Quality assurance of pharmaceuticals:
MEETING A MAJOR PUBLIC HEALTH CHALLENGE

THE WHO EXPERT COMMITTEE ON SPECIFICATIONS FOR PHARMACEUTICAL PREPARATIONS

World Health Organization

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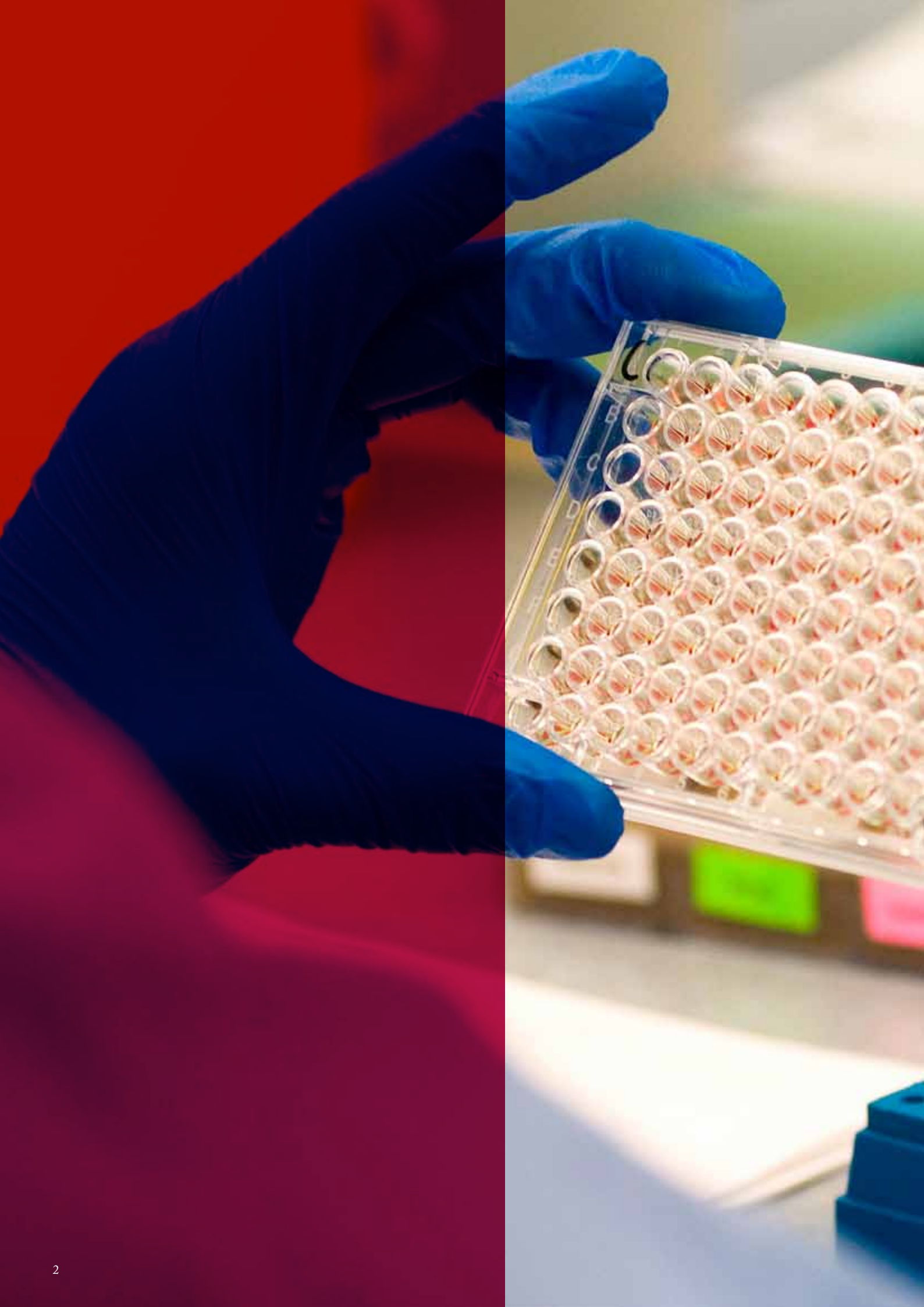

INTRODUCTION

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 the World Health Organization (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 then evaluated by the Expert Committee on Specifications for Pharmaceutical Preparations. If the Expert Committee approves, the guidelines are adopted as international standards. The Expert Committee's rigorous consultative process involves WHO Member States, national authorities and international agencies such as the United Nations Children's Fund (UNICEF).

The Constitution of 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". Even before the Organization was formally created in 1948, an Expert Committee on the Unification of Pharmacopoeias met under WHO's auspices. This Expert Committee has adjusted its role and changed its name over the years, and today is called the WHO Expert Committee on Specifications for Pharmaceutical Preparations. The Expert Committee is convened annually and the report of each meeting includes newly adopted guidelines in its annexes.

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 United Nations Prequalification Programme, the Medicines for Malaria Venture, and Stop TB.

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 pharmaceutical 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.

Medicines that are ineffective or harmful not only damage lives but also waste public resources. Consequently the Expert Committee's original role of developing The International Pharmacopoeia has expanded over time and in light of the new technologies to include 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 most recent meetings of the Expert Committee were the 40th, 41st, 42nd, 43rd, 44th and 45th. 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 at those meetings.

VITAL TOOLS FOR GOOD-QUALITY MEDICINES

The 40th, 41st, 42nd, 43rd and 44th meetings of the Expert Committee were notable for the large number of tools that were produced or revised.

THE INTERNATIONAL PHARMACOPOEIA

The International Pharmacopoeia **is a collection of quality specifications for pharmaceutical substances (active ingredients and excipients) and dosage forms, together with supporting general methods of analysis. It is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements.**

The selection of monographs for inclusion in *The International Pharmacopoeia* reflects the needs of specific disease programmes and the essential medicines nominated under these programmes. The pharmacopoeia is based primarily on medicines included in the current *WHO Model List of Essential Medicines*. For inclusion in *The International Pharmacopoeia*, monographs must be formally adopted by the Expert Committee.

THE 40TH EXPERT COMMITTEE: 14 NEW MONOGRAPHS

The 40th Expert Committee on Specifications for Pharmaceutical Preparations adopted eight new monographs for antiretrovirals (covering five active substances and three finished products) for inclusion in the Fourth Edition of The International Pharmacopoeia. The monographs on the five active substances relate to: abacavir sulfate; efavirenz; lamivudine; stavudine; and zidovudine. The finished products relate to: nelfinavir mesilate tablets; nelfinavir mesilate oral powder; and saquinavir mesilate capsules. The Committee also adopted six monographs for antituberculosis (TB) medicines: rifampicin tablets; rifampicin capsules; rifampicin + isoniazid tablets; rifampicin + isoniazid + pyrazinamide + ethambutol hydrochloride tablets; isoniazid + ethambutol hydrochloride tablets; and rifampicin + isoniazid + pyrazinamide tablets.

THE 41ST EXPERT COMMITTEE: 16 NEW MONOGRAPHS

The 41st Expert Committee adopted 12 monographs for antiretrovirals for inclusion in *The International Pharmacopoeia*: abacavir oral solution; abacavir sulfate tablets; didanosine tablets; didanosine oral solution (adult formulation); lamivudine oral solution; lamivudine tablets; stavudine capsules; zidovudine capsules; zidovudine IV infusion; zidovudine oral solution; zidovudine + lamivudine tablets; and zidovudine, lamivudine + abacavir tablets. The Committee also adopted four monographs for antimalarial medicines, two of which are new: doxycycline hyclate capsules; and lumefantrine; and two of which are revisions: doxycycline hyclate tablets; and doxycycline hyclate.

Dissolution tests for the following monographs, adopted by the 41st Expert Committee, are included in the First Supplement of *The International Pharmacopoeia*, Fourth Edition: chloroquine phosphate; doxycycline tablets; ethambutol hydrochloride tablets; isoniazid tablets; metronidazole tablets; primaquine diphosphate tablets; pyrazinamide tablets; rifampicin capsules; and rifampicin tablets.

THE 42ND EXPERT COMMITTEE: NINE NEW MONOGRAPHS

At its 42nd meeting the Expert Committee adopted nine new monographs for pharmaceutical substances and dosage forms for inclusion in *The International Pharmacopoeia*, subject to minor modifications and the inclusion of comments. Of these monographs, two were related to the treatment of malaria, namely the active pharmaceutical ingredient (API) lumefantrine, and the dosage form artemether + lumefantrine tablets; three were for the treatment of tuberculosis (the dosage forms rifampicin + isoniazid + ethambutol tablets; rifampicin + isoniazid dispersible tablets for paediatric use; rifampicin + isoniazid + pyrazinamide dispersible tablets for paediatric use). Three monographs were for oral rehydration therapy (the API zinc sulfate; and the dosage forms zinc sulfate oral solution, paediatric; zinc sulfate tablets, paediatric), and one was an anticonvulsant dosage form (magnesium sulfate injection). The 42nd Expert Committee also agreed a new work plan for the development of monographs, which included giving priority to medicines of importance to developing countries.

MONOGRAPHS ADOPTED BY THE EXPERT COMMITTEE AT ITS 43RD MEETING

The 43rd Expert Committee, in accordance with the new work plan approved by the 42nd meeting, adopted a number of monographs for APIs and dosage forms for inclusion in *The International Pharmacopoeia*, subject to minor modifications and the inclusion of comments. These included, for HIV and related conditions the API emtricitabine and three dosage forms (efavirenz capsules; efavirenz oral solution; zidovudine + lamivudine + nevirapine tablets), for malaria three dosage forms (artemether + lumefantrine oral suspension; chloroquine sulfate oral solution; quinine sulfate tablets), for tuberculosis the API cycloserine and two dosage forms (cycloserine capsules; ethambutol hydrochloride tablets, revised earlier monograph) and, for other conditions, the APIs mebendazole (revised earlier monograph) and oseltamivir phosphate, plus the dosage form chewable mebendazole tablets (revised earlier monograph). In addition, this meeting of the Expert Committee adopted three further monographs for HIV/AIDS medicines, namely: nevirapine tablets; nevirapine oral suspension; and nevirapine (in consequence of the preparation of new monographs for dosage forms), subject to final written confirmation by Committee members.

MONOGRAPHS ADOPTED BY THE EXPERT COMMITTEE AT ITS 44TH MEETING

At the 44th meeting of the Expert Committee, the adopted monographs of APIs and dosage forms were as follows: for HIV and related conditions, three APIs (lopinavir; tenofovir disoproxil fumarate; efavirenz (revised earlier monograph) and four dosage forms (indinavir capsules; saquinavir tablets; tenofovir tablets; lopinavir + ritonavir tablets), for malaria, three dosage forms (amodiaquine tablets; quinine bisulfate tablets; quinine sulfate tablets (revised earlier monograph), for tuberculosis, four APIs (amikacin; amikacin sulfate; kanamycin monosulfate; kanamycin acid sulfate) and two dosage forms (amikacin injection; kanamycin injection), and for other conditions, oxytocin and the dosage form oxytocin injection.

RELATED SUBSTANCES TESTS: DOSAGE FORM MONOGRAPHS

The primary purpose of a test for related substances for dosage form monographs is to control degradation impurities. Where possible, its objective is also to limit impurities arising during synthesis of the API. 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.

The limits set for degradation impurities in dosage form monographs depend on a number of general considerations. For example, such limits may need to be higher than those for the same impurities in the corresponding API monograph. Different limits may also need to be set for different types of dosage forms. For example, higher limits may be set for an oral solution than for tablets. If there is no evidence to indicate that the limit set for any particular impurity should be based on its toxicity, then the limit set will be based on batch data for pharmaceuticals manufactured in compliance with GMP. Factors such as the number of impurities present, the type of dosage and dose regimen, will also be taken into account.

In applying this overall approach to individual dosage form monographs, these guidelines provide a detailed decision process to follow in order to adapt the test to individual circumstances.

INTERNATIONAL CHEMICAL REFERENCE SUBSTANCES

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 – to focus on essential medicines and medicines used in treating large populations, for which international quality requirements are often not publicly available.

WHO's collection of ICRS is now 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.

The 42nd Expert Committee adopted seven new ICRS – abacavir sulfate, anhydrotetracycline hydrochloride, 4-epianhydrotetracycline hydrochloride, 4-epitetracycline hydrochloride, medroxyprogesterone acetate, nevirapine impurity B, and pyrazinamide. The 43rd Expert Committee adopted a further five ICRS – abacavir sulfate for system suitability, amoxicillin trihydrate, lamivudine for system suitability, norethisterone enantate, and zidovudine impurity B – as well as two ICRS replacements (levothyroxine sodium and paracetamol).

GENERAL GUIDELINES FOR THE ESTABLISHMENT, MAINTENANCE AND DISTRIBUTION OF CHEMICAL REFERENCE SUBSTANCES – REVISION

The growing requirements of national and regional pharmacopoeias, coupled with the need for greater availability and cost-effectiveness, led to the establishment of chemical reference substances external to the then WHO Collaborating Centre for Chemical Reference Substances, and to the development of WHO guidelines to ensure the integrity of national and regional collections. First recommended by the Committee in 1975, the *General guidelines for the establishment, maintenance and distribution of chemical reference substances* have undergone several revisions since then.

The most recent revision is concerned with both primary and secondary chemical reference substances. Part A provided guidance on primary chemical reference substances, materials whose assigned content when used as an assay standard are accepted without requiring comparison to another chemical substance. In response to the Committee's 2004 recommendations, a new Part B provides more detailed guidance on establishing secondary reference substances, materials whose characteristics are calibrated by comparison with a primary chemical reference substance. This guidance applies primarily to secondary reference substances supplied as regional or national standards.

Since producing, maintaining and distributing ICRS is costly and time-consuming, the guidelines also cover needs assessment (among other protocols). The most important steps addressed are: procuring source material, testing methods, and packaging, distribution and supply.

NEW GUIDELINES ON WHO GOOD MANUFACTURING PRACTICES

The following GMP guidelines are intended to be read in conjunction with the 2003 parent guide *Good manufacturing practices for pharmaceutical products: main principles*. They provide new standards and guidance on GMP, including revisions of previously published test methods for quality control of medicinal plant materials.

SUPPLEMENTARY GUIDELINE ON WHO GOOD MANUFACTURING PRACTICES FOR HEATING, VENTILATION AND AIR-CONDITIONING (HVAC) SYSTEMS

Ensuring that pharmaceuticals are manufactured, packaged and stored in a controlled, uncontaminated environment is a necessary part of the quality assurance process. During production and storage, medicines must remain free from impurities, dust and foreign matter. Toxic substances must be contained to prevent their cross-contaminating other medicines in adjacent areas or escaping into the outside environment. HVAC systems make this possible by maintaining the proper temperature, humidity and ventilation for medicines and equipment used during manufacture and storage.

This guideline advises both manufacturers of solid dosage medicines and inspectors of these facilities about the design, installation, qualification and maintenance of HVAC systems. However, most of the system design principles will also apply to facilities that manufacture medicines in other forms such as liquids, creams and ointments.

Since the primary function of a pharmaceutical manufacturer's HVAC system is to prevent contamination and cross-contamination, its design should be part of the facility's blueprint. HVAC design influences the architectural layout of such elements as airlocks, which regulate airflow between rooms of differing classes of cleanliness, and environmentally controlled "clean rooms".

The guideline places particular emphasis on the HVAC system's role in the protection of pharmaceutical products, personnel and the environment during the manufacturing process.

SUPPLEMENTARY GUIDELINES ON WHO GOOD MANUFACTURING PRACTICES: 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 a component of quality assurance associated with a particular product, system or process and is essential to GMP.

Each major stage of the manufacturing process must, therefore, be validated to maximize the likelihood that the finished product will meet all quality and design protocols. Through design and validation a manufacturer establishes confidence that its products will consistently meet their specifications.

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.

The implementation of validation often requires considerable resources, including expensive technology, the collaboration of multidisciplinary teams, and documentation such as qualification protocols, standard operating procedures and specifications.

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

WHO GOOD MANUFACTURING PRACTICES FOR ACTIVE PHARMACEUTICAL INGREDIENTS

A number of Expert Committee meetings have discussed revision of WHO's GMP for APIs, published in 1992, and the Committee has closely followed the development of guidelines on GMP for active ingredients by the International Conference on Harmonisation (ICH). The Expert Committee consequently asked WHO to revise its GMP for APIs in order both to reflect current GMP requirements and to take other published guidelines into account.

At its 44th meeting, therefore, the Expert Committee reviewed a revision of WHO's GMP for APIs. This had been prepared in accordance with the principles of the ICH text in order to avoid obstacles to implementing the standard internationally. The text had also been reviewed extensively with inspectors, experts and interested parties. Members of the 44th Expert Committee added several notes and explanations to the text to clarify a number of points. They subsequently endorsed the revision and agreed to its publication, together with the explanatory notes, to replace the text of 1992.

The document endorsed by the Expert Committee 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 as these are governed by national laws.

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 should be performed in accordance with GMP guidelines for FPPs as defined by local authorities.

WHO GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS CONTAINING HAZARDOUS SUBSTANCES

These guidelines describe good practices for facilities handling pharmaceutical products (including APIs) that contain hazardous substances such as some hormones, steroids or cytotoxins.

A working document containing WHO guidance on the inspection of facilities that manufacture hormone products was presented to the 43rd meeting of the Expert Committee. However, at that meeting Committee members noted that, although the guidelines were intended to provide GMP principles for the production and control of products containing certain hormones, they could equally be applied to other hazardous products. Thus a small expert group was set up to propose a new draft which, after circulation for comments, was presented to the 44th meeting of the Expert Committee in 2009.

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. The United Nations Prequalification Programme, which is managed by WHO, includes reproductive health products, and the Expert Committee had earlier recommended that guidance should be provided in this area.

When the new working document was presented to the 44th Expert Committee, both the contents and the title reflected the wider group of products containing hazardous substances. After discussion, and following a review of all outstanding questions, the guidelines were adopted. They state that facilities handling pharmaceutical products containing hazardous substances should be designed and operated in accordance with the main GMP principles, as follows:

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

The document applies to all areas where the handling of products could lead to cross-contamination, exposure of personnel, or discharge to the environment – including research and development facilities, manufacturing and storage sites of APIs, and sites of FPP manufacturing. The guidelines do not replace national legislation for safety of personnel and protection of the environment.

WHO GOOD MANUFACTURING PRACTICES FOR STERILE PHARMACEUTICAL PRODUCTS

In 1999 the Expert Committee adopted GMP for sterile pharmaceutical products. However, following the implementation of these GMP within the context of the Prequalification Programme it was felt that a revision was necessary.

The revision of the GMP guidelines was made in light of new developments since the original document was drawn up and in order to bring the GMP into line with the relevant International Organization for Standardization (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 revision of the GMP guidelines was then submitted to the 44th meeting of the Expert Committee.

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 of sterile preparations should be carried out in clean areas, entry to which should be through airlocks for personnel and/or for equipment and materials. Clean areas should be maintained to an appropriate standard of cleanliness and supplied with air that has passed through filters of the required efficiency. The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within the clean area.

The revised guidelines were adopted by the 44th Expert Committee which pointed out that certain parts of these new GMP might need to be implemented using a stepwise approach. This was felt to apply especially to the part on provisions for capping in a clean or sterile environment as this is currently not implemented in most industries.

WHO GOOD MANUFACTURING PRACTICES FOR HERBAL MEDICINES

While the general principles of GMP apply to all types of pharmaceuticals, herbal medicines differ from conventional pharmaceutical products in that they are prepared from herbal rather than synthetic substances. Herbal substances include materials derived from leaves, seeds, bark, essential oils and resins. Because of their unique origin, herbal medicines often require procedures for their processing, manufacture and storage that differ from those used for conventional pharmaceuticals.

Naturally grown medicinal plants thus present a degree of complexity in their manufacture. Moreover, they are frequently derived from different geographical sources, subject to diverse conditions, and vary in composition and properties. Moreover, herbal materials 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. For example, management of storage facilities should include quarantining of incoming herbal matter to prevent the spread of microorganisms, and maintenance of segregated areas for different herbal materials and of appropriate environmental conditions. Production areas should be controlled for dust, fumes and vapours generated by the processing of these substances, and should ensure the cleanliness of equipment in order to avoid microbiological contamination.

DISTRIBUTION/ SUPPLY

WHO GOOD DISTRIBUTION PRACTICES FOR PHARMACEUTICAL PRODUCTS

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. In some cases, a person or entity may be responsible for only a part of the supply process. Thus, at its 40th meeting in 2005, the Expert Committee adopted guidelines on good distribution practices (GDP) to assist in fulfilling the responsibilities involved in all steps in the supply chain. The Committee noted the need to eliminate mix ups, and to help avoid the contamination and cross-contamination that may result from a lack of adequate control over the numerous activities that occur during distribution.

Subsequent to the 40th Expert Committee meeting, these guidelines were revised by the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) partnership in order to strengthen steps to prevent substandard/spurious/falsely-labelled/falsified/counterfeit medicines from entering the distribution chain. At this time it was noted that, even in highly regulated countries, substandard/spurious/falsely-labelled/falsified/counterfeit medicines had reached patients through regulated distribution.

The revised text went through several stages of discussion – including by WHO Member States – as well as further revision, and was submitted to the 43rd meeting of the Expert Committee in 2008 as a recommendation from the IMPACT partners. At that meeting, the Expert Committee recommended further discussion of the guidelines between WHO, IMPACT and the European Union. That resulted in a further revision which was presented at the Expert Committee's 44th meeting where the main comments received before the date of that meeting were discussed. A subgroup was formed to review all comments received by the permissible deadline. The Expert Committee adopted the text subject to input from this subgroup and provided that no major additional comments were received. The Expert Committee members were informed of the outcome and reconfirmed their decision in light of the discussions of the subgroup.

The guidelines on GDP 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, 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.

MODEL QUALITY ASSURANCE SYSTEM (MQAS) FOR ASSESSMENT OF PROCUREMENT AGENCIES

Low-cost pharmaceuticals of assured quality hold the greatest potential for maximizing the impact of efforts to combat communicable diseases such as HIV/AIDS, malaria and TB. Pharmaceutical supply has been a major concern at both country and international levels, with efforts to accelerate access to medicines highlighting the inadequacies of the quality assurance mechanisms applied by procurement agencies.

While some of these agencies have quality assurance systems in place, their extent and quality may vary widely. Without a harmonized system that seeks to ensure procurement of quality medicines for supply to patients, procurement agencies risk sourcing substandard/spurious/falsely-labelled/falsified/counterfeit or contaminated medicines. This undermines their credibility and results in product recalls, wasted money and, particularly, health risks to patients.

In response, 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.

PREQUALIFICATION

PROCEDURE FOR PREQUALIFICATION OF PHARMACEUTICAL PRODUCTS

The Prequalification Programme aims to make quality priority medicines available for the benefit of persons in need in countries with limited access to medicines. Established in 2001, the Programme originally focused on medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis. Since then it has been expanded to include medicines and products for reproductive health, and in 2008 the prequalification of zinc – for the management of acute diarrhoea in children – was added. Manufacturers who wish their medicines to be included in the prequalified products list may apply so long as the medicines are on the Programme's "invitations for expression of interest".

The original aim of the Prequalification Programme was to give United Nations procurement agencies such as UNICEF the option to choose from a range of quality medicines. As the list of prequalified medicines that meet the required standards has grown, it has become a useful tool for anyone purchasing medicines in bulk – including national authorities and other organizations.

A revised working document on the procedure for prequalification of pharmaceutical products was reviewed by the 43rd Expert Committee and adopted, subject to some changes in nomenclature and final clearance by the WHO Legal Counsel. The procedure comprises the assessment of product dossiers that should include information on all relevant aspects of manufacture and control of the specified products, the inspection of manufacturing sites of both FPPs and APIs (which must adhere to GMP) and, if applicable, inspection of clinical sites (which must adhere to good clinical practice (GCP)) and of laboratories for which good practices for pharmaceutical quality control laboratories should be applied.

PREQUALIFICATION OF ACTIVE PHARMACEUTICAL INGREDIENTS

The need for quality assurance of APIs was discussed by the Expert Committee at its 40th and 41st meetings, and then again at the 42nd and 43rd. The 42nd Expert Committee heard a presentation on the proposed procedure, which followed the procedure for the finished products, and which would be implemented by the United Nations Prequalification Programme. Members of the Committee heard that the aim of the procedure was to enable procurement agencies and others to validate the quality of products they were purchasing and to enable manufacturers of finished products to choose APIs from reliable sources.

The 43rd Expert Committee stressed that the quality of the API is a significant factor in the quality of the FPP. Manufacturers of FPPs must choose their suppliers and manufacturers of active ingredients but, 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.

The 42nd meeting of the Expert Committee endorsed the suggested procedure in principle but, since the procedure had been distributed for comment, it was further reviewed at the 43rd meeting. The revised working document on the *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* was adopted by the 43rd Expert Committee.

The 43rd Expert Committee also suggested that WHO should focus on the prequalification of APIs related to medicines for HIV/AIDS, tuberculosis and malaria, as well as on reproductive health, in accordance with the priorities of the Prequalification Programme.

PREQUALIFICATION OF PRIORITY ESSENTIAL MEDICINES AND DEVICES: INTRAUTERINE DEVICES AND CONDOMS

Two guidelines discussed by the 42nd Expert Committee related to the prequalification of intrauterine devices (IUDs) and of male condoms for purchase by United Nations agencies. Both procedures, which stemmed from collaboration with UNFPA, followed that for the prequalification of medicines and summarized the experience from quality evaluation carried out by agencies that had procured IUDs and condoms.

Both IUDs and condoms have been shown to be effective contraceptives and they are included in the WHO Model List of Essential Medicines 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. 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 Expert Committee adopted the proposed procedures for prequalification of IUDs and male condoms. UNFPA will be the agency implementing the prequalification procedures for these products. The proposed procedure on each product includes a list of standards and specifications published by WHO and by ISO.

GUIDANCE ON VARIATIONS TO A PREQUALIFIED PRODUCT DOSSIER

Over their lifetime, pharmaceuticals evolve in line with technological and scientific advances. Therefore, the listing of a product on the list of prequalified products is only a temporary status, awarded for a defined period of time.

Irrespective of regular WHO reviews, prequalified suppliers are responsible for the prequalified product throughout its lifetime. In the event of product modification, this includes making any necessary amendments to the product dossier. Amendments may include administrative or more substantial alterations, such as introducing an additional safeguard. Any changes to prequalified products are subject to WHO approval.

To facilitate the task of suppliers and WHO, and to ensure that alterations to pharmaceuticals do not create public health concerns, this guidance indicates how a manufacturer should present an application to implement different types of changes to a prequalified product. This guidance applies a priori to APIs and excipients manufactured by chemical synthesis or semisynthetic processes, and to finished generic pharmaceuticals containing WHO-prequalified APIs and excipients.

GUIDELINES ON THE REQUALIFICATION OF PREQUALIFIED DOSSIERS

The procedure for prequalification of pharmaceutical products adopted at the 43rd 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 re-evaluated 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.

In order to define exactly what information and documentation should be required from the applicants or manufacturers in order for a prequalified product to be re-evaluated, draft guidelines on the "requalification of prequalified dossiers" were developed by the quality assessors of the Prequalification Programme. These draft guidelines were circulated for discussion and comment and, following revision, were submitted for consideration to the 44th Expert Committee.

Following discussion the 44th Expert Committee adopted the new guidelines. These state that the objective of the regular quality review is to enable WHO to requalify a prequalified product on the basis of an assessment of the data and information submitted by the holder of that product. The review will include verification of the acceptability of the product and its conformity to current norms and standards, and assessment of consistency of the quality of the prequalified FPP and its manufacturing process over the identified period.

ACTIVE PHARMACEUTICAL INGREDIENT MASTER FILE

The active pharmaceutical ingredient master file (APIMF) is one option for the provision of scientific data by applicants submitting products to the Prequalification Programme. 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 FPP 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. Alternatively, applicants submitting products for prequalification must use other means of providing scientific data – backed up by 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 prequalification dossier.

The 42nd Expert Committee adopted a set of guidelines on the APIMF procedure. The guidelines are intended to help prequalification applicants and holders of prequalification dossiers to compile information on APIs in support of their application. The Expert Committee suggested that the terminology in the guidelines should be harmonized with definitions already adopted by the Committee in related guidelines on quality assurance. The Expert Committee also asked WHO to promote discussions on sharing regulatory information between NMRAs to conserve resources in APIMF and in dossier assessment.

LABORATORIES

PROCEDURE FOR ASSESSING THE ACCEPTABILITY, IN PRINCIPLE, OF QUALITY CONTROL LABORATORIES FOR USE BY UNITED NATIONS AGENCIES

As with pharmaceuticals for purchase by United Nations agencies, WHO has devised a quality assessment procedure to determine whether quality control laboratories (used for analysing prequalified pharmaceuticals) meet WHO-recommended requirements. Participation in the prequalification procedure is open to laboratories in the private and public sectors. Certification, such as ISO, is encouraged and taken into account during an assessment.

The WHO quality assessment procedure considers: information about the laboratory supplied by the NMRA; the laboratory's quality control activities; information submitted by the laboratory; and the laboratory's level of quality control consistency attained through compliance with GMP and WHO guidelines.

If the laboratory is deemed acceptable for use by United Nations agencies following the quality assessment process, it is placed on the list of quality control laboratories meeting WHO norms and standards, published on the WHO medicines web site.

WHO GOOD PRACTICES FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

As part of the process of prequalifying medicines in the Prequalification Programme, quality control laboratories – that have themselves been prequalified – test the quality specifications for products submitted for prequalification. This work is expected to be carried out in line with good practices for national pharmaceutical control laboratories and GMP recommended by WHO for such laboratories.

At its 36th meeting in 1999, before the Prequalification Programme came into being, the Expert Committee adopted a revised version of *WHO good practices for national pharmaceutical control laboratories*. Subsequent experience showed, however, that some of the text was not sufficiently clear. At its 43rd meeting, therefore, the Expert Committee indicated which areas of the document needed clarification and asked the WHO Secretariat to initiate the revision. In addition, the Expert Committee proposed that the title of the document should be made more broadly applicable.

The first draft of the revision was widely commented on, resulting in a second draft that was also discussed widely. The third draft of the revision was presented to the 44th meeting of the Expert Committee which noted the range of changes that had been made – including, for instance, explanatory notes introduced in the text in order to make a clear distinction between requirements and advice.

The 44th Expert Committee adopted the revised good practice guidelines, now titled *WHO Good practices for pharmaceutical quality control laboratories*. The revised good practice guidelines are to be used by pharmaceutical quality control laboratories that analyse APIs, excipients and pharmaceutical products. The guidelines provide advice on the quality management system within which the analysis should be performed in order to demonstrate that reliable results are obtained. Compliance with the recommendations provided in the guidelines is expected to promote international harmonization of laboratory practices and to facilitate cooperation among laboratories and mutual recognition of results.

BIOEQUIVALENCE/ INTERCHANGEABILITY

GUIDELINES ON REGISTRATION REQUIREMENTS TO ESTABLISH THE INTERCHANGEABILITY OF MULTISOURCE GENERIC PHARMACEUTICAL PRODUCTS AND THE PROPOSAL TO WAIVE IN VIVO BIOEQUIVALENCE REQUIREMENTS

If a generic product is to be considered interchangeable with a comparator product (a medicine whose efficacy, safety and quality has been proven), the generic product must be shown to be therapeutically equivalent to the comparator product. Direct demonstration of this in a clinical study usually requires many patients, is sometimes costly and often unnecessary – and in some cases may be unethical.

Over the past 40 years, the science of bioequivalence testing has been 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. To enable reliable prediction of therapeutic effect, the performance of a pharmaceutical preparation should be well established by in vivo and in vitro tests.

However, in some circumstances, in vivo bioequivalence studies can be waived. Following recent scientific developments, criteria for determining whether such a waiver is appropriate were revised for certain active APIs. In what is know as a "biowaiver" procedure, the in vivo bioequivalence test is waived if certain generic API solid-dose oral formulations are submitted to a strictly defined dissolution test (in vivo bioequivalence). This simplified process will reduce the time it takes for new product approval and thus lower the cost of bringing products to market.

In this context, the 40th Expert Committee adopted a proposal that provides currently available information on orally applied APIs, which are on the WHO Model List of Essential Medicines. The proposal's aim is to help national authorities – especially those planning to start implementing bioequivalence requirements – to make an informed decision as to the generic formulations for which in vivo bioequivalence studies should be required as a priority. In these cases a biowaiver can be applied. Thus many APIs on the WHO Model List of Essential Medicines may be considered for a biowaiver, subject to the approval of the relevant national authority.

GUIDELINES FOR ORGANIZATIONS PERFORMING IN VIVO BIOEQUIVALENCE STUDIES

Generic products must adhere to the same quality standards as originator products, as well as being therapeutically interchangeable. In other words, they must have essentially the same safety and efficacy profile as the originator product, i.e. they are therapeutically equivalent. One way of showing therapeutic equivalence, without having to conduct a clinical trial involving many patients, is to compare a generic medicine with a suitable comparator (usually an innovator [brand name] product) in a pharmacokinetic study, where the number of subjects is limited.

A pharmacokinetic study must 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. In this way the bioequivalence study provides indirect evidence of the efficacy and safety of a generic 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. However, the guidelines are not meant to stand alone and should be used in conjunction with the WHO guidelines on GMP, GCP, good laboratory practices (GLP) and good practices for quality control laboratories.

GUIDELINES FOR THE PREPARATION OF A CONTRACT RESEARCH ORGANIZATION MASTER FILE

A contract research organization master file (CROMF) is a document prepared by, and containing specific information about, a contract research organization (CRO). The master file (MF) includes information about the conduct of clinical studies, the analyses of samples and related operations (including clinical trials, clinical data management, pharmacokinetics and statistical analysis and regulatory affairs) carried out at a named site.

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 MF also gives an overview of the organization's approach to GCP, GLP and other guidelines related to its activities.

Several regulatory authorities as well as WHO have in the past recommended that manufacturers submit a site master file (SMF) for review (with GMP information about the pharmaceutical manufacturing operations at a specific site) when applying for registration of a medicine. Some regulatory authorities have also inspected clinical trials conducted at CROs. However, WHO prequalification inspectors found that not all information regarding CROs was available to inspectors when preparing for their inspections. Additionally, in several cases, significant changes had 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.

The proposal to establish a CROMF was welcomed by all parties contacted and was seen as an extension of the existing recommendation for the SMF of a manufacturing facility.

The document was adopted following the usual consultation process, provided that no major comments were received.

STABILITY

STABILITY TESTING OF ACTIVE PHARMACEUTICAL INGREDIENTS AND FINISHED PHARMACEUTICAL PRODUCTS

The 43rd 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 on stability testing and on climatic conditions led to a number of modifications in the 1996 guidelines. For instance, as a result of more precise data on climatic conditions in hot/humid areas, the level of "relative humidity" for testing was modified in 2003. The following year, the Expert Committee recommended further discussion at international level due to the availability of further information on climatic conditions based on real meteorological data. In October 2005 the Expert Committee reviewed the feedback received and recommended 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 40th Expert Committee regarding possible adoption of the regional guidelines as global guidelines. The regional guidelines were circulated to WHO Member States and comments were also sought from major regional harmonization groups. By 2010, following three revisions of the draft guidelines that elicited growing numbers of comments, the Expert Committee recognized that it was difficult to incorporate all of the remarks and that a less-than-ideal guideline would be better than a non-published one.

The 43rd Expert Committee gave careful consideration to all the comments submitted and made decisions on controversial issues. As a compromise, the labelling statements linked with testing conditions were moved from the main text of the draft guidelines and added as annexes in order to avoid any misunderstanding as to their 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. The importance of a table in the draft guidelines, specifying the stability testing conditions actually employed in WHO Member States, was emphasized. To complete this table, the Expert Committee requested that NMRAs, regional regulatory harmonization groups and the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) should again be contacted for their input.

The guidelines were thus adopted, subject to the inclusion of the above changes that would be overseen by a small working group composed of members of the Expert Committee. The experts further recommended that the annex, including the requirements of the NMRAs, should be updated when new information was made available to WHO.

NOMENCLATURE

INTERNATIONAL NONPROPRIETARY NAMES FOR BIOLOGICAL AND BIOTECHNICAL SUBSTANCES: A REVIEW

WHO has the responsibility for assigning International Nonproprietary Names (INN) to medicinal substances, so that each substance can be recognized globally by a unique name. A number of members of the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations are designated to serve on the INN Expert Group which consults on proposed INN and recommends whether or not they should be adopted. The INN have been regularly published by WHO as *International Nonproprietary Names for pharmaceutical substances*.

INN have been assigned to biological products since the early days of WHO's INN Programme. In the period up to 1980, names were assigned to antibiotics, synthetic peptides, hormones and other proteins. In 1982, the name *insulin human* was proposed for the recombinant protein identical to natural human insulin and afterwards names were assigned to a growing number of recombinant products. Since then, the range of biological and biotechnological products has increased in size and complexity. Examples of new products include 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 was duly prepared as an inventory of policy decisions taken by the INN Expert Group and of the names assigned to biological and biotechnological substances. In view of the potential for further developments in this field, the review will be regularly updated to include new policies and future INN assigned. Thus it was considered by the 42nd Expert Committee which adopted the principles contained in the document.

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 between future WHO guidelines included in the Expert Committee's future 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

In terms of direct financial support, the Expert Committee's work is made possible through regular budget and extrabudgetary support. The regular budget has diminished 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 is also supported by the Bill & Melinda Gates Foundation and by UNITAID.

The total costs of the Committee's activities are easily underestimated since they benefit immensely from in-kind laboratory studies conducted on WHO's behalf 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, the International Pharmaceutical Federation (FIP) has contributed its members' expertise and also assisted the 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 GFATM and UNICEF – in their efforts to combat substandard/spurious/falsely-labelled/falsified/counterfeit medicines.

The Committee's dedication to defining and harmonizing independent guidelines makes it possible for NMRAs, 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.

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