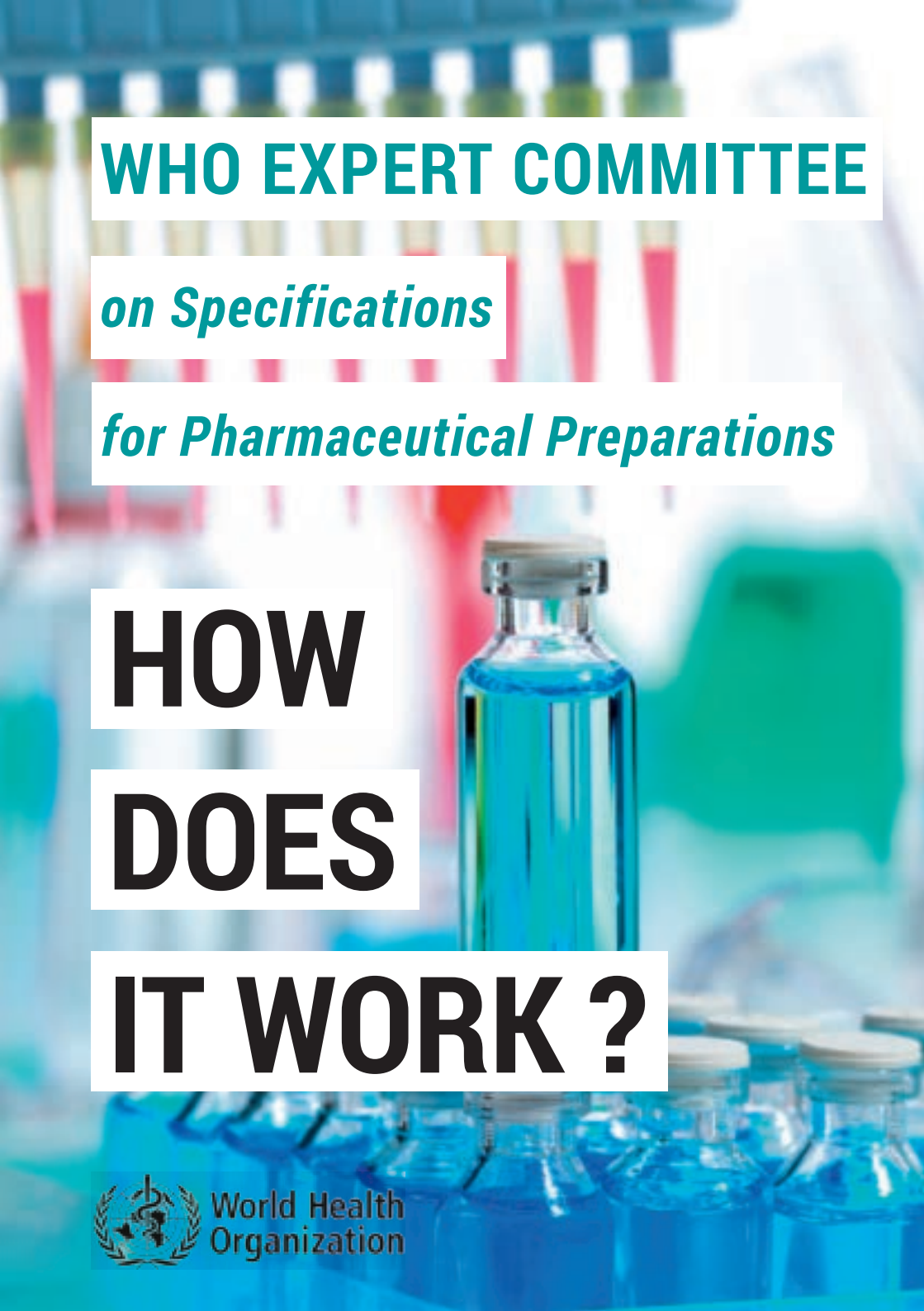




WHO EXPERT COMMITTEE

on Specifications

for Pharmaceutical Preparations

HOW

DOES

IT WORK ?



World Health
Organization



/// HOW DOES IT WORK ?

This booklet describes the basic working procedures of the World Health Organization (WHO) Expert Committees, and goes on to address specifically the WHO Expert Committee on Specifications for Pharmaceutical Preparations, which has provided formal WHO advice on medicines testing and quality assurance to Member States for more than half a century.

What is a WHO Expert Committee? An Expert Committee is the highest official advisory body to the Director-General of WHO as well as to the Organization's Member States. An Expert Committee is established by the WHO World Health Assembly by an Executive Board decision. It is governed by strict rules and procedures.

The WHO Constitution makes reference to Expert Committees in Chapter V, article 18, as well as in Chapter VIII, articles 38-40, and it has a special annex entitled "Regulations for Expert Advisory Panels and Committees". These regulations are published in *Basic Documents*, an official WHO publication.

The WHO Expert Committees each have their own scope of work in making technical recommendations on a subject of interest to the Organization. The two oldest committees are the Expert Committee on Specifications for Pharmaceutical Preparations and the Expert Committee on Biological Standardization. In addition there is the Expert Committee on Drug Dependence, the Expert Committee on the Selection and Use of Essential Medicines and there is a joint WHO/FAO Expert Committee on Food Additives. These Expert Committees are presently the most active in WHO.

Participants at WHO Expert Committee meetings include "members" who are selected from WHO Expert Advisory Panels, "temporary advisers", representatives from international organizations, nongovernmental organizations and professional associations, as well as "observers" from national pharmacopoeias. The members of WHO Expert Advisory Panels are selected through an official nomination process. Proposals for membership are based on education, background and experience. Nominations are subject to consultation with, and clearance by, the Member State of which the expert is a citizen. The respective WHO regional office and colleagues at WHO headquarters are also consulted. The first term of service is for four years, with the possibility of a renewal for one, two, three or four years.

THE EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

What is this Committee's scope of work? This Expert Committee is in charge of WHO's normative function for pharmaceuticals, which is stated in Chapter 2, article 2 (u) of the WHO Constitution, which reads that "the function of WHO is to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products".

When did the Committee's work start? This goes back far into the 20th century. The so-called Brussels Agreement, signed in 1929, mentioned the "International Pharmacopoeia" for the first time. The work continued under the League of Nations, and in 1937 the first International Pharmacopoeia meeting brought together experts from Belgium, Denmark, France, Netherlands, Switzerland, United Kingdom and United States of America, again under the auspices of the League of Nations.

In 1947 the Interim Commission of WHO took up the health-related work of the League of Nations and with that also the work of *The International Pharmacopoeia*. The first meeting of the group that was to become the WHO Expert Committee was thus held prior to the first World Health Assembly, namely from 13 to 17 October 1947. The report of that first meeting was published in 1947 in English and French in the official records of WHO, No. 8, page 54ff.

In 1948 during the first World Health Assembly, the Expert Committee was established under the name of "Expert Committee on the Unification of Pharmacopoeias". In 1951 the World Health Assembly renamed it "Expert Committee on the International Pharmacopoeia". In 1959 it was renamed the "Expert Committee on Specifications for Pharmaceutical Preparations", a title which remains to this day.

How has the work of the Committee evolved? As its early name suggests, the initial work of the Committee focused on *The International Pharmacopoeia*. Nowadays this Expert Committee covers far more than just pharmacopoeial issues. It covers all the quality assurance aspects within the medicines area, as well as recently the development of medicines. For a long time it has covered production, quality control, quality control regulatory guidelines, inspection and distribution. Thus it covers the entire life-cycle of medicines, from development through manufacture and supply chains, to delivery to the patient.

/// GUIDELINE DEVELOPMENT



How are topics for new guidelines proposed? Trigger action to start the development of a guideline or a new guidance is given at the highest level in the World Health Assembly, for instance in a resolution. The next level of trigger action can be an Executive Board resolution. Further trigger actions can be from other programmes and clusters within WHO. Expert Committee members themselves can also, of course, recommend certain courses of action or certain work to be carried out by the Secretariat.

How does the WHO Expert Committee consultation process work? The first step is usually either a first draft written by an expert in the area or the development of a first draft in the area bringing together experts in a specific field. The WHO Secretariat edits the draft, puts it into the correct format and circulates it worldwide for comments. All comments received are assembled and discussed at an informal consultation by experts in the relevant field. The draft guideline is then again circulated for comments. This process is repeated as often as necessary.

Once the Expert Committee adopts a guideline, it is included in its meeting report as an annex. Before the report is made available it is cleared within WHO up to the Director-General's office and then presented to the WHO Governing Bodies for final comments and endorsement, and for recommendation of implementation to WHO Member States and other parties. At this point the report plus the attachments, i.e. the actual guidelines, constitute WHO technical guidance in a specific area.



TRIGGER ACTION FOR NEW PHARMACEUTICAL GUIDANCE

In the history of the WHO Expert Committee on Specifications for Pharmaceutical Preparations there are examples of these different levels of trigger action. Good manufacturing practices (GMP) were triggered by WHO World Health Assembly Resolution 20.34. The Executive Board Resolution EB.37.r9 delegated certain functions of the International Nonproprietary Names (INN) Programme to the Director-General based on advice from experts.

A more specialized body that can trigger work of the Expert Committee is the International Conference of Drug Regulatory Authorities (ICDRA). For example, during the 10th and 11th ICDRAs, the fixed-dose combination guidelines and the WHO Certification Scheme for Pharmaceutical Starting Materials Moving in International Commerce were recommended. Other WHO units expressed the necessity for quality control specifications for specific medicines of major public health interest.

The Committee itself makes recommendations for future work at each of its meetings. This includes advice on the work in progress, revisions of existing guidelines and new topics to be covered, a workplan for specifications for new monographs to be developed for inclusion in *The International Pharmacopoeia*, advice on the WHO External Quality Assurance Assessment Scheme for quality control laboratories, and so forth.

DEVELOPMENT OF GUIDELINES AND SPECIFICATIONS

Guidelines are developed in consultation with the 70-member WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations, partners and other stakeholders, before they are evaluated by the Expert Committee on Specifications for Pharmaceutical Preparations. The Committee meets every year, and all the work that is in process in the field of medicines' quality assurance is presented. Should the experts consider that more work needs to be carried out then the guidelines or monograph go back into the consultation process. If the members of the Expert Committee consider that guidelines or a specification have passed through enough rounds of consultation and a consensus has been formed for certain guidelines or specification, they will be recommended for formal adoption during that meeting.

The development of pharmaceutical specifications includes additional practical steps. For instance all manufacturers of a specific product or active ingredient are contacted and asked to provide samples or specifications to WHO. Laboratory studies or scientific research are then carried out by a qualified unit, such as a WHO collaborating centre, on the suitability of the specification concerned.

PARTNERS

Partners who contribute to drafting the guidance provided through the Expert Committee on Specifications for Pharmaceutical Preparations are specialists from different quality assurance areas. For instance, when there is work on heating and ventilation systems engineers are consulted to ensure that the guidelines reflect the current knowledge in this specific area. The Committee also works closely with WHO collaborating centres which are nominated through an official process by representatives of WHO Member States. Most of the time in connection with this Expert Committee the WHO collaborating centres are situated within the national authorities and usually constitute national quality control laboratories. WHO also works closely with pharmacopoeia commissions and secretariats, national institutions and institutes that deal with matters concerning quality assurance of medicines. There is also close collaboration with regional and interregional groupings such as the International Conference on Harmonisation (ICH), the Association of Southeast Asian Nations (ASEAN), and Pan American Network for Drug Regulatory Harmonization (PANDRH).

CONSULTATION

Feedback on the draft guidance is obtained from a wide range of entities ensuring that the guidance adopted by the Expert Committee is useful, implementable and accepted by all stakeholders. Comments are invited from representatives from national and regional authorities, international organizations such as the Joint United Nations Programme on HIV/AIDS (UNAIDS), United Nations Population Fund (UNFPA), United Nations Children's Fund (UNICEF), the World Bank, World Intellectual Property Organization (WIPO), World Customs Organization (WCO), World Trade Organization (WTO), patient-centred organizations including consumer associations and humanitarian organizations such as Médecins sans Frontières (MSF), industry associations such as the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), International Generic Pharmaceutical Alliance (IGPA) and World Self-Medication Industry (WSMI); and professional organizations such as the International Pharmaceutical Federation (FIP) and the World Medical Association (WMA).



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/// OUTCOMES

What is the outcome of a WHO Expert Committee? The outcomes of the Expert Committees' work are formal WHO guidelines, which will be made available in printed form and online as part of the Expert Committees' meeting reports. These reports are published in the WHO Technical Report Series (WHO TRS) and are structured as follows: there is a summary of the discussions, and all the recommendations to WHO and its Member States are listed therein. The most important part of each report comprises the recently adopted guidelines, which are attached as annexes to the report.

OUTCOMES OF THE EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

This Expert Committee's meeting reports date back to the very beginning of the WHO TRS. The report of its fourth meeting - then still under the name of the "Expert Committee on the Unification of Pharmacopoeias" - was published in English and French as the first issue of the WHO TRS, No. 1 in January 1950.

By the time the forty-seventh Expert Committee meeting report was published as WHO TRS, No. 981 in 2013, the collection of updated guidance texts published as formal annexes to the consecutive meeting reports had grown to more than 80. Being up to date is of prime importance. Many of these texts are revised every few years to reflect new technology and international practice.

In the case of the Expert Committee on Specifications for Pharmaceutical Preparations the outcome can also be a pharmaceutical specification, which will be made available to Member States in *The International Pharmacopoeia*.

THE INTERNATIONAL PHARMACOPOEIA

The International Pharmacopoeia was the initial area of work for the Expert Committee on Specifications for Pharmaceutical Preparations. *The International Pharmacopoeia* is available for implementation and is ready for use by WHO Member States. In the beginning, it encompassed all the medicines that were available and sold globally. Since 1975 *The International Pharmacopoeia* focuses on the WHO Model List of Essential Medicines, and more recently on priority medicines in developing countries recommended by specific WHO disease programmes, for instance medicines to treat malaria, tuberculosis and HIV/AIDS, as well as medicines for children.

The International Pharmacopoeia includes: general notices; monographs for pharmaceutical substances; monographs for dosage forms and radiopharmaceutical preparations; texts on

methods of analysis; International Chemical Reference Substances (ICRS); International Infrared Reference Spectra (IIRS); reagents, test solutions and volumetric solutions. *The International Pharmacopoeia* is available in printed form and on CD-ROM, and can be freely accessed online.¹ *The International Pharmacopoeia* is updated regularly, including the newly adopted specifications.

In addition, WHO has published three volumes in the “basic test” series for pharmaceutical substances, medicinal plant materials and dosage forms. This series provides simple tests to confirm the identity of medicinal substances when a fully equipped laboratory is not available.

International reference materials, including ICRS and IIRS adopted by the Committee serve to validate the procedures described in the monographs of *The International Pharmacopoeia*. ICRS were managed by the WHO Collaborating Centre for Chemical Reference Substances in Sweden from 1946 until 2009. Since 2010 the European Directorate for the Quality of Medicines and HealthCare (EDQM) located in the Council of Europe, Strasbourg, France, has been taking care of the establishment, maintenance and distribution of ICRS. WHO has recently invited national control laboratories to participate in collaborative studies to characterize ICRS.

MEDICINES QUALITY ASSURANCE GUIDELINES

The Expert Committee on Specifications for Pharmaceutical Preparations provides guidance on pharmaceutical quality assurance at every step of a medicine's life-cycle. The guidelines are published as annexes to the annual Expert Committee meeting reports, and are freely available on the Web.² A more detailed overview is given in the booklet *Expert Committee on Specifications for Pharmaceutical Preparations: Meeting a Major Public Health Challenge*.

Guidance on quality control includes good laboratory practices and related training materials, procedures for establishment of chemical reference standards, model certificate of analysis, and prequalification of quality control laboratories for use by United Nations (UN), agencies, to test whether pharmaceutical products meet the specifications that have been set for them.

1 www.who.int/entity/medicines/publications/pharmacopoeia/en/index.html.

2 www.who.int/medicines/publications/pharmprep/en/index.html (meeting reports and annexes published in the WHO Technical Report Series since 1965).

Or: www.who.int/medicines/areas/quality_safety/quality_assurance/guidelines
(guidelines by broad areas, including “Current Projects”, i.e. texts still open for comment).



Guidelines on manufacture and production aim to ensure that quality is built into pharmaceutical products, so that each batch produced is likely to conform to its specifications. These guidelines mainly cover the aspects of GMP, which consist of a parent guideline and a large number of specific good practices. WHO also provides training materials with slides, a training video and the full GMP text on a CD-ROM and in printed form. More recently, the Committee has adopted guidelines on pharmaceutical quality risk management, transfer of technology, as well as points to consider in development of multisource (generic) products and medicines designed especially for children.

Guidelines on prequalification comprise the norms and standards used by the WHO Prequalification of Medicines Programme to provide assurance that a product or service is acceptable, in principle, for use by UN agencies. The first list of prequalified medicines was published in 2002 with regular updates and rapidly became the vital tool for bulk purchasing of medicines that it is today used by a wide range of organizations. Prequalification was then extended to other areas: the first quality control laboratories became prequalified in 2005, and the first active pharmaceutical ingredients in 2011, based on norms and standards adopted by the Expert Committee. These prequalification guidelines can also be used or adapted by regulatory authorities to control the quality of medicines circulating in their territories. Building on WHO's detailed assessment work, a collaborative procedure for medicines' registration was published in 2013: prequalification assessment information can be shared confidentially with regulatory authorities at the applicant's request to help expedite national registration.



Guidance on distribution of pharmaceutical products aims to secure the pharmaceutical supply chains from the manufacturer to the end-user. WHO guidance on distribution includes certification schemes for finished products circulating in international commerce and for pharmaceutical starting materials, a model quality assurance system for procurement, good distribution practices for starting materials and finished products, and good storage practices. Importantly, this guidance also covers good pharmacy practice: in providing pharmaceutical products to the end-users, pharmacists and other health professionals play a pivotal role in ensuring that medicines are used rationally, achieving the best possible outcomes for individual patients and public health.

Regulatory guidelines other than the texts mentioned above have been provided in a number of areas. On inspection, they include a quality system for inspectorates, pre-approval inspection and inspection of manufacturers and distribution channels. On dossier assessment, guidance is provided on stability testing requirements, assessment of bioequivalence to establish the interchangeability of generic/multisource products, and assessment of fixed-dose combinations. More generally, WHO has provided guidance for small regulatory authorities, and guidelines on submission of product dossiers in common technical document format to facilitate regulatory collaboration and harmonization.

Detailed regulatory guidance is also provided in the 2011 WHO manual entitled *Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for National Medicines Regulatory Authorities (NMRAs)*, known as “The Blue Book”.³

/// BENEFITS AND COSTS

WHO's Expert Committees are at the heart of the Organization's work to provide independent expert advice to Member States and other stakeholders in accordance with WHO's mandate. As increasing budget constraints in Member States affect WHO'S resources and ability to obtain expert support, this service is challenging to maintain.

ADVANTAGES OF EXPERT COMMITTEE MEDICINES QUALITY ASSURANCE STANDARDS

The advantages of the Expert Committee's standards and ways of working include the following : firstly, all guidelines and specifications are validated internationally through an independent scientific process and adopted by the members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations; secondly, collaboration with standard-setting organizations and parties includes regional and international pharmacopoeias and thus has a vast network of organizations that work in this specific field; thirdly, there is networking and close collaboration with WHO Member States, medicines regulatory authorities, national medicines quality control laboratories and any national or regional authority involved in this type of work; fourth, there are links with other WHO activities; fifth, there is a reality check and input is taken into account from manufacturers, including international associations of research, global generic and self-medication associations; sixth, there is a consideration of costs which are kept as low as possible to achieve maximum benefit, for instance, the need for reference standards for monographs is kept to a minimum without compromising the quality; and seventh, the service is free for use by all Member States, although in light of increasing funding challenges WHO reserves the right to introduce costs for some of its services in the future.



/// FUNDING



While funding for the Expert Committee and its related activities was largely covered by WHO's regular budget in the past, this funding source has decreased to virtually zero in recent years. A small part of costs has been assumed by the European Union and WHO Member States, while the major part comes from donors, mainly the Bill and Melinda Gates Foundation and UNITAID. The future of funding is uncertain.

In addition, the Programme can count on additional in-kind contributions and support by Member States, which are valued at a multiple of its operational budget. These contributions come especially from national quality control laboratories and national support to WHO collaborating centres as well as, very importantly, time given by individual experts.

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