Regulatory harmonization

WHO collaboration with world pharmacopoeias

The International Pharmacopoeia is a result of WHO’s focus on quality medicines. It provides publicly available standards for quality control testing of pharmaceuticals.

With the advent of globalization the need for harmonized pharmaceutical standards has become increasingly urgent. In recent years, WHO has supported regulatory convergence among Member States in various ways. The Organization has taken the lead in bringing together all active pharmacopoeias to work towards convergence of their standards and practices. This initiative is starting to deliver.

The use of pharmacopoeial standards

A pharmacopoeia is an official publication that lays down quality standards for pharmaceutical products in a country or region. It contains quality specifications for active pharmaceutical ingredients and finished dosage forms. A quality specification, as described in a monograph, is composed of a set of appropriate tests which will confirm the identity and purity of the substance or product, the amount of certain known impurities contained in it, as well as other characteristics such as its dissolution or disintegration properties.

Pharmacopoeial standards enable independent testing to verify that pharmaceutical products conform to official specifications. Pharmacopoeial testing is used in regulatory assessment of product data to ensure that medicines are consistently produced and controlled according to internationally accepted quality standards.

Pharmacopoeias around the world

National and regional pharmacopoeias form part of the legislation that governs the production and testing of medicinal substances, including all starting materials, including active and inactive substances, and finished products. According to the information available to WHO (1), there are 46 national pharmacopoeias around the world, some of them dating back to the 18th and 19th centuries. Regional pharmacopoeias include the European Pharmacopoeia, first published in 1967, as well as the African Pharmacopoeia and the recently launched Mercosur pharmacopoeia developed by Argentina, Brazil, Paraguay, Uruguay and Venezuela.

Three major pharmacopoeias, namely those of Japan, Europe and the United States, came together in 1989 in the Pharmacopoeial Discussion Group (PDG) to discuss harmonization topics. WHO subsequently joined the PDG as an observer.
**The International Pharmacopoeia**

Efforts to establish a unified pharmacopoeia have been pursued for over a century. WHO was mandated to coordinate this work in 1948 through the WHO Expert Committee on Unification of Pharmacopoeia – today named WHO Expert Committee on Specifications for Pharmaceutical Preparations. The first volume of *The International Pharmacopoeia* was published in 1951.

WHO provides *The International Pharmacopoeia* free of charge, with quality specifications that are ready for use by Member States. The focus is on essential medicines, i.e. those products that satisfy the health care needs of the majority of the population.

Many of the medicines included in *The International Pharmacopoeia* are not found in any other pharmacopoeia because they are not being used in the respective countries or regions, and/or their quality control is not considered a priority by the local authorities. By making technical information available for these medicines, WHO promotes access to quality medicines for all.

In 2003 WHO proposed future directions for *The International Pharmacopoeia*. Beyond essential medicines, priority would be given to new therapeutic agents and new combinations of medicines used to treat diseases most prevalent in low- and middle-income countries, notably HIV/AIDS, malaria and tuberculosis (3). More recently, the planning for updating of monographs has been aligned with the needs of the WHO Prequalification Programme.

Monographs for *The International Pharmacopoeia* are developed through a clear stepwise process described on the WHO website (4). This process provides a unique global forum for consultation among experts and stakeholders.

**Continued need for global harmonization**

With the advent of globalization, export and import of pharmaceutical substances and finished medicinal products have increased. However, national and regional pharmacopoeias have evolved separately from each other and differences in pharmacopoeial standards therefore persist. For medicines that are manufactured for international trade and placed on the market in various countries, a multitude of different requirements may apply, resulting in costs and delays that can compromise access to needed medicines.

**Recent harmonization efforts**

The discussion on global harmonization of pharmacopoeias was reopened during the 2002 International Conference of Drug Regulatory Authorities (ICDRA). The recommendations of the 2002 and 2004 ICDRA meetings led to renewed global harmonization efforts. A number of international events followed, enabling strategic discussions and networking.

In 2012 WHO convened the First International Meeting of World Pharmacopoeias, bringing together representatives of 23 pharmacopoeias around the world. This has become an important recurring event which is co-organized by WHO and the relevant authorities of the host country or region, i.e.:

- Second International Meeting of World Pharmacopoeias, 2013 – India;
- Third meeting, 2014 – United Kingdom;
- Fourth meeting, October 2014 – Council of Europe;
- Fifth meeting, June 2015 – United States; and
- Sixth meeting, autumn 2015 – China.
Good pharmacopoeial practices
One of the salient recommendations of the 2012 meeting of world pharmacopoeias was to develop a guidance text on good pharmacopoeial practices. It was agreed that this should be done under the auspices of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, benefiting from its well-established, transparent, consultative approach to international standard-setting.

The primary objective of the WHO Good Pharmacopoeial Practices (GPhP) guidance is to harmonize approaches and policies in establishing pharmacopoeial standards. The implementation of GPhP by national and regional pharmacopoeial authorities is voluntary.

It is envisaged that adherence to GPhP will:

- strengthen global pharmacopoeial cooperation;
- increase transparency on how pharmacopoeial standards are developed and maintained; and
- improve cooperation between pharmacopoeial authorities and stakeholders (e.g. regulators, industry).

Adherence to GPhP can foster exchanges, work sharing and acceptance of monographs among pharmacopoeias. This will make it easier for pharmacopoeial authorities, regulators and manufacturers to ensure that medicines moving on the global market comply with stringent standards and meet the local requirements.

Progress to date
A comprehensive draft guidance text on GPhP was circulated for comment in October 2012 and subsequently developed further by an initial drafting group. In addition, a shorter concept paper describing the purpose and benefits of good pharmacopoeial practice was drafted and published for comment (5).

As a next step the world pharmacopoeias will continue to work jointly on the GPhP guidance text. The draft is expected to be shared in 2015 with regulators, laboratory specialists, manufacturers and other stakeholders for their input.

Challenges
It has been recognized that retrospective harmonization of existing pharmacopoeial standards is difficult to achieve. Ongoing efforts therefore aim at prospective harmonization of new monographs. This endeavour is facing two main challenges.

Firstly, pharmacopoeias are embedded in national or regional regulatory systems with different public health priorities, business models and capacities. Regulatory systems themselves need to converge to make pharmacopoeial harmonization possible.

Secondly, developments in science and medical practice, globalization and the presence of adulterated products require pharmacopoeias to evolve constantly. While these adjustments present opportunities for prospective harmonization, it also means that a coordinated maintenance process is required to preserve harmonization over time. The process must also extend to related logistics, such as the establishment and maintenance of reference standards.

Future perspectives
The renewed, global effort towards pharmacopoeial harmonization has led to stepwise progress being achieved. Bilateral agreements are being concluded for example on sharing of monographs for medicines used to treat diseases which are not of major public health importance.
in industrialized countries, such as malaria and tuberculosis.

Good pharmacopoeial practice is a promising new approach to support convergence of global initiatives in this important area through a single forum. The higher the level of participation, the greater will be the benefits to the stakeholders and ultimately to patients in WHO Member States.

References