The International Pharmacopoeia

International Meeting of World Pharmacopoeias

A pharmacopoeia is a legally binding collection of standards and quality specifications for medicines used in a country or region. Within the pharmacopoeia, a quality specification is a set of appropriate tests that will confirm the identity and purity of the product, ascertain the strength (or amount) of the active substance and, when needed, the performance characteristics. Reference substances are used in testing to help ensure the quality, such as identity, strength and purity, of medicines.

A pharmacopoeia also covers pharmaceutical starting materials, excipients, intermediates and finished pharmaceutical products (FPPs). General requirements may also be given on important subjects related to medicines quality, such as analytical methods, microbiological purity, dissolution testing, or stability (1).

The role of a modern pharmacopoeia is to furnish quality specifications for active pharmaceutical ingredients (APIs), FPPs and general requirements. The existence of such specifications and requirements is necessary for the proper functioning or regulatory control of medicines production. Pharmacopoeial requirements form a basis for establishing quality requirements for individual pharmaceutical preparations.

According to the information available to the World Health Organization (WHO), 140 independent countries are at present employing thirty national as well as African, European and International Pharmacopoeias (2).

Compared to national and regional pharmacopoeias, The International Pharmacopoeia (Ph. Int.) is issued by WHO as a recommendation with the aim of providing international standards – including less technically demanding alternatives where needed — for adoption by Member States and to help achieve a potentially global uniformity of quality specifications for selected pharmaceutical products, excipients and dosage forms.

In response to a call for input, and as follow-up to discussions with representatives of world pharmacopoeias during the International Conference of Drug Regulatory Authorities in Hong Kong in 2002 and in Madrid in 2004, WHO organized the International Meeting of World Pharmacopoeias in early 2012. The aim was to discuss topics of common interest and address identified challenges.

In order to prepare for the meeting, WHO provided a set of preliminary questions on pharmacopoeias to meeting participants in an effort to inspire input to the agenda. The questions, presentations and final report are now available on a dedicated web site (3). This article is a summary of the report.

Pharmacopoeia: publication and frequency of updates

The pharmacopoeia, as a public tool, maintains quality of medicines by collecting the recommended procedures for analysis and specifications for the determination of pharmaceutical substances, excipients and dosage forms and, in most cases, consists of a general part (tests, methods and general requirements) and a specific part in the
Questions proposed to pharmacopoeias

1. Name of pharmacopoeia.
2. Is pharmacopoeia referred to in national/regional legislation – if yes, which?
3. Does national/regional legislation make reference to other national, regional, or international pharmacopoeias(s) – if yes, which?
4. When was publication of latest edition?
5. What is the update frequency – annually, biannually, other (please specify).
6. For which products does the pharmacopoeia provide specifications? APIs, dosage forms, herbal products, biologicals, traditional medicines, etc. (please specify)
7. What number of texts are included in the pharmacopoeia monographs for APIs, finished dosage forms, biologicals, and general monographs?
8. Is there collaboration with and/or being part of a (different) national/regional pharmacopoeia – if yes, which?
9. Is there publication of harmonized pharmacopoeial texts within the pharmacopoeia if yes, which pharmacopoeia, which type, how many?
10. Interaction with stakeholders, including regulators?
11. What is the strategy for the future?

form of monographs for pharmaceutical substances. Pharmaceutical analysis represents a platform through which state-of-the-art research can affect the quality, safety and efficacy of medicines directly by pharmacopoeial application of scientific results into everyday practice.

Transparency and scientific progress are the driving forces behind the need to constantly update all pharmacopoeias. Discussion of internationalization and unifying principles for the quality of medicines will require mindful consideration of the different languages and medicines regulatory activities among countries.

Most pharmacopoeial commissions take measures to update their pharmacopoeias in a timely manner. The updates are performed through the publication of supplements and addenda or by partial revision. More than half the pharmacopoeias represented at the meeting are updated annually.

Legal basis and references to other pharmacopoeias
Pharmacopoeias are referred to in legislation which confirms their legally binding status in the relevant country or region.

In Europe, a regional approach is used. the European Pharmacopoeia (Ph. Eur.) was created by eight Member States in 1964 and today consists of 36 Member States and the European Union (EU) which are signatories to the Convention on the Elaboration of a European Pharmacopoeia. Ph. Eur. members are: Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, (the former Yugoslav Republic of) Macedonia, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden,
Switzerland, Turkey, United Kingdom, and the EU. In addition, there are 24 observers, comprising 23 countries and WHO.

EU Directives stipulate that “the monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia.” These directives are transposed into national legislation of EU Member States.

Some of the 36 Member States of the Ph. Eur. Convention have decided to discontinue their own national pharmacopoeia and use only the Ph. Eur. Examples are Sweden and Finland. Other Member States of the Ph. Eur. Convention have decided to continue their national pharmacopoeia for products of solely national interest. In Switzerland, for instance, the Pharmacopoea Helvetica (Ph. Helv.) exists alongside the Ph. Eur. and the two together form the legally binding pharmacopoeia. In France, the pharmacopoeia consists of the texts of the European Pharmacopoeia and of the French Pharmacopoeia, including the “overseas” pharmacopoeia. Other countries, such as the United Kingdom, have decided to fully integrate the texts of the Ph. Eur. into their national pharmacopoeia; hence the British Pharmacopoeia (BP) contains the texts of the Ph. Eur. in addition to the national texts of the BP.

National/regional legislation often includes reference to other pharmacopoeias in the event that their own pharmacopoeial texts are not available. Thus the EU pharmaceutical legislation and hence the legislation of all EU Member States includes references both at the national/regional and international levels. Historic and language ties also play a role. For example, the Portuguese pharmacopoeia is also accepted in legislation for Brazil and other countries where Portuguese is an official language.

WHO’s International Pharmacopoeia (Ph. Int.) is «ready for use» by Member States. The Ph. Int. is referred to in a number of national legislations due to its applicability.

For which products does the pharmacopoeia provide specifications?
A large number of products are usually covered, reflecting the diligence and commitment of pharmacopoeial authorities and their appointed experts to develop a comprehensive working tool with up-to-date scientific data. The complexity and diversity of most pharmacopoeias results from mutual integration and interdependence with monographs for various types of products such as active pharmaceutical ingredients (APIs), excipients, herbal products, biologicals (vaccines, blood products), radiopharmaceuticals, dosage forms and homeopathic preparations.

It may be noted that there is a majority of finished dosage forms, which generally can be defined as the form of active ingredient which is or is intended to be dispensed or administered to the patient and requires no further manufacturing or processing other than packaging and labelling. This is in parallel to the decreasing tendency of specific national monographs for APIs within some national pharmacopoeias due to replacement with monographs from regional or international pharmacopoeias.

As the pharmacopoeia itself has emerged from experience gained throughout the centuries, the roots of this valuable knowledge can still be seen in contemporary medicine as traditional medicine monographs, represented mainly in the pharmacopoeias of China, France (overseas), Japan and Ph. Eur.
Likewise, homeopathic approaches are represented in pharmacopoeias in Brazil, Germany and Mexico, for example.

The pharmacopoeias reviewed at the International Meeting of World Pharmacopoeias contain standards for chemical and biological drug substances, dosage forms, compounded preparations, excipients, medical devices and dietary supplements. During the current meeting some countries, such as Brazil, France, Germany, Mexico, Serbia and Switzerland, provided examples of incorporating a national formulary for hospital and/or community pharmacy preparations into their pharmacopoeias. In Portugal, there is a non-official national formulary which is published by the Portuguese Pharmacies Association. During the meeting, examples were given of types of monographs with less frequent occurrence than other types.

For example, monographs for blood products were presented by Argentina (12), Brazil (20) and India (21), while monographs for vaccines were presented by Argentina (21), India (57), Kazakhstan (15) and Ukraine (26). Homeopathic preparations described in monographs were presented mainly by France (320), Germany (120) and Mexico (558) and finally monographs for traditional medicine were given as an example by China (2165). A total of 92 herbal, traditional herbal and homeopathic monographs are present in the British Pharmacopoeia 2012. Supplementary information is included in some of the pharmacopoeias, for example general texts, reference tables, and texts on methods of analysis, reagents, materials/containers, sutures, and reference substances used in national monographs.

Collaboration among pharmacopoeias
Pharmacopoeial authorities collaborate at both regional and international levels for the sake of harmonization and exchange of experience. Active and passive forms of participation occur. Active participants, such as members of Ph. Eur., can contribute their share of pharmacopoeial development, while passive forms of participation may include observational missions to benefit from the experience of other countries in specific areas and gain access to the work on quality control of medicines and methods of analysis used.

Leading world pharmacopoeias promote constant progress within pharmacopoeial development, “good pharmacopoeia practice” and recommendations of procedures for analysis intended to serve as source material for reference or adaptation by any of their Member States wishing to establish pharmaceutical requirements.

Ph. Int. provides an opportunity to comment on drafts by all world pharmacopoeias and offers participation in meetings, such as consultations and Expert Committees during the WHO consultation process. There are also WHO special projects covering quality assurance of medicines worldwide, such as collaboration with the African Pharmacopoeia, British Pharmacopoeia, Chinese Pharmacopoeia, Council of Europe/Ph. Eur. and the Pharmacopoeial Discussion Group (PDG).

Ph. Eur. covers all national pharmacopoeias of the signatory parties to the Convention, who are members of the Ph. Eur. with emphasis on complementarity, thereby reducing duplication of work. In some member countries of the Ph. Eur. national pharmacopoeias complement the Ph. Eur. for texts of interest to one Member State only. Some member countries also republish Ph. Eur. monographs in their national pharmacopoeias. Membership and observership enables States to participate in Ph. Eur. Commission sessions even if only Members are entitled to vote. Within these sessions, each Member State is represented by its national delegation consisting of not more...
than three members. On all technical matters delegations cast a vote. The EU decides on behalf of EU Member States in all non-technical issues of the Ph. Eur. Each Member State and observer can also propose national experts for each group of experts or working party.

The European Medicines Agency (EMA) participates in the sessions of the Ph. Eur. Commission and working parties of interest. The European Directorate for the Quality of Medicines and HealthCare (EDQM) participates in relevant committees and working parties at the level of the EMA alongside national competent authorities. In addition, annual meetings are organized between EDQM and national pharmacopoeial authorities. Thirty-six Member States and the EU are signatories to the Convention on the Elaboration of a European Pharmacopoeia.

Observership to the Ph. Eur. allows for participation in the scientific work of the European Pharmacopoeia Commission. Observer examples are Belarus, Brazil, China, Russia, the United States of America, and WHO.

The Pharmacopoeial Discussion Group (PDG) consists of representatives of three pharmacopoeias: Ph. Eur., Japanese Pharmacopoeia (JP) and the United States Pharmacopeial Convention (USP). Its main activities are retrospective harmonization of general chapters and excipient monographs. In addition, Ph. Eur. and USP are running a pilot project on prospective harmonization of active pharmaceutical ingredient monographs.

MERCOSUR, as an example of intensive collaboration at the regional level, and is formed by Argentina, Brazil, Paraguay and Uruguay. Texts and chapters are discussed for inclusion in the MERCOSUR Pharmacopoeia.

Some collaboration is historically and geographically related. Traditional collaboration of the Czech Republic with the Slovak Republic results from a common history. Agreements for collaboration have been signed between countries to increase the degree of compatibility, such as the USP with Mexico. Ukraine has also signed a collaborative agreement with USP, while intensively working with Kazakhstan. A memorandum of understanding has been signed by both the British Pharmacopoeia (BP) and Ph. Int. to use and incorporate developed monographs mutually.

Intensive collaboration with China’s pharmacopoeial authorities was described by representatives of the British and French Pharmacopoeias and USP during the meeting. France collaborates with Algeria, Morocco and Tunisia due to the fact that the French language is used in those pharmacopoeias. Brazil and Viet Nam are also named as collaborators with the French Pharmacopoeia. In information sent to WHO, Korean pharmacopoeial representatives mentioned bilateral memoranda of understanding with Ph. Eur. and USP.

Publication of harmonized pharmacopoeial texts within the pharmacopoeia

The PDG has defined harmonization of a pharmacopoeial monograph or general chapter as follows:

“A pharmacopoeial general chapter or other pharmacopoeial document is harmonized when a pharmaceutical substance or product tested by the document’s harmonized procedure yields the same results and the same accept/reject decision is reached.” (4).

When using a fully harmonized pharmacopoeial monograph or general chapter, an analyst will perform the same procedures and reach the same accept/reject decisions irrespective of which PDG pharmacopoeia is referenced. This is called interchangeability and
each pharmacopoeia identifies, in an appropriate manner, each fully harmonized monograph and general chapter.

The realization that it was important to have an independent evaluation of medicinal products before they are allowed on the market was reached at different times in different regions. In many cases action was driven by tragedies, such as that with sulfanilamide in the USA in 1937 and with thalidomide in the 1960s. Therefore, the urgent need to rationalize and harmonize regulation was impelled by concerns over rising costs of health care, escalation of the cost of research and development and the need to meet public expectations for a minimum delay in making safe and efficacious new treatments available to patients in need.

Eastern Europe
The majority of the State Pharmacopoeia of the Republic of Kazakhstan is formed from harmonized texts, including general chapters and monographs, monographs on pharmaceutical substances, monographs on vaccines for human use and human immunoglobulins. In the Ukrainian Pharmacopoeia Supplement, there are seven harmonized monographs for finished dosage forms, four are pursuant to the "Grant of Rights to Copy and Adapt the USP-NF" contract. Eleven draft monographs for the 2nd Edition have already been elaborated.

Asia
Japan contributes to harmonization efforts with its counterparts – Ph. Eur. and USP – within the PDG and the Japanese Pharmacopoeia contains general tests (14), general information (11) and excipient monographs (31) as harmonized texts. The Korean Pharmacopoeia has harmonized PDG texts for general tests.

North America
USP incorporates PDG-harmonized texts in the USP-NF, where 41 of 61 of excipient monographs and 28 of 35 of general chapters have been harmonized so far.

Latin America
Countries participating within MERCOSUR have included harmonized texts in their national pharmacopoeias after discussion. PDG texts are also considered during discussions of the Brazilian Pharmacopoeia Committee. Mexico does not have a formal process for the harmonization of information with other pharmacopoeias, but its drug monographs are consistent in their specifications with the BP, Ph. Eur. and USP in 60–100%.

Ph. Int. collaborates worldwide and has texts harmonized from various sources due to its rich collaboration. With the British Pharmacopoeia, this resulted in three texts adopted in 2010, with 19 in the pipeline. Also, through collaboration with PDG, 12 general methods were adopted in Ph. Int. in 2011 with more in the pipeline for methods of analysis and supplementary information.

Interaction with stakeholders, including regulators
There are many ways for national/regional pharmacopoeial authorities to interact and be influenced by stakeholders, particularly through public forums.

The most common interactions are at national level between national and regional regulatory authorities, quality control laboratories and different institutions related to quality assurance of medicines. Fusion of academic, clinical and industrial fields, such as universities and other academic bodies, hospital and community pharmacies organized in expert groups, and manufacturers worldwide through their organizations, represent a platform for comprehensive and progressive discussion.

To enable harmonization and a reliable
source of fluid information exchange at the global level, international organizations (UNAIDS, UNFPA, UNICEF, World Bank, WIPO, WTO, WCO), international professional and other associations, nongovernmental organizations (FIP, IFPMA, IGPA, MSF, WMA, WSMI), quality control laboratories (other than national/regional), United Nations-related organizations such as the Global Fund to Fight AIDS, Tuberculosis and Malaria, and WHO programmes including International Nonproprietary Names, Prequalification of Medicines, Medicines Regulatory Support, Medicines Safety, Traditional Medicines, Quality, Safety and Standards and specific disease programmes, are all stakeholders in collaboration.

Specific harmonization issues are discussed within regional and inter-regional harmonization groups (ASEAN, GCC, ICH, PANDRH, SADC, etc.). To ensure discussion and pragmatic approaches, annual science and standard symposia are organized, as well as public forums, for an unbiased outside view on particular issues.

**Strategy for the future**

Strategies of the individual pharmacopoeias differ for geographical and economic reasons and depending on the level of integration to respective regional international systems. There was a commitment to establish comprehensive, updated editions with highly compatible standards at a national or regional level, as well as intentions to harmonize intensively with emphasis on increased quality assurance of medicines around the world.

**International**

Ph. Int. commits to fulfilling the mandate of WHO given by its Member States and responds to the needs of the latter. As an international body, it also responds to the needs of quality control laboratories for post-marketing surveillance and maintains the international applicability of Ph. Int. specifications. Keeping the costs of analysis in mind, especially in the case of developing countries, Ph. Int. provides standards for major public health needs.

**Regional**

Ph. Eur. supports innovation and flexibility without losing the aim of a pharmacopoeia to provide official, recognized and technically sound quality standards. It also remains at the forefront in the biofield and constantly increases pharmacopoeial harmonization through collaboration, i.e. as part of PDG, and maintains observers within other pharmacopoeial institutions worldwide. Ph. Eur. Member States Sweden and Finland continue to cooperate and be active in the elaboration of the Ph. Eur.

**National**

Croatia is currently preparing a publication of a new edition of the Croatian Pharmacopoeia.

The Czech Republic would like to complete a national formulary, mainly in the field of paediatrics through cooperation with the chamber of paediatricians. Assessment of stability in the pharmacopoeia formularies for small-scale products and products prepared in pharmacies have also been mentioned as a future plan by Czech representatives, as well as establishment of a new group of experts from hospital pharmacies and certified laboratories.

France presented its strategy for the future at both the national and European levels. Publication online will define new policy and reinforce the code of practice in line with the new French Public Health Law. France defines the work programme based on both interest of patients or professionals (paediatric, ophthalmic and homeopathic preparations) and conforms to regulation and national strategy (French overseas territories). As a key player within the Ph. Eur., France would like to contribute to specific topics such as biological products, cell
and tissue therapies, anti-allergenic products, antiseptic preparations, paediatric preparations, traditional herbal preparations and collaboration with P4 procedures.

In addition to its contribution to the Ph. Eur., Germany focuses on particular technical issues in terms of pharmaceutical analysis such as identification of materials by the evaluation of analytical fingerprinting, use of non-destructive spectroscopic methods, imaging techniques for the intact pharmaceutical preparations, trace analysis of impurities and simplified analytical identification tests for certified substances.

As a country collaborating closely with the Ph. Eur., Portugal is focusing on its future plan to update national texts and to tighten the links with Portuguese-speaking countries and stakeholders.

Serbia will prepare its national addition to Ph. Eur., update national “Magistral Formularies” and continue cooperation with the Ph. Eur.

Spain plans to follow the timetable for publication of the in-force Ph. Eur. successive editions (simultaneous translation), to work with internal Spanish groups that support work of the experts and specialists in European and international groups and continue its efforts to cooperate with the work of the Ph. Eur. and international groups.

Switzerland focuses on participation in the activities of the Ph. Eur. in the framework of the legally binding mandate of the Ph. Eur. Convention.

Introduction of quality standards of the Russian Federation Pharmacopoeia (SP RF) 12th edition (Vols 1–5) in the territory of the Russian Federation, development of new quality standards for medicinal products and review of the older ones, will help to upgrade the national regulatory system. Plans for the future also include harmonization of the SP RF monographs with the corresponding monographs of the leading world pharmacopoeias. This will be assisted by participation of the Federal State Budgetary Institution “Scientific Centre for Expert Evaluation of Medicinal Products” of the Ministry of Health of the Russian Federation in the work of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, work of the EDQM (as an observer) and work of the WHO Working Group on Good Pharmacopoeial Practices.

United Kingdom representatives presented priorities at the international level. Contributions and intensive collaboration within the Ph. Eur. were also described. National activities of the BP will focus on the Annual BP and BP (Vet) Publications, British Approved Names Supplements, increase in New Formulated Preparation Monographs (licensed and unlicensed), Supplementary Chapters for BP and BP (Vet), Red Tape Challenge, Stakeholder Cooperation (manufacturers, practitioners, pharmacies, etc.) and tailored publications.

Japan’s efforts toward internationalization of its pharmacopoeia are based on prompt publication and further improvement of the JP English edition and web site. Building up the framework for international information exchange among pharmacopoeias will also be intensified. For its next revision JP commits itself to follow-up of the revision of “General Rules for Preparations” in JP16: general quality tests for preparations would be newly set, containers and storage section revised, and a new framework for monographs of drugs created whose manufacturing processes are different, including impurities (including residual solvents), process-related substances, impurities in biotechnology products and tests for preparations.

China provided information to WHO stating that the country is committed to more cooperation with other world leading pharmacopoeias.
India, in terms of sharing of information among pharmacopoeias, would like to focus on resources, working in pockets where there is a need for sharing information and providing commitment to monitoring, harmonizing with leading pharmacopoeias. Provision of quality medicines will be improved through harmonized drug standards and monitoring the quality of medicines through an effective regulatory system.

Indonesia’s plans are to publish a new edition of the Indonesian Pharmacopoeia every five years, to publish the supplement annually for the existing pharmacopoeia and to publish the pharmacopoeia in an English version.

Korea has informed WHO that it aims to include in its pharmacopoeia all medicines which are relevant from the viewpoint of health care and medical treatment. It will revise it in a timely manner for more efficient application and will follow international harmonization. Transparency will be important in revision of the Korean Pharmacopoeia, and the document will be publicly available and include up-to-date analytical methods and preparation of reference standards.

**Eastern Europe**

A future strategy for Kazakhstan will include the introduction of the State Pharmacopoeia, further harmonization with Ph. Eur. and USP and development, edition and revision of its own monographs.

Ukraine would like to transform its status from observer at the Ph. Eur. Commission to membership, support leading pharmacopoeias and implement harmonized standards. It aims to facilitate the movement of high-quality medicines through developing pharmacopoeial educational programmes and expanding visiting scientist programmes.

**Latin America**

The priorities for Argentina’s Pharmacopoeial Commission are strengthening of regional harmonization through joint development of reference standards and harmonization of general methods and monographs in order to establish similar quality standards within the region.

Brazil commits to continuing its integration with the MERCOSUR Pharmacopoeia and aligning the Brazilian Pharmacopoeia with public health needs and public policy development.

Mexico wants to stay tuned to the needs of the health authority and users, to maintain its current pharmacopoeia, continue promoting the approach of users to participate in the development of monographs and establish closer communication with colleagues in other parts of the world.

**North America**

USP strategy focuses on creating monographs in ways that rely on both the traditional donor model as well as on research and development in its own laboratories. In support of the second approach, USP has created the Medicines Compendium (MC), a freely available, online-only compendium of public standards for medicines approved in any country. The MC monographs provide performance tests for critical quality attributes and acceptance criteria, a source-independent reference procedure and one or more acceptable procedures submitted by manufacturers.

The MC strives to make available reference materials for all possible impurities associated with a particular monograph, and to expand approaches to include USP-NF, where many monographs are missing and more need updating. USP is also strengthening its ability to develop impurity reference materials independently through synthetic capabilities.

In addition, USP is working on standards with allied activities in...
support of manufacturers, regulatory bodies and others. Examples include a “global comparator product”, as well as emphasis on biological medicines standards in support of new, biosimilar and interchangeable biological products.

USP is working on spectral imaging approaches that allow field approaches to assure identity. These latter efforts align with the more elaborate laboratory testing approaches in a pharmacopoeial monograph or a private specification.

Conclusion
Participants at the meeting agreed to focus in the future on acceleration of international harmonization between world pharmacopoeias, and also on the establishment of an international bank of harmonized texts for substances and finished dosage forms of the most common vital medicines. It was also agreed that there should be a build-up of frameworks for international information exchange among pharmacopoeias, an introduction of new techniques, including analytical fingerprinting, non-destructive spectroscopic methods and imaging. Lastly, support was reiterated for maintenance of the international applicability of Ph. Int. specifications.

Individual presentations, the full report and conclusions are to be found on the WHO web site (3).

References


