947.
- 2 WHO. Technical Report Series No. 1. Expert Committee on the Unification of Pharmacopoeias. Report on the Fourth Session. Geneva, 20-30 April 1949. WHO; 1950.
- 3 Annex 12. In: Official Records of the World Health Organization. No. 176. Twenty-second World Health Assembly. Boston, Massachusetts, 8-25 July 1969. WHO; 1969.
- 4 Thirty-ninth World Health Assembly. WHO's revised drug strategy: report by the Director-General. Geneva: WHO; 1986.
- 5 't Hoen EF, Hogerzeil HV, Quick JD, Sillo HB. A quiet revolution in global public health: The World Health Organization's Prequalification of Medicines Programme. *J Public Health Policy.* 2014 May;35(2):137-61.
- 6 17<sup>th</sup> International Conference of Drug Regulatory Authorities. *WHO Drug Information.* 2016; 30(4): 547-57.

**Appendix 1: WHO guidelines on medicines quality assurance**

Only the latest revised versions of the guidelines are listed.

The guidelines shown under each heading are listed in chronological order of their adoption. The texts are available in the different sections of the WHO medicines "Guidelines" website ([www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/guidelines/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines/en/)),

Texts marked with an **asterisk (\*)** are under revision or under development. The draft texts or revisions are available in the public consultation section of the above website, titled "Current Projects", at [www.who.int/entity/medicines/areas/quality\\_safety/quality\\_assurance/projects/](http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/projects/).

**Quality control****Pharmacopoeial standards and practices**

<i>The International Pharmacopoeia</i> , Sixth Edition	(1)	2016
Recommendations on Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products	TRS 908 Annex 1	2003
<i>The International Pharmacopoeia</i> – related substances tests: dosage form monographs guidance notes	TRS 943 Annex 1	2007
General guidelines for the establishment, maintenance and distribution of chemical reference substances	TRS 943 Annex 3	"
List of available International Chemical Reference Substances and International Infrared Reference Spectra	TRS 953 Annex 1	2009
List of reference substances of other pharmacopoeias found to be suitable for use according to <i>The International Pharmacopoeia</i>	Living document (2)	
Release procedure of International Chemical Reference Substances	TRS 981 Annex 1	2013
Procedure of the development of monographs and other texts for <i>The International Pharmacopoeia</i>	TRS 992 Annex 1	2015
Trade names of stationary phases found suitable in performing chromatographic tests described in <i>The International Pharmacopoeia</i>	Living document (3)	
Updating mechanism for the section on radiopharmaceuticals in <i>The International Pharmacopoeia</i>	TRS 992 Annex 2	2015
Good pharmacopoeial practices	TRS 996 Annex 1	2016
*Glossary		
* <i>The International Pharmacopoeia</i> : revised concepts and future perspectives (Update of TRS 908, Annex 2)	To be published	2017

**Quality control testing**

*Considerations for requesting analyses of drug samples	TRS 902 Annex 4	2002
*Model certificate of analysis	TRS 902 Annex 10	"

*Continued*

(1) Available on CD ROM and on the WHO website at <http://apps.who.int/phint/en/p/about/>

(2) Since 2010 the European Directorate for the Quality of Medicines & HealthCare (EDQM) is responsible for the distribution of WHO's International Chemical Reference Substances (ICRS). See [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/qas\\_icrs/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/qas_icrs/en/) for information on ICRS

(3) Available at [www.who.int/medicines/publications/pharmacopoeia/en/](http://www.who.int/medicines/publications/pharmacopoeia/en/)



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*Continued***Quality control laboratories**

WHO good practices for pharmaceutical quality control laboratories Appendix 1: Equipment for a first-stage and medium-sized pharmaceutical quality control laboratory	TRS 957 Annex 1	2010
WHO good practices for pharmaceutical microbiology laboratories	TRS 961 Annex 2	2011
WHO guidelines for preparing a laboratory information file	TRS 961 Annex 13	“
<i>Prequalification of quality control laboratories, see under “WHO Prequalification”</i>		

**Development**

Pharmaceutical development of multisource (generic) finished pharmaceutical products – points to consider	TRS 970 Annex 3	2012
Development of paediatric medicines: points to consider in formulation	TRS 970 Annex 5	“

**Production****Good manufacturing practices (GMP)***General guidelines*

WHO GMP for pharmaceutical products: main principles	TRS 986 Annex 2	2014
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*Supplementary guidelines*

Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans	TRS 863 Annex 7	1996
GMP: authorized person - role, functions and training	TRS 885 Annex 4	1999
Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients	TRS 885 Annex 5	“
Guidelines on Good Manufacturing Practices for radiopharmaceutical products	TRS 908 Annex 3	2003
Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines	TRS 937 Annex 3	2006
*Guidelines on validation (includes 7 appendices)	TRS 937 Annex 4	“
*Appendix 4: Analytical method validation		
*Appendix 5: Validation of computerized systems		
*Appendix 6: Qualification of systems and equipment		
Appendix 7: Non-sterile process validation	TRS 993 Annex 3	2015
WHO good manufacturing practices for active pharmaceutical ingredients	TRS 957 Annex 2	2010
WHO good manufacturing practices for pharmaceutical products containing hazardous substances	TRS 957 Annex 3	“
WHO good manufacturing practices for blood establishments	TRS 961 Annex 4	2011
*WHO guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms	TRS 961 Annex 5	“
*WHO good manufacturing practices for sterile pharmaceutical products	TRS 961 Annex 6	“
Water for pharmaceutical use	TRS 970 Annex 2	2012
Good Manufacturing Practices (GMP) for biological products <sup>(4)</sup>	TRS 996 Annex 3	2016

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*Continued***Technology transfer**

WHO guidelines on transfer of technology in pharmaceutical manufacturing	TRS 961 Annex 7	2011
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**Inspections**

*Provisional guidelines on the inspection of pharmaceutical manufacturers	TRS 823 Annex 2	1992
*Inspection of drug distribution channels	TRS 885 Annex 6	1999
*Quality system requirements for national GMP inspectorates	TRS 902 Annex 8	2002
*Guidelines on pre-approval inspections	TRS 902 Annex 7	"
WHO guidelines for drafting a site master file	TRS 961 Annex 14	2011
General guidance on "hold-time" studies	TRS 992 Annex 4	2015
Guidance on GMP: Inspection Report (includes Model certificate of GMP in Appendix 1)	TRS 996 Annex 4	2016

**Distribution**

Proposed guidelines for implementation of the WHO certification scheme	TRS 823 Annex 3	1992
*Guidelines on import procedures for pharmaceutical products	TRS 863 Annex 12	1996
WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation	TRS 917 Annex 3	2003
WHO good distribution practices for pharmaceutical products	TRS 957 Annex 5	2010
WHO Certification scheme on the quality of pharmaceutical products moving in international commerce: Questions and Answers (Q & A)	WHO Drug Information 30 (3)	2016
Good trade and distribution practices for starting materials	TRS 996 Annex 6	2016

**Procurement**

Procedure for assessing the acceptability, in principle, of procurement agencies for use by United Nations agencies	TRS 917 Annex 6	2003
Guidelines for the preparation of a procurement agency information file	TRS 917 Annex 7	
Model quality assurance system for procurement agencies (Includes Appendix 6: Interagency finished pharmaceutical product questionnaire based on the model quality assurance system for procurement agencies)	TRS 986 Annex 3	2014
Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection	TRS 986 Annex 4	"
A harmonized self-assessment tool for procurement agencies	WHO Drug Information 28 (4)	2014

**Storage**

Guide to good storage practices for pharmaceuticals	TRS 908 Annex 9	2003
Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products	TRS 961 Annex 9	2011

*Continued*

- (4) Also adopted by the Expert Committee for Biological Standardization (ECBS)
- (5) The TRS annex includes the introductory sections and an overview of the 15 technical supplements. The latter are available online at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/distribution/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/distribution/en/)

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Technical supplement materials to the WHO guidance for storage and transport of time- and temperature-sensitive pharmaceutical products	TRS 992 Annex 5 (5)	2015
<b>Monitoring medicines quality</b>		
Guidelines on the conduct of surveys of the quality of medicines	TRS 996 Annex 7	2016
*WHO guidance on testing of "suspect" substandard/spurious/falsely-labelled/falsified/counterfeit medicines	In preparation	
<b>Good pharmacy practice</b> (6)		
Joint FIP/WHO guidelines on good pharmacy practice: standards for quality of pharmacy services	TRS 961 Annex 8	2011
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	TRS 996 Annex 2	2016
<b>WHO prequalification</b> (6)		
<b>Medicines</b> (7)		
Guidelines on the requalification of prequalified dossiers	TRS 957 Annex 6	2010
Procedure for prequalification of pharmaceutical products	TRS 961 Annex 10	2011
Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format	TRS 961 Annex 15	
Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part	TRS 970 Annex 4	2012
Guidance on variations to a prequalified product	TRS 981 Annex 3	2013
Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities	TRS 986 Annex 5	2014
Collaborative procedure between the World Health Organization (WHO) prequalification team medicines and national medicines regulatory authorities in the assessment and accelerated national registration of WHO- prequalified pharmaceutical products and vaccines	TRS 996 Annex 8	2016
<b>Active pharmaceutical ingredients</b>		
Guidelines on active pharmaceutical ingredient master file procedure	TRS 948 Annex 4	2008
Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products	TRS 953 Annex 4	2009
<b>Other related products</b>		
Procedure for Assessing the acceptability, in principle of male latex condoms for purchase by United Nations agencies	TRS 948 Annex 2	2008
Procedure for Assessing the acceptability, in principle of TCU 380A intrauterine devices for purchase by United Nations agencies	TRS 948 Annex 3	"

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(6) The guidelines are available in the "Related regulatory standards" section of the WHO guidelines website, [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/regulatory\\_standards/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/)

(7) Prequalification of vaccines is conducted in line with standards provided by the WHO Expert Committee for Biological Standardization; prequalification of diagnostics is largely based on standards proposed by the International Medical Device Regulators Forum (IMDRF).

*Continued***Quality control laboratories**

*Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies (Update of TRS 962, Annex 12)	To be published	2017
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**Regulatory guidelines****General**

WHO Guideline on quality risk management	TRS 981 Annex 2	2013
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**Contract research, data management**

Guidelines for the preparation of a contract research organization master file	TRS 957 Annex 7	2010
Guidance on good data and record management practices	TRS 996 Annex 5	2016

**Interchangeability of comparator and generic products**

Multisource (generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability <sup>(8)</sup>	TRS 992 Annex 7	2015
Guidance for organizations performing in vivo bioequivalence studies	TRS 996 Annex 9	2016
*Equilibrium solubility experiments for the purpose of classification of active pharmaceutical ingredients according to the Biopharmaceutics classification system	To be published	2017
*General Background notes on the list of international comparator pharmaceutical products (Update of TRS 992, Annex 8)	To be published	"
*International Comparator Products List for equivalence assessment of interchangeable multisource (generic) products	Living document	

**Stability**

*Stability testing of active pharmaceutical ingredients and finished pharmaceutical products	TRS 953 Annex 2	2009
Stability conditions for WHO Member States by Region (Table 2 of TRS 953 Annex 2)	Living document <sup>(9)</sup>	2015

**Other**

*Guidelines on packaging for pharmaceutical products	TRS 902 Annex 9	2002
*Guidelines for registration of fixed-dose combination medicinal products	TRS 929 Annex 5	2005
WHO guidelines for sampling of pharmaceutical products and related materials	TRS 929 Annex 4	2005
Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part	TRS 986 Annex 6	2014

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(8) Includes information on WHO's current policy regarding biowaivers. The table with classifications according to the Biopharmaceutics Classification System (BCS) in the 2006 *Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms* (TRS 937, Annex 8) is under revision and will be made available as a living document. The 2006 biowaiver guidance remains on the website as it includes some useful information, e.g. in Sections 1.4 and 1.6 on the rationale for the setting of criteria.

(9) The updated table is available at [www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/regulatory\\_standards/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/regulatory_standards/en/)

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Recommendations for quality requirements when plant-derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients	TRS 992 Annex 6	2015
WHO general guidance on variations to multisource pharmaceutical products	TRS 996 Annex 10	2016
<b>Regulatory practice and collaboration</b>		
Good review practices: guidelines for national and regional regulatory authorities	TRS 992 Annex 9	2015
*Good regulatory practices: guidelines for national regulatory authorities for medical products	In preparation	2016
*Collaborative procedure in the assessment and accelerated national registration of pharmaceutical products approved by stringent regulatory authorities	In preparation, based on a pilot procedure <sup>(10)</sup>	
<b>Herbal products</b>		
Guidelines for the assessment of herbal medicines	TRS 863, Annex 11 <sup>(11)</sup>	1996
*WHO guidelines on good herbal processing practices (GHPP) for herbal medicines	In preparation	
*WHO guidelines for selecting marker substances of herbal origin for quality control of herbal medicines	In preparation	
<b>Medical devices</b>		
*WHO global model regulatory framework for medical devices including IVD medical devices	To be published	2017



(10) See <https://extranet.who.int/prequal/content/faster-registration-fpps-approved-sras>

(11) Available at: <http://apps.who.int/medicinedocs/en/d/Js5516e/>