WHO EXPERT COMMITTEE on Specifications for Pharmaceutical Preparations

MEETING A MAJOR PUBLIC HEALTH CHALLENGE

Quality assurance of pharmaceuticals:
This booklet provides an overview of guidelines on pharmaceutical quality assurance as adopted by the Expert Committee on Specifications for Pharmaceutical Preparations in recent years.

MEETING A PUBLIC HEALTH CHALLENGE

Quality assurance of pharmaceuticals has become a major public health challenge. Diseases know no borders; to combat the effects of diseases, countries need medicines that are manufactured to the same standards of safety and effectiveness so that they can be relied on everywhere. And as international demand for medicines grows, substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products have been found in both developing and developed countries. Such products are at best ineffective, resulting in the growth of drug resistance and prolonged or ineffective treatment for patients, and at worst they are dangerous, putting lives at risk, even resulting in death.

Medicines that are ineffective or harmful not only damage lives but also waste public resources. The Constitution of the World Health Organization (WHO) states that one of the Organization’s primary functions is “to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products”. WHO provides global standards for pharmaceutical ingredients, good manufacturing practices (GMP), testing of products, regulatory guidelines for authorization of marketing, and correct storage and distribution practices.
THE EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

The development of norms, standards and guidelines for the quality assurance and quality control of pharmaceuticals is an essential global task. As a fundamental role of WHO, this task has been endorsed by many resolutions of the World Health Assembly. It is a task that WHO is uniquely suited to carry out.

Thus, guidelines on the quality assurance of pharmaceuticals are prepared in consultation with the 70-member WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and are then evaluated by the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Expert Committee’s original role of developing The International Pharmacopoeia has expanded over time and in light of new technologies. The Committee’s rigorous consultative process involves WHO Member States, national authorities and international agencies such as the United Nations Children’s Fund (UNICEF).

The Expert Committee is convened annually to decide on adopting the guidelines as international standards. The report of each meeting includes the newly adopted guidelines in its annexes.
VITAL TOOLS FOR GOOD-QUALITY MEDICINES

Through the quality assurance tools and systems developed under the auspices of the Expert Committee, WHO aims to ensure that all essential medicines, including those used in treating large populations, meet identical standards of quality, safety and efficacy.

Not only the health services and national medicines regulatory authorities (NMRAs) of WHO Member States worldwide, but also pharmaceutical manufacturers, international bodies – such as the Global Fund to Fight, AIDS, Tuberculosis and Malaria – and procurement agencies all depend on the Expert Committee’s international guidelines, specifications and nomenclature. The output of the Expert Committee additionally supports global initiatives such as the WHO Prequalification of Medicines Programme, the Medicines for Malaria Venture, and Stop TB.

This brochure aims to give an insight into the Expert Committee’s work by summarizing some of the vital tools for ensuring pharmaceutical quality that were discussed and approved in recent years. All current WHO quality assurance guidelines adopted by the Expert Committee on Specifications for Pharmaceutical Preparations, together with related training materials, are available in a structured format on CD-ROM and on the Internet. A list of current guidelines is included at the end of this document.
The International Pharmacopoeia (Ph.Int.) is a collection of quality specifications for pharmaceutical substances (active ingredients and excipients) and dosage forms, together with supporting general methods of analysis. Its texts can be used or adapted by any WHO Member State wishing to establish legal pharmaceutical requirements.

The Ph.Int. is based primarily on medicines included in the current WHO Model List of Essential Medicines (EML). In recent years, priority has been given to medicines of importance in developing countries, including child-friendly dosage forms. International health funders and implementers of treatment programmes to combat AIDS, tuberculosis (TB) and malaria also rely heavily on the Ph.Int.

WHO collaborates with other organizations worldwide towards harmonization of pharmacopoeias. An Index of national, regional and international pharmacopoeias is maintained on WHO’s website. In 2012 WHO hosted the first international meeting of world pharmacopoeias in Geneva and the forty-seventh Expert Committee endorsed the resulting recommendation to develop harmonized guidance on good pharmacopoeial practices under the aegis of WHO.

This section provides an overview of Ph.Int. monographs and general texts adopted by the Expert Committee in recent years.
MONOGRAPHS

The *International Pharmacopoeia* is freely available online,¹ as a CD-ROM and in printed format. It is currently in its Fourth Edition, comprising two main volumes published in 2006, a First Supplement published in 2008, a Second Supplement published in 2011, including a section on monographs for radiopharmaceuticals, and a Third Supplement in 2013, containing 439 monographs on pharmaceutical substances, 161 specific monographs on dosage forms, nine general monographs on dosage forms, 60 texts on methods of analysis and 27 monographs on radiopharmaceuticals.

Since 2005 nine antiretroviral active pharmaceutical ingredient (API) monographs and 29 antiretroviral dosage form monographs have been newly adopted or revised; six of the latter (didanosine capsules, efavirenz tablets, emtricitabine and tenofovir tablets, emtricitabine capsules, emtricitabine + tenofovir + efavirenz tablets, and ritonavir tablets) were recently adopted.

Similarly, significant work was accomplished for antimalarials. Six API monographs (artenimol, artesunate, artemisinin, lumefantrine, mefloquine hydrochloride and doxycycline hyclate), and 11 dosage form monographs have been added and/or revised since 2005. Monographs for artemisinin tablets and capsules were withdrawn as these dosage forms are no longer recommended.

For antituberculosis (anti-TB) medicines, the Expert Committee has added or revised eight substance monographs since 2005 (amikacin, amikacin sulphate, capreomycin sulphate, kanamycin acid sulphate, kanamycin monosulfate, ofloxacin, levofloxacin and rifampicin), and 15 dosage form monographs, including two dispersible forms for children.

A total of 41 monographs for other essential medicines were adopted at the Committee’s meetings held since 2007, including anti-infective, antiparasitic, anticonvulsant and analgesic medicines, as well as medicines for reproductive health and for the management of diarrhoea. Fourteen were API monographs and 27 were dosage form monographs, including four developed in collaboration with the British Pharmacopoeia. Of the 27 dosage form monographs 11 were for child-friendly dosage forms such as oral solutions or chewable tablets.

QUALITY REQUIREMENTS FOR ARTEMISININ AS A STARTING MATERIAL

Artemisinin is extracted from plant material with no prior intermediates, and it is therefore logical to designate this compound as the starting material for its derivatives – such as artemether or artesunate – in applications for marketing authorizations for antimalarial medicines. The purpose of this document is to offer a global approach to defining the level of quality requirements of artemisinin extracted from *Artemisia annua L.* – regardless of variations in agricultural environment or in extraction and purification steps – when it is used as a starting material for the production of its API derivatives used in artemisinin-based combination therapy (ACT) formulations. The document does not apply to cases where artemisinin itself is used as an API.

The aim of the recommendations is to define acceptable levels of impurities that ensure safety and efficacy of the finished products without adding unnecessary cost. Competent authorities may accept other impurity profile levels to lead to artemisinin-derived APIs at least compliant with the relevant monographs of *The International Pharmacopoeia*. Manufacturers may add additional tests, such as tests for residual solvents and heavy metals, and/or require tighter specifications. Other requirements may be applicable to artemisinin produced using synthetic chemical processes or by fermentation.

RADIOPHARMACEUTICAL MONOGRAPHS

Monographs for radiopharmaceuticals are maintained in *The International Pharmacopoeia* in collaboration with the International Atomic Energy Agency (IAEA). The forty-eighth Expert Committee approved a 13-stage process for updating the relevant section in line with the thorough review and consultation process used for content of *The International Pharmacopoeia*. 
HARMONIZED GENERAL METHOD TEXTS

To support harmonization of pharmacopoeial texts, during its forty-second and forty-fourth meetings, the Expert Committee endorsed the suggestion to synchronize revisions of method texts of The International Pharmacopoeia in line with finalized, harmonized texts of the Pharmacopoeial Discussion Group (PDG), comprising the European Pharmacopoeia, Japanese Pharmacopoeia and United States Pharmacopeia. All three pharmacopoeias subsequently gave their authorization that the sign-off text could be used as a basis for publication in The International Pharmacopoeia. At its forty-sixth and forty-seventh meetings the Expert Committee adopted a number of internationally-harmonized general texts after the usual consultative review process, and agreed on a maintenance procedure for these texts. At the forty-eighth meeting information was added on reference substances used in calibration of melting-point instruments, on strengths of medicines in line with the 18th Edition of the EML, and on the applicability of the revised monograph on dissolution testing.

GUIDANCE NOTES ON RELATED SUBSTANCES TESTS FOR DOSAGE FORM MONOGRAPHS

The purpose of a test for related substances is to control degradation impurities in medicines, and to limit impurities arising during synthesis of the API where possible. This approach enables an independent control laboratory, without access to the manufacturer’s data, to determine whether an API of pharmacopoeial quality has been used to produce the dosage form being tested.

Unless there is evidence that limits for related substances should be set based on toxicity, they will be based on batch data for pharmaceuticals manufactured in compliance with GMP. Limits may need to be set higher in dosage form monographs than in the corresponding API monograph and higher for oral solutions than for tablets. Factors such as the number of impurities present, the type of dosage and dose regimen, will also be taken into account.

These guidelines provide a detailed decision process to follow in order to adapt the related substances test to individual circumstances of specific dosage form monographs.
International Chemical Reference Substances (ICRS) are used by laboratories to test pharmaceuticals for the purpose of quality control. These substances are mainly used for validating the results from specific tests and, as primary standards, for calibrating secondary standards. ICRS are primarily intended for use by NMRAs and quality control laboratories of pharmaceutical manufacturers in physical and chemical tests and assays described in the specifications for quality control of medicines in The International Pharmacopoeia. They can also be used in tests and assays not described in The International Pharmacopoeia, but in that case the responsibility for assessing suitability of substances rests with the user or the body that authorized their use.

Following a complex procedure aligned with the WHO Guidelines on the establishment, maintenance and distribution of chemical reference substances, lists of these substances have been adopted by the Committee and are regularly updated. The focus is on essential medicines and on medicines used to treat large populations, for which international quality requirements are often not publicly available.

Since 2010 WHO’s collection of ICRS is maintained by the Council of Europe’s European Directorate for Quality of Medicines and HealthCare (EDQM), which also distributes the substances worldwide. EDQM is responsible for obtaining candidate material, testing it to ensure its purity and suitability and reporting results with recommendations to WHO.
AVAILABLE ICRS

A complete, searchable list of available ICRS is publicly available on the Internet in the EDQM online database. The list had 236 entries as at October 2013. The first ICRS developed by EDQM, lumefantrine for system suitability testing, was adopted by the forty-sixth Expert Committee. The forty-seventh Expert Committee adopted nine new ICRS, one International Infrared Reference Spectrum (IIRS), as well as new policies on naming ICRS in The International Pharmacopoeia, and on analytical testing of high-purity candidate material. The forty-eighth Expert Committee endorsed the adoption of 11 ICRS approved by the ICRS Board, and the withdrawal of 13 ICRS that no longer had a pertinent monograph in The International Pharmacopoeia.

ESTABLISHMENT, MAINTENANCE AND DISTRIBUTION OF CHEMICAL REFERENCE SUBSTANCES

WHO guidelines aim to ensure the integrity of national and regional collections of primary chemical reference substances – materials whose assigned content when used as an assay standard are accepted without requiring comparison to another chemical substance – as well as secondary reference substances – materials whose characteristics are calibrated by comparison with a primary chemical reference substance.

The revised guidelines adopted by the forty-first Expert Committee contain an expanded section on secondary reference substances supplied as regional or national standards, and guidance on needs assessments to rationalize the costs of procuring source material, testing methods, and packaging, distribution and supply. The forty-eighth Expert Committee approved a chapter on reference substances and reference spectra for inclusion in the supplementary section of The International Pharmacopoeia, describing the principles applied during the establishment and use of ICRS.

RELEASE PROCEDURE OF INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

The forty-fifth Expert Committee adopted a new process for release of ICRS to expedite the establishment of new reference substances, enabling WHO to react faster to the urgent demand. The forty-seventh Expert Committee established the ICRS Board which became operational immediately after the meeting, and agreed on a new release procedure that was implemented successfully.

LABORATORIES

Although quality control testing of pharmaceutical product samples by laboratories cannot replace proactive quality assurance measures at all stages of the medicine’s life-cycle, it is an essential tool in verifying that products continue to conform to the specifications that have been set for them. National laboratories evaluate samples as part of registration to test the specifications submitted with product dossiers, and as part of subsequent post-marketing surveillance.

Laboratory analysis is expensive. WHO guidance promotes a rational, risk-based approach to testing, recommends measures to reduce the likelihood of invalid results and need for retesting, and provides a basis for collaboration and sharing of results.

WHO also offers the only global, independent scheme to measure laboratories’ quality control testing capabilities. The External Quality Assurance Assessment Scheme (EQAAS), established in 2000, is organized with EDQM as a reference laboratory. Over 60 laboratories across WHO’s six regions, many of them in Africa, have participated in comparative proficiency testing.

In 2004 WHO, in collaboration with United Nations (UN) agencies, started the Prequalification of Quality Control Laboratories Programme. Prequalified laboratories perform testing of specifications for medicines submitted for prequalification, product testing in WHO quality surveys, and product testing as part of procurement by UN agencies and other entities.
PREQUALIFICATION OF QUALITY CONTROL LABORATORIES

WHO offers a procedure to prequalify quality control laboratories for use by UN agencies. Participation is open to laboratories in the private and public sectors. Certification, such as the International Organization for Standardization (ISO), is encouraged and taken into account during assessments. The procedure considers: information about the laboratory supplied by the national regulatory authority and by the laboratory itself; the laboratory’s quality control activities; and the level of quality control consistency attained through compliance with GMP and WHO guidelines. If the laboratory is deemed acceptable, it is placed on the list of WHO-prequalified quality control laboratories and published on the website of the WHO Prequalification Team-Medicines.

Based on experience from implementation and growing interest of laboratories to become prequalified, the procedure was revised in 2011 to align it with other updated WHO guidelines, to clarify the possibility for recognition of inspections or audits by other stringent authorities, to set rules for priority assessment of interested laboratories and to monitor performance after prequalification.

WHO GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

This document, originally entitled *WHO Good practices for national pharmaceutical control laboratories*, came into being before the WHO Prequalification Programme. Its use as one of the standard texts for prequalification of quality control laboratories showed that some of the text was not sufficiently clear. At its forty-third meeting in 2008, the Expert Committee identified areas of the document that needed clarification and proposed that the title of the document should be made more broadly applicable.

The forty-fourth Expert Committee adopted the revised good practice guidelines, which are intended for pharmaceutical quality control laboratories that analyse APIs, excipients and/or pharmaceutical products. The guidelines provide advice on the quality management system within which the analysis should be performed to obtain reliable, traceable results. References to relevant GMP texts are also included. Implementation of these guidelines is expected to promote international harmonization of laboratory practices and to facilitate cooperation among laboratories and mutual recognition of results.
WHO GOOD PRACTICES FOR PHARMACEUTICAL MICROBIOLOGY LABORATORIES

During the inspections carried out when prequalifying laboratories, WHO inspectors had noticed that an additional specific text for pharmaceutical microbiology laboratories might be useful to supplement the *WHO good practices for pharmaceutical quality control laboratories*. A draft text was developed through the usual wide consultation process and was adopted by the forty-fifth Expert Committee.

The guidelines relate to all microbiology laboratories, whether they are independent or a department or unit of a pharmaceutical manufacturing facility, involved in sterility testing, detection, isolation, enumeration and identification of microorganisms (bacteria, yeast and moulds) as well as testing for bacterial endotoxins in different materials (e.g. starting materials, water), products, surfaces, garments and the environment and assay using microorganisms as part of the test system.

WHO GUIDELINES FOR PREPARING A LABORATORY INFORMATION FILE

A laboratory information file (LIF) is a document prepared by the laboratory with specific and factual information about the operations carried out at the named site and any closely integrated operations of the laboratory, intended to facilitate audits and inspections. Revised guidelines for preparing a LIF were published in 2011 in line with the revised *Good practices for pharmaceutical quality control laboratories and procedures for prequalification of laboratories*.
WHO GOOD MANUFACTURING PRACTICES

GMP is 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. GMP is aimed primarily at diminishing the risks inherent in any pharmaceutical production, which may broadly be categorized in two groups: contamination and mix ups, as well as false labelling.

*WHO good manufacturing practices for pharmaceutical products: main principles* are the parent guidelines. They are updated periodically to take into account the latest developments and current thinking in GMP globally. The revision published in 2011 incorporates the concepts of validation and risk management. A further revision was adopted by the forty-eighth Expert Committee to introduce the concept of a pharmaceutical quality system for the manufacturer’s operations and outsourced activities, extending to the pharmaceutical development stage as appropriate to facilitate innovation and continual improvement.

Twelve supplementary guidelines on specific aspects of pharmaceutical manufacturing form an integral part of the parent GMP guidelines. Eight of these have been introduced or revised since the fortieth Expert Committee meeting, as summarized below; the other four are listed in *Annex 1*.

These GMP standards underpin WHO prequalification and collaboration with regulatory authorities in inspections and serve as model guidelines for implementation in Member States.
SUPPLEMENTARY GMP GUIDELINES

• Heating, ventilation and air-conditioning (HVAC) systems

Pharmaceuticals must be manufactured, packaged and stored in a controlled, uncontaminated environment, free from impurities, dust and foreign matter. HVAC systems maintain the proper temperature, humidity and ventilation throughout the pharmaceutical manufacturing site, and contain toxic substances. HVAC systems’ design must be considered in the architectural layout of sites, including airlocks to regulate airflow between rooms of differing classes of cleanliness, and environmentally controlled “clean rooms”. HVAC protects pharmaceutical products, personnel and the environment, and should be part of every facility’s blueprint.

These guidelines, which are rather unique in the regulatory context, advise both manufacturers and inspectors of these facilities about the design, installation, qualification and maintenance of HVAC systems. They focus on solid dosage forms, although most of the system design principles will also apply to facilities that manufacture medicines in other forms such as liquids, creams and ointments. The document was updated in 2011 to allow for inclusion of new trends and harmonization with other new guidance published, e.g. by ISO.

• Validation

Validation is the documented act of proving that a procedure, process, activity, material, piece of equipment or system actually achieves its expected results. It is an essential concept in GMP. Through validation a manufacturer establishes confidence that each stage of the manufacturing process is designed in such a way that the end-products will consistently meet the specifications that have been defined for them. In other words, the principles of quality assurance recognize that quality, safety and efficacy must be designed and built into a product. They cannot be inspected or tested into it. Validation often requires considerable resources, collaboration of multidisciplinary teams and documentation.

These guidelines help pharmaceutical manufacturers and regulatory inspectors to optimize the use of resources by guiding them on validation requirements, including those for HVAC systems, water systems for pharmaceutical use and computerized systems.

• GMP for active pharmaceutical ingredients

WHO’s GMP guidance for APIs was first published in 1992. It aims to ensure that APIs meet the requirements for quality and purity that they are represented to possess. The guide does not cover the safety of manufacturing personnel or aspects of environmental protection; these aspects are governed by national laws. The text adopted by the forty-fourth Expert Committee was revised in extensive consultation with inspectors, experts and interested parties to reflect current GMP requirements in line with International Committee on Harmonisation (ICH) principles and other published guidelines, facilitating international implementation.
The document applies to the manufacture of APIs by chemical synthesis, extraction, cell culture or fermentation, by recovery from natural sources, or by any combination of these processes for use in finished pharmaceutical products (FPPs). It does not apply to the sterilization and aseptic processing of sterile APIs; these processes should be performed in accordance with GMP guidelines for finished products as defined by local authorities.

**• GMP for pharmaceutical products containing hazardous substances**

These guidelines describe good practices for facilities handling pharmaceutical products (including APIs) that contain hazardous substances. The guidance was drafted at a time of international concern about the low quality of reproductive health products and the lack of compliance with GMP principles in manufacturing facilities. While the initial draft focused on certain hormones, its scope was extended to cover other hazardous substances such as steroids and cytotoxins.

The guidelines, adopted by the forty-fourth Expert Committee, recommend measures to apply in all areas where the handling of hazardous products could lead to cross-contamination, exposure of personnel or discharge into the environment. Such areas include research and development facilities, manufacturing and storage sites of APIs and sites of finished product manufacturing. The guidelines do not replace national legislation for safety of personnel and protection of the environment.

**• GMP for sterile pharmaceutical products**

These guidelines, first adopted in 1999, were revised based on experience of their implementation within the context of the Prequalification Programme to align them with new developments in technology, relevant ISO and Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) standards, and recent practices in the European Union, Japan and the United States of America.

The guidelines stress that the sterility test applied to the finished product should be regarded only as the last in a series of control measures by which sterility is assured: production in clean areas accessible only through airlocks for personnel and/or for equipment and materials; appropriate standards of cleanliness and air filter efficiency; and separate areas within the clean area for preparation of containers and closures, product preparation, filling and sterilization.

In adopting the revised guidelines, the forty-fourth Expert Committee recommended a stepwise approach for implementation, especially to the part on provisions for capping in a clean or sterile environment, which was not implemented in most industries at the time. The text was republished with editorial revisions in 2011.
• GMP for herbal medicines

While the general principles of GMP apply to all types of pharmaceuticals, herbal substances derived from leaves, seeds, bark, essential oils and resins often require different procedures than pharmaceuticals of synthetic origin. This is because herbal substances are frequently derived from different geographical sources, subject to diverse conditions, and vary in composition and properties, and are especially susceptible to contamination, degradation and infestation with certain pests.

These guidelines detail those protocols for hygiene, sanitation and processing that are specific to herbal medicines, such as quarantining of incoming matter to prevent the spread of microorganisms, maintenance of segregated areas for different herbal materials, appropriate environmental control, including control for dust, fumes and vapours generated by the processing of these substances, and cleanliness of equipment to avoid microbiological contamination.

• GMP for blood establishments

Amidst concerns about the availability, safety and quality of blood products, the World Health Assembly, in its Resolution WHA63.12, stressed the need to strengthen regulatory oversight for blood products as a measure to increase global availability of plasma that meets internationally-recognized standards. Relying on the expertise of the specialists in the Expert Committee on Biological Standardization, the Expert Committee on Specifications for Pharmaceutical Preparations agreed to provide this GMP text as part of its comprehensive WHO GMP guidance. The text is intended for blood establishments and regulatory authorities.

The text covers topics specific to the manufacturing of blood components, from donor selection to distribution of the final product. To cater for users that do not routinely work with the overall applied GMP principles, it also covers general GMP principles and concepts. It does not address the practice of transfusion medicine or management of emergencies where specific national policies apply. Aspects of personnel and environmental protection are also outside the scope of this document.
• Water for pharmaceutical use

Control of the quality of water throughout the production, storage and distribution processes, including microbiological and chemical quality, is a major element of GMP. Unlike other product and process ingredients, water is usually drawn from a system on demand, and is not subject to testing and batch or lot release before use. Assurance of quality to meet the on-demand expectation is therefore essential. Additionally, certain microbiological tests may require periods of incubation and therefore the results are likely to lag behind the water use.

The guidelines provide information about the available specifications for water for pharmaceutical use, about the quality grades of water to use for specific applications such as the manufacture of APIs and dosage forms, and about good practices regarding the design, installation, qualification, validation and operation of pharmaceutical water systems. They do not relate to water for administration to patients in the formulated state or the use of small quantities of water in pharmacies to compound individually-prescribed medicines.

• Drafting a site master file

This document aims to guide manufacturers of pharmaceutical products in preparing a site master file (SMF) for use by the regulatory authority or other entities in planning and conducting GMP inspections, whether or not it is required by regional and/or national regulations. The SMF gives details on all areas of manufacturing operations such as production, packaging and labelling, testing, relabelling and repackaging of all types of pharmaceutical products.
QUALITY RISK MANAGEMENT

Quality risk management (QRM) is the overall and continuing process of appropriately managing risks to product quality throughout the life-cycle of a product in order to optimize its benefit/risk balance. Building on the earlier approach of hazard analysis and critical control point (HACCP) methodology as applied to pharmaceuticals at the turn of the millennium, it is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

This document is aligned with ICH and other current international guidance. It guides manufacturers and regulatory authorities in implementing effective QRM in research and development, sourcing of materials, manufacturing, packaging, testing, storage and distribution. The QRM outputs can serve as reference documents to support product development and control strategy discussions in regulatory filings.

TRANSFER OF TECHNOLOGY

Transfer of technology is a systematic procedure that is followed in order to pass the documented knowledge and experience gained during development and/or commercialization of a product to an appropriate, responsible and authorized party. While transfer of processes to an alternative site occurs at some stage in the life-cycle of most products, the ever-changing business strategies of pharmaceutical companies increasingly involve transfers of technology for reasons such as the need for additional capacity, relocation of operations or consolidations and mergers. The forty-second Expert Committee therefore recommended that WHO provide guidelines on this matter.

These guidelines describe a planned approach to transfer of technology, leading to documented evidence that the receiving unit can routinely reproduce the transferred product, process or method against a predefined set of specifications to the satisfaction of all concerned parties and any applicable regulatory bodies. Because each transfer project is unique, these guidelines outline general principles which must be adapted to the specific circumstances. The document does not provide guidance on legal, financial or commercial considerations.
DEVELOPMENT OF MULTISOURCE (GENERIC) PHARMACEUTICAL PRODUCTS – POINTS TO CONSIDER

Multisource pharmaceutical products are considered equally safe and effective as the comparator product – usually the innovator product – if they have been shown to be bioequivalent to the relevant comparator product and if they meet the same standards of manufacturing quality. In the development of multisource products, pharmaceutical development studies and the manufacture of primary batches are essential elements for a science- and risk-based approach to establish the critical quality attributes of the product and the critical process parameters of the manufacturing process.

These guidelines, adopted by the forty-seventh Expert Committee, provide a structured approach to the development of high-quality, multisource FFP containing existing APIs of synthetic or semisynthetic origin. The guideline follows the ICH common technical document (CTD) format, which allows for a logical, progressive description of the development process.
DISTRIBUTION

Distribution of pharmaceutical products covers every step of their division and movement from the manufacturer’s premises to the end-user. Great care must be taken at every step to preserve product quality, to protect the supply chain and to ensure rational medicines use, so that the greatest possible benefits are achieved for individual patients and for public health.

Accordingly, WHO guidelines on distribution of pharmaceutical products in its widest sense cover a range of aspects, including transport, storage, procurement and dispensing of medicines to patients.

GOOD DISTRIBUTION PRACTICES (GDP)

The process of handling, storing and distributing pharmaceutical products involves a range of people and entities, including pharmaceutical manufacturers, brokers, suppliers and wholesalers, transport companies and forwarding agents. Control measures are needed to prevent mix ups, contamination and cross-contamination throughout the numerous activities that occur during distribution, and to protect the supply chains against infiltration by illegitimate products.

Amidst growing concerns about SSFFC medical products, which are reaching patients even in highly-regulated countries through regulated distribution, the WHO guidelines on distribution were revised by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) partnership in 2008 and further discussed between WHO, IMPACT and the European Union in 2009. The revised guidelines were adopted by the Expert Committee at its forty-fourth meeting.

The guidelines are designed to help ensure the quality and integrity of medicines through all stages of distribution. They provide the steps for meeting GDP responsibilities, including protocols for personnel who handle medicines, warehousing and storage precautions, management of shipment containers and transport, labelling and relabelling, procedures for vehicles and equipment, and steps to be taken when “suspicious” pharmaceutical products are found in the distribution chain. Further revision of WHO guidance on good trade and distribution practices was discussed at the forty-seventh Expert Committee meeting.
STORAGE AND TRANSPORT OF TIME-AND TEMPERATURE-SENSITIVE PHARMACEUTICAL PRODUCTS

These guidelines were developed jointly with the Expert Committee on Biological Standardization. They set out the principal requirements for the safe storage and distribution of time- and temperature-sensitive pharmaceutical products, supplementing local legislation and regulations.

The document is designed to give a balanced overview of the major aspects of good storage and distribution practice for time- and temperature-sensitive pharmaceutical products, as found in general guides to good practice referenced in this guideline. Experience with vaccine supply chain assessments in many less-developed countries demonstrates that the mandatory standards set out in this document can be achieved and that some countries are also capable of meeting many of the optional requirements.

MODEL QUALITY ASSURANCE SYSTEM (MQAS) FOR PROCUREMENT AGENCIES

Low-cost pharmaceuticals of assured quality hold great potential for combating communicable diseases such as HIV/AIDS, malaria and TB. While some procurement agencies have quality assurance systems in place, their extent and performance may vary widely. Without a harmonized system that seeks to ensure that quality medicines are supplied to patients, procurement agencies risk sourcing substandard medicines. This can undermine their credibility and can result in product recalls, wasted money and health risks to patients.

The MQAS was designed by an expert team, including specialists from UNICEF, the United Nations Population Fund (UNFPA), WHO and the World Bank, to help these agencies achieve the goal of a quality procurement system. The model is intended to guide them in developing their own quality assurance systems. It focuses on four key activities – the prequalification of pharmaceutical products and manufacturers, and the purchase, storage and distribution of pharmaceuticals. Among its annexes is a product questionnaire that has since been widely used for product assessment in international procurement, including submissions to the WHO-hosted Expert Review Panel that advises organizations on the quality-related risks of procuring products that have not yet completed a stringent review by the WHO Prequalification Team or a stringent regulatory authority (SRA).

The forty-eighth Expert Committee approved a revision of the guidelines developed with input from a wide range of organizations. The document is in line with current WHO guidance on storage and distribution and addresses the practical issues to consider in procurement of quality-assured medicines. It includes an assessment tool for use by procurement agencies in self-inspection to harmonized standards as defined in the consultative development process of these guidelines.

GOOD PHARMACY PRACTICE

Pharmacists have a central role in improving access to health care and in ensuring that the actual value of medicines is realized. The first joint document by the International Pharmaceutical Federation (FIP) and WHO on good pharmacy practice was published in 1999. FIP subsequently conducted a pilot study on improving pharmacy practice standards in seven of its member organizations around the world. This was followed by the “Bangkok declaration on good pharmacy practice in the community pharmacy settings” in the South-East Asia Region, adopted by FIP in 2007. Significant changes led to the revision of the good pharmacy practices published earlier.

The guidelines were revised in a wide consultative collaboration led by FIP to reflect evolving standards of practice, applied science and technology and pharmaceutical policy, and were adopted by the forty-fifth Expert Committee. The text serves as a standard-forming baseline, to be adjusted to the needs in each specific country. It provides detailed standards for the functions of the pharmacist in preparing, obtaining, storing, securing, distributing, administering, dispensing and disposing of medical products, providing effective medication therapy management, maintaining and improving professional performance and contributing to improve effectiveness of the health-care system and public health.
PREQUALIFICATION

The WHO Prequalification Team-Medicines aims to make quality priority medicines available in all countries. Established in 2001 the Team originally focused on medicines for HIV/AIDS and was then expanded to include medicines to treat malaria and TB, selected other anti-infectives, reproductive health products, and zinc for the management of acute diarrhoea in children.

Over the years the prequalification procedures were extended to include inspection of contract research organizations (CROs) and API manufacturing sites, and they were aligned with ICH principles and formats such as the CTD. As the list of prequalified medicines that meet unified quality standards has grown, it has become a mainstay of procurement for UN agencies, international organizations such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and anyone purchasing medicines in bulk. Procedures were also devised to prequalify APIs and quality control laboratories in their own right.

PREQUALIFICATION OF PHARMACEUTICAL PRODUCTS (PARENT GUIDELINES)

These are the parent guidelines that describe the prequalification procedure overall. They are supplemented by guidelines on specific aspects of assessment. Prequalification is open to manufacturers who wish their medicines to be included in the list of WHO-prequalified products, provided that the medicines are on the Team’s invitations for Expression of Interest (EOI). The procedure comprises the assessment of product dossiers on all relevant aspects of manufacture and product control, as well as inspection of manufacturing sites and, if applicable, clinical sites.

Revisions of the procedure were published in 2009 and in 2011 to align it with new developments and ICH principles, and to provide for variation control and requalification as described in more detail in supplementary guidelines.
• Prequalification of pharmaceutical products approved by stringent regulatory authorities

In prequalifying medicines, WHO recognizes the scientific evaluation of innovator FPPs by regulatory authorities which apply similarly stringent standards for quality, safety and efficacy as those recommended by WHO. These guidelines list the information that applicants and SRAs can agree to share so that WHO will consider a product for inclusion in the list of WHO-prequalified products. The forty-eighth Expert Committee approved a revised version that is applicable to both innovator and multisource (generic) products.

• Preparation of product dossiers in common technical document (CTD) format

Through the ICH process, considerable harmonization has been achieved in the organization of the registration documents through the CTD format for registration applications. This format has become widely accepted by regulatory authorities both within and beyond the ICH Regions.

When submitting an EOI for prequalification, applicants submit a product dossier for evaluation by the WHO Prequalification Team-Medicines. To support harmonization and cross-referencing of information, prequalification dossiers must be submitted in the CTD format. These guidelines assist applicants to organize and present their prequalification dossiers.

• Preparation of product dossiers in CTD format: quality part

Separate guidelines on data required for the quality part of product dossiers in CTD format were recommended by the Expert Committee at its forty-sixth meeting in 2011. A revised version for use not only in prequalification but also in registration of pharmaceutical products by NMRAs was approved two years later. A short description of the guidelines is included at the end of the section titled “Regulatory guidance”.

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• Active pharmaceutical ingredient (API) master file procedure

The API master file (APIMF) is one of four options for applicants to provide information on APIs in the “quality part” of their CTD dossiers for finished products to the Prequalification Team. (The other three options are: the use of an API that is prequalified in its own right; a certificate of suitability of pharmacopoeial monographs with which the API complies; or a signed declaration by the manufacturer of the active ingredient that the synthesis and purification are conducted in accordance with the information included in the prequalification dossier submitted by the finished product manufacturer.)

The main aim of the APIMF procedure is to protect the confidential intellectual property of the manufacturer of the API, while at the same time permitting the applicant – or holder of the prequalification dossier – to take full responsibility for the finished product and for both the quality and the quality control of the API. The APIMF procedure gives the Prequalification Team access to all the information necessary to evaluate the suitability of the use of the API in the finished product.

The forty-second Expert Committee adopted a set of guidelines on the APIMF procedure to help prequalification applicants and holders of prequalification dossiers to compile information on APIs in support of their application. The Expert Committee asked WHO to promote discussions on sharing regulatory information between national authorities to conserve resources in APIMF and in dossier assessment.

• Guidance on variations to a prequalified product dossier

Over their lifetime pharmaceuticals evolve in line with technological and scientific advances. Irrespective of regular WHO reviews, manufacturers are responsible for their prequalified product throughout its lifetime. In the event of product modification this includes making any necessary amendments to the product dossier. Any changes to prequalified products are subject to WHO approval.

This guidance indicates how a manufacturer should present an application to implement different types of changes to a prequalified product. The guidance applies to APIs and excipients manufactured by chemical synthesis or semisynthetic processes and to finished generic pharmaceuticals containing WHO-prequalified APIs and excipients. It was updated and expanded to include additional post-approval/post-prequalification changes and establish the level of risk inherent in each change. The change categories are organized according to the structure of the CTD, with specific CTD sections identified for individual data requirements in order to assist in the filing of documentation.
Guidelines on the requalification of prequalified dossiers

The procedure for prequalification of pharmaceutical products adopted at the forty-third meeting of the Expert Committee included a section on “maintenance of prequalification status”. This stated that products and manufacturing sites included in the prequalified list should be reevaluated at regular intervals (and at least once every five years) and – if found to no longer comply with the recommended standards – such products and sites should be removed from the list.

These guidelines were developed by the quality assessors of the Prequalification Team to define what information and documentation is required from the applicants or manufacturers in order for a prequalified product to be reevaluated. Based on this information WHO will verify that the product conforms to current norms and standards and that its quality and its manufacturing process have remained consistent over the identified period.

Collaborative registration of WHO-prequalified pharmaceutical products

Prequalified medicines must be registered in the countries of destination before they can be used. This can take time, and to some extent it may duplicate the assessment work already done by WHO. The forty-seventh Expert Committee adopted a collaborative procedure for accelerated registration of WHO-prequalified pharmaceutical products: the manufacturer can authorize WHO to share prequalification assessment and inspection information with regulatory authorities in countries where registration is sought. If a participating authority agrees to apply the procedure to the specific product, it commits to issuing its independent decision within 90 days and to communicate it within another 30 days.

The procedure applies only to products for which the WHO Prequalification Team-Medicines has conducted its own assessment, not those prequalified in recognition of assessments conducted by other stringent mechanisms. National submissions must contain the same technical data as has been approved by WHO, and it is highly recommended that regulatory authorities accept registration dossiers in CTD format.

The procedure promotes communication among participating national authorities and with WHO about relevant regulatory issues, including variations and regulatory actions after product registration. In this way the procedure contributes to regulatory collaboration, and to ensuring that a product registered in individual countries is identical to the WHO-prequalified product.
PREQUALIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENTS

The quality of APIs is a significant factor in the quality of finished products. In the context of globalization, the ingredients are sourced in a worldwide market and the risk of sourcing substandard or contaminated products is high. Thus only a proper system of qualification of suppliers can ensure the continuous sourcing of active ingredients of an appropriate quality that will safeguard public health interests.

A procedure was adopted by the forty-third Expert Committee to prequalify APIs in their own right, independently of specific finished products containing them. The aim of the procedure is to enable procurement agencies and other stakeholders to validate the quality of products they are purchasing and to enable manufacturers of finished products to choose APIs from reliable sources. The forty-third Expert Committee suggested that WHO should focus on the prequalification of APIs in accordance with the priorities of the WHO Prequalification Team-Medicines.

PREQUALIFICATION OF REPRODUCTIVE HEALTH PRODUCTS: INTRAUTERINE DEVICES AND CONDOMS

Intrauterine devices (IUDs) and condoms have been shown to be effective contraceptives and they are included in the EML as essential products. Prequalification of these products was considered to be important in order to prevent unwanted pregnancies and, in the case of condoms, transmission of sexually-transmitted infections, including HIV.

Two guidelines adopted by the forty-second Expert Committee related to the prequalification of IUDs and of male condoms for purchase by UN agencies. Both procedures, which stemmed from collaboration with UNFPA, summarized the experience from quality evaluation carried out by agencies that had procured IUDs and condoms. A technical review committee convened by WHO in 2006 recommended the TCU380A IUD as the most appropriate IUD for bulk procurement by UNFPA, and thus the prequalification procedure relates to this type of device. The procedure on each product includes a list of standards and specifications published by WHO and by ISO; UNFPA is the implementing agency.
Apart from the guidelines described in the previous sections of this booklet, most of which can be used in medicines regulation, WHO has provided guidance on regulatory functions as listed in Annex 1. The texts adopted by the Expert Committee in recent years focus on assessment of fixed-dose combination products, bioequivalence and stability. These aspects are among the most relevant for medicines assessment in developing countries, where regulatory capacity and resources are often limited.

BIOEQUIVALENCE

Generic products – legal “copies” of an innovator (branded) medicine – have saved the lives of millions of patients who could not have been treated at the cost of the originator products. Generic products must meet the same manufacturing quality standards as originator products, and they must be therapeutically interchangeable; in other words, they must have essentially the same safety and efficacy profile as the originator product. Direct demonstration of safety and efficacy in a clinical study usually requires many patients and is costly.

For generic medicines direct proof of safety and efficacy is usually unnecessary and in some cases may be unethical. Over the past 40 years the science of bioequivalence testing has advanced to address these concerns. This science postulates that therapeutic equivalence is demonstrated when the generic medicine is shown to be both pharmaceutically equivalent and bioequivalent, meaning that it releases the same API into the body at the same rate and to the same extent as the comparator product. Assessment of bioequivalence is essential for regulators to ensure that generic products are safe and efficacious.
• Guidelines on registration requirements to establish interchangeability

The fortieth Expert Committee adopted a revised version of these guidelines, which provide appropriate in vivo and in vitro requirements to assure interchangeability of multisource (generic) products with their respective comparators.

• Additional guidelines for organizations performing in vivo bioequivalence studies

One way of showing bioequivalence is to conduct an in vivo study with a limited number of subjects, to prove that the pattern of concentration of the active ingredient in the blood of healthy volunteers is the same for the generic product as for the comparator product. Since a bioequivalence study is often the only evidence that a product is safe and effective, it is essential that it is performed appropriately.

These guidelines are directed at organizations conducting bioequivalence studies. They include information on: organization and management; study protocols; the clinical and bioanalytical phases of a study; and pharmacokinetic and statistical analysis. The guidelines should be used in conjunction with the WHO guidelines on GMP, good clinical practices (GCP), good laboratory practices (GLP) and good practices for quality control laboratories.

• Preparing a contract research organization (CRO) master file

Some regulatory authorities are inspecting clinical trials conducted at CROs. The WHO Prequalification Team-Medicines started doing so in 2004. However, WHO inspectors found that not all information regarding CROs was available to them when preparing for their inspections. Additionally, significant changes had sometimes been made by the organizations between the time when the trial was conducted and the time when the study report became available, making inspections problematic as some of the core information regarding the site could no longer be verified. It was therefore proposed to establish a contract research organization master file (CROMF), similar to the SMF that serves to prepare for GMP inspections. The CROMF serves as general information for regulators. It can be used by regulatory inspectors as they prepare for inspections, in addition to the trial-specific data and information submitted for assessment. The master file also gives an overview of the organization’s approach to GCP, GLP and other guidelines related to its activities.
• Biowaivers

In some circumstances the requirement for in vivo bioequivalence studies can be waived, depending on the physical, chemical and absorption properties of the API and after consideration of the risks to patients associated with the product’s use in the respective country. In what is known as a “biowaiver” procedure, the in vivo bioequivalence test is replaced by a strictly-defined dissolution test (in vitro bioequivalence). This simplified process will reduce the time it takes for new product approval and thus lower the cost of bringing products to market.

Following recent scientific developments, criteria for biowaivers were revised for certain APIs. In this context the fortieth Expert Committee adopted a proposal for consideration of biowaivers, based on currently available information about orally applied APIs which are on the EML. The aim of this proposal is to help national authorities make an informed decision as to the generic formulations for which in vivo bioequivalence studies should be required as a priority and which ones may be considered for a biowaiver.

STABILITY

• Stability testing of active pharmaceutical ingredients and finished products

The forty-third Expert Committee discussed and adopted a set of guidelines on stability testing of APIs and FPPs. This was the latest stage in the Expert Committee’s work on stability which began in 1988 and led to the finalization of WHO’s first guidelines on stability testing requirements in 1996.

The 1996 WHO guidelines were developed in parallel with guidance from ICH, which was working on recommendations for stability testing of new chemical entities and products during the same period. The WHO guidelines focused on well-established pharmaceutical products – i.e. generic products in conventional dosage forms – as these were considered to be the priority at the time. The storage conditions for different climatic zones were derived from references and calculated data.

The world at that time was considered to have four climatic zones: Zone I: temperate; Zone II: subtropical, with possible high humidity; Zone III: hot/dry; and Zone IV: hot/humid. Subsequent discussion led to a number of modifications in the 1996 guidelines.
As a result of new, more precise data on climatic conditions in hot/humid areas, the level of “relative humidity” for testing was modified in 2003. As further information became available based on real meteorological data, the Expert Committee recommended in October 2005 that climatic Zone IV (i.e. hot/humid areas) should be divided into Zones IVA and IVB to take into account differences in hot and humid areas.

In early 2006 the WHO Eastern Mediterranean Regional Committee adopted a set of regional guidelines on stability studies of medicines and biological products, leading to a discussion by the fortieth Expert Committee as to whether these regional guidelines could be adopted as global guidelines. Input was widely sought, resulting in extensive revision. In view of the growing numbers of comments received, the Expert Committee decided that less-than-ideal guidelines would be better than non-published ones and made decisions on controversial issues at its forty-third meeting to finalize the guidelines. The labelling statements linked with testing conditions were moved from the main text to the annexes to make it clear that they were of non-mandatory character, and to facilitate their revision should new information become available.

The Expert Committee stressed that the national and regional regulatory authorities would decide on the stability testing requirements and the storage conditions given on the label and requested that stakeholders should again be contacted to complete a table specifying the stability testing conditions actually employed in WHO Member States. The table was provided in December 2010 and included in the guideline as “Table 2: Stability conditions for WHO Member States by Region”. These tables are updated when new information is provided to WHO by the Member States’ regulatory authorities.

**PREPARATION OF PRODUCT DOSSIERS IN CTD FORMAT: QUALITY PART**

The “quality part” of the CTD format, as defined in the ICH M4Q guideline, is the module which contains the actual information on the quality of drug substances (i.e. APIs) and drug products (i.e. FPPs) in product dossiers. These guidelines provide clear general guidance to applicants in preparing the quality module of their product dossiers submitted for prequalification of multisource (generic) products containing existing APIs of synthetic or semi-synthetic origin.

A revised guideline for wider use by NMRAs was approved by the forty-eighth Expert Committee. The guidelines are intended to promote effective and efficient processes for the development of product dossiers by applicants and the subsequent assessment procedures by NMRAs. Alternate approaches to the principles and practices described in this document could be acceptable provided they are supported by adequate scientific justification.
Terminology is extremely important in dealing with medicines. WHO has the responsibility for assigning International Nonproprietary Names (INN) to pharmaceutical substances, so that each substance can be recognized globally by a unique name – helping to ensure, for example, that a prescription filled abroad is “what the doctor ordered back home”. Similarly, all the technical terms in WHO’s quality guidance must be defined so that they mean the same thing to all readers and across guidelines.
INTERNATIONAL NONPROPRIETARY NAMES FOR BIOLOGICAL AND BIOTECHNICAL SUBSTANCES: A REVIEW

INN are regularly published by WHO. Their adoption is recommended by the INN Expert Group, which comprises a number of designated members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations.

INN have been assigned to biological products such as antibiotics, synthetic peptides, hormones and other proteins since the early days of WHO's INN Programme. In 1982 the first name was proposed for a recombinant product, namely “insulin human” for the recombinant protein identical to natural human insulin. Since then INN have been assigned to a growing number of biological and biotechnological products, including recombinant blood products, transgenic products (human proteins expressed in animals or plants), products for gene therapy and novel vaccines.

As this area is growing more complex and challenging, the INN Expert Group requested WHO to prepare a document reviewing the INN situation in this field. The review presents an inventory of policy decisions taken by the INN Expert Group and of the names assigned to biological and biotechnological substances. The forty-second Expert Committee adopted the principles contained in the document. The review will be regularly updated.

QUALITY ASSURANCE OF MEDICINES TERMINOLOGY DATABASE

The Quality Assurance of Medicines Terminology database (QAS Terminology database) was created in August 2005 to harmonize terminology and ensure consistency across WHO guidelines included in the Expert Committee's reports. This simple tool for editing and retrieving terminology records provides precise definitions of terms and is updated and expanded regularly.
SUPPORT AND BENEFITS

INVESTMENT, COSTS AND SUPPORT

Direct financial support of the Expert Committee’s work comes mainly from extrabudgetary sources, as the regular WHO budget has decreased to a very low amount over the past three biennia. Generous extrabudgetary contributions have been received from several Member States, including the People’s Republic of China, Germany, Luxembourg, Singapore and Sweden, as well as from the European Union and UNAIDS. Funding from the Swedish International Development Agency was also highly valued. The Committee’s work also receives significant support from the Bill & Melinda Gates Foundation and from UNITAID.

The total costs of the Expert Committee’s activities are easily underestimated since they benefit immensely from in-kind laboratory studies conducted on behalf of WHO by national medicines quality control laboratories, as well as from expertise provided by NMRAs, universities, pharmacopoeias, nongovernmental organizations (NGOs) and other institutions. China, Luxembourg and Singapore are just some of the countries that have contributed significant national laboratory assistance in recent years. Additionally, FIP has contributed its members’ expertise and also assisted the Expert Committee by organizing technical meetings. Such in-kind support enables salary costs and other overheads to be minimized.

WHO BENEFITS?

The Expert Committee’s advice and recommendations are vital to national and regional authorities – particularly NMRAs, procurement agencies and major international bodies, such as the Global Fund and UNICEF – in their efforts to combat SSFFC medical products. The Expert Committee’s dedication to defining and harmonizing independent guidelines makes it possible for regulatory authorities, pharmacopoeia commissions, the pharmaceutical industry, academics, health workers and professionals, NGOs, policy-makers, researchers, development agencies, and – most importantly – patients, to be assured that medicines meet the criteria of quality, safety and efficacy.
This Annex lists the pharmaceutical quality guidelines published as annexes to the WHO Technical Report Series (WHO TRS), available on the WHO website. Only the most recent revisions of the respective guidelines are listed.

**The International Pharmacopoeia**

- **2003**
  - Recommendations on Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products
  - *The International Pharmacopoeia: revised concepts and future perspectives*
- **2007**
  - *The International Pharmacopoeia* – related substances tests: dosage form monographs guidance notes
  - General guidelines for the establishment, maintenance and distribution of chemical reference substances. Revision
- **2012**
  - Development of monographs for *The International Pharmacopoeia*
  - Recommendations for quality requirements for artemisinin as a starting material in the production of antimalarial active pharmaceutical ingredients

**International Chemical Reference Substances (ICRS)**

- **2009**
  - List of available International Chemical Reference Substances and International Infrared Reference Spectra
- **2013**
  - Release procedure of International Chemical Reference Substances
- **2014**
  - *The International Pharmacopoeia* updating mechanism

**Laboratories**

- **2002**
  - Considerations for requesting analyses of drug samples
  - Model certificate of analysis
- **2005**
  - WHO guidelines for sampling of pharmaceutical products and related materials
- **2010**
  - WHO good practices for pharmaceutical quality control laboratories
- **2011**
  - WHO good practices for pharmaceutical microbiology laboratories
  - Prequalification of quality control laboratories. Procedure for assessing the acceptability, in principle, of quality control laboratories for use by United Nations agencies
  - WHO guidelines for preparing a laboratory information file
  - Quality control methods for herbal materials (Manual)

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Good manufacturing practice (GMP)

1993  •  Good manufacturing practices for biological products  
Annex 3, WHO TRS 834

1996  •  Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans  
Annex 7, WHO TRS 863

1999  •  Good manufacturing practices: supplementary guidelines for the manufacture of pharmaceutical excipients  
Annex 5, WHO TRS 885

2003  •  Guidelines on good manufacturing practices for radiopharmaceutical products  
Annex 3, WHO TRS 908

2006  •  Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines  
Annex 3, WHO TRS 937

2010  •  WHO good manufacturing practices for active pharmaceutical ingredients  
Annex 2, WHO TRS 957

2011  •  WHO good manufacturing practices for blood establishments  
(jointly with the Expert Committee on Biological Standardization)  
Annex 4, WHO TRS 961

2014* •  WHO good manufacturing practices for pharmaceutical products: main principles  
*Approved at the 2013 Expert Committee meeting

Production

2011  •  WHO guidelines on transfer of technology in pharmaceutical manufacturing  
Pharmaceutical development of multisource (generic) pharmaceutical products - points to consider  
Annex 7, WHO TRS 961

2012  •  Development of paediatric medicines: points to consider in formulation  
Annex 5, WHO TRS 970

2013  •  WHO Guideline on quality risk management  
Annex 2, WHO TRS 981

Distribution

2003  •  Guide to good storage practices for pharmaceuticals  
Annex 9, WHO TRS 908

2004  •  Good trade and distribution practices for pharmaceutical starting materials  
WHO pharmaceutical starting materials certification scheme  
(SMACS): guidelines on implementation  
Procedure for assessing the acceptability, in principle, of procurement agencies for use by United Nations agencies  
Guidelines for the preparation of a procurement agency information file  
Annex 2, WHO TRS 917

2010  •  WHO good distribution practices for pharmaceutical products  
Annex 5, WHO TRS 957
### Distribution (next)

#### 2011
- Good pharmacy practice: standards for quality of pharmacy services (joint FIP/WHO)
  - Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products (jointly with the Expert Committee on Biological Standardization)

#### 2014*
- Model quality assurance system for procurement agencies, including annexes (model inspection report and product questionnaire)
- Assessment tool based on the model quality assurance system for procurement agencies: aide-memoire for inspection
  *Approved at the 2013 Expert Committee meeting

### Prequalification

#### 2008
- Procedure for assessing the acceptability, in principle of male latex condoms for purchase by United Nations agencies
- Procedure for assessing the acceptability, in principle of TCU 380A intrauterine devices for purchase by United Nations agencies
- Guidelines on active pharmaceutical ingredient master file procedure

#### 2009
- Procedure for assessing the acceptability, in principle of active pharmaceutical ingredients for use in pharmaceutical products

#### 2010
- Guidelines on the requalification of prequalified dossier

#### 2011
- Procedure for prequalification of pharmaceutical products
  - Guidelines on submission of documentation for a multisource (generic) finished product: general format: preparation of product dossiers in common technical document format

#### 2013
- Guidance on variations to a prequalified product
- Collaborative procedure between the World Health Organization Prequalification of Medicines Programme and national medicines regulatory authorities in the assessment and accelerated national registration of WHO-prequalified medicinal products

#### 2014*
- Guidelines on submission of documentation for prequalification of finished pharmaceutical products approved by stringent regulatory authorities
  *Approved at the 2013 Expert Committee meeting

### Regulatory guidance

#### 1992
- Provisional guidelines on the inspection of pharmaceutical manufacturers

#### 1996
- Guidelines for the assessment of herbal medicines
- Guidelines on import procedures for pharmaceutical products

#### 1999
- Guidelines on inspection of drug distribution channels
- National drug regulatory authority legislation: guiding principles for small drug regulatory authorities

#### 2002
- Guidelines on packaging for pharmaceutical products
  - Guidelines on pre-approval inspections
  - Quality system requirements for national GMP inspectorates
  - Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products
Regulatory guidance (next)

2003 • Model Certificate of good manufacturing practices
  • Guidance on good manufacturing practices (GMP): Inspection Report
2005 • Guidelines for registration of fixed-dose combination medicinal products
  • WHO guidelines for sampling of pharmaceutical products and related materials
2006 • Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability
  • Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms
  • Additional guidance for organizations performing in vivo bioequivalence studies
2009 • Stability testing of active pharmaceutical ingredients and finished pharmaceutical products (and see 2013)
2010 • Guidelines for the preparation of a contract research organization master file
2011 • Marketing authorization of pharmaceutical products with special reference to multisource (generic) products: a manual for national medicines regulatory authorities (NMRAs)
2013 • (Update) Table 2: Stability conditions for WHO Member States by Region. Updated 2013
2014* • Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part

Nomenclature

2002 • Guidelines on the use of International Nonproprietary Names (INNs) for pharmaceutical substances
2008 • International Nonproprietary Names for biological and biotechnological substances: a review