

Annex 2

The International Pharmacopoeia: revised concepts and future perspectives

General Context and Overview

WHO Constitution and World Health Assembly

The quality of pharmaceuticals has been a concern of WHO since its inception. The setting of global standards is requested in Article 2 of the WHO constitution which cites as one of the Organization's functions that it should "develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products". The World Health Assembly has adopted many resolutions requesting the Organization to develop international standards, recommendations and instruments to assure the quality of medicines, whether produced and traded nationally or internationally. In addition, many national governments support the activities of WHO Collaborating Centres financially.

Expert Committee and activities related to The International Pharmacopoeia

In response to the World Health Assembly resolutions, the WHO Expert Committee on Specifications for Pharmaceutical Preparations, which was originally established to prepare *The International Pharmacopoeia*, has made numerous recommendations relevant to quality assurance and control.¹

The activities related to *The International Pharmacopoeia* are an essential element in overall quality control and assurance of pharmaceuticals contributing to the safety and efficacy of drugs. Compared to other pharmacopoeias, priority is given to drugs included in the WHO Model List of Essential Drugs and to drugs important for WHO health programmes which may not be included in other pharmacopoeias, e.g. new antimalarials. The quality control specifications published in *The International Pharmacopoeia* are developed independently via an international consultative procedure. The

¹ See, for example, *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 1.* Geneva, World Health Organization, 1997; *Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2. Good manufacturing practices and inspection.* Geneva, World Health Organization, 1999.

needs of developing countries are taken into account and, whenever possible, classical analytical procedures are used. The policy is to include robust alternative methods when more complex methods are suggested. This publication undoubtedly strengthens the scientific credibility of WHO.

Revised concepts and future perspectives

The first volume of the first edition of *The International Pharmacopoeia* was published in 1951 with the aim of harmonizing quality requirements for pharmaceutical substances worldwide. After 50 years of existence and in the light of the development of the three major pharmacopoeias, namely the *European Pharmacopoeia*, *Japanese Pharmacopoeia* and *United States Pharmacopoeia*, and their current involvement in the Pharmacopoeial Discussion Group¹, it would seem appropriate to propose revised concepts and future perspectives for *The International Pharmacopoeia*. A more global approach to the quality control of pharmaceuticals in direct relation to the needs of developing countries and with WHO's Disease Control Programmes, is therefore suggested, including not only essential drugs but also the development of new therapeutic agents and/or new drug combinations.

Targets and priorities

The ultimate goals remain unchanged, namely the promotion of good quality pharmaceutical products, and the development of quality control methods for detecting counterfeit drugs so as to assure the safety and efficacy of medical treatments worldwide. This is also essential in promoting successful programmes for the eradication or control of diseases and in avoiding the emergence of drug resistance.

The development of screening tests and pharmacopoeial monographs for therapeutic agents, including combination products, to treat tuberculosis, malaria and AIDS, is the top priority.

New WHO quality control strategy

Sequential and graduated approach (step-wise strategy)

The priority is the development of quality control methods at different levels depending on the analytical methods and expertise (instrumentation, trained personnel, etc.) which are available and/or applicable in the countries concerned. Each level of analysis is designed to meet specific objectives and therefore should be selected for its intended purpose.

¹ WHO was recently granted observer status in the Pharmacopoeial Discussion Group.

Basic tests. These are intended to provide simple and readily applicable methods of confirming the identity of active ingredients. They are especially useful when a fully equipped laboratory and/or analytical expertise are not available and when indicative and rapid control is needed. Basic tests therefore have a clearly defined but limited role and are valuable tools for primary testing and for the detection of counterfeit drugs, but cannot replace a full analysis. When the identity is in doubt, further testing should be performed. Basic tests should be promoted and further developed.

Screening tests. The WHO Expert Committee on Specifications for Pharmaceutical Preparations has endorsed on several occasions the usefulness of thin-layer chromatography (TLC) in screening the identity of drugs and detecting counterfeit drugs and gross degradation. The method may be used for qualitative purposes and requires the use of appropriate Chemical Reference Substances. The development and validation of robust experimental conditions for TLC, both for field and laboratory testing, especially in the context of WHO's disease control programmes (i.e. those on malaria, tuberculosis and AIDS), is the principal objective of the Department of Essential Drugs and Medicines Policy.

Screening tests cannot replace a full analysis. When the result indicates deficiencies in quality, a full pharmacopoeial analysis must therefore be performed.

Pharmacopoeial monographs. *The International Pharmacopoeia* provides international standards for the content, purity and quality of active ingredients, pharmaceutical products and excipients moving in international commerce. Each monograph must be interpreted in accordance with all the general requirements and testing methods, texts or notices pertaining to it. A product is not of pharmacopoeial quality unless it complies with all the requirements stated in the respective context. Moreover, the underlying principle of a pharmacopoeia is that pharmaceutical substances and products intended for medical use should be manufactured according to Good Manufacturing Practices since quality cannot be tested into a product.

The recently adopted approach to include — in newly developed monographs — alternative analytical procedures when more sophisticated methods are described in the monographs concerned should be maintained.

The development of monographs in the context of WHO's disease control programmes (i.e. those on malaria, tuberculosis and AIDS) is a priority.

Monographs in *The International Pharmacopoeia*, together with related general methods and notices have an added value as discussed above and can also be used as references in the development of national (local) quality standards as well as for the assessment of sections on quality control in registration dossiers.

Independence of WHO and independent worldwide validation

Independent worldwide validation of analytical methods is very important, particularly in the context of the use of generics traded and sourced internationally. The active assistance of numerous WHO collaborating centres worldwide is therefore essential in developing international requirements and must be encouraged. The validation of newly developed analytical methods, e.g. for antiretrovirals, should be performed too. The independence of WHO in this matter is unique and of fundamental importance.

International Chemical Reference Substances

The establishment of International Chemical Reference Substances is also an essential part of quality control. This major task is directly related to pharmacopoeial activities and is performed by the WHO Collaborating Centre for Chemical Reference Substances in Kungens Kurva, Sweden. This work should be fully supported to ensure the supply of International Chemical Reference Substances and thus the success of WHO programmes.

List of priorities

In the context of drug quality control priorities are as follows:

- Continuation of the development of international requirements for testing pharmaceuticals.
- Promotion of the global and step-wise approach in the quality control of pharmaceuticals.
- Increasing the availability of documents and information on WHO activities in quality control.
- Providing advice to WHO priority programmes on quality control matters.
- Strengthening collaboration with the Pharmacopoeial Discussion Group.
- Providing information to WHO Member States on the harmonization process and collaboration.
- Promotion of external assessment schemes to improve the performance and recognition of laboratories.
- Coordination of training courses for quality control laboratories on essential sophisticated techniques.