The International Pharmacopoeia

Overview

Prepared by Caroline Mendy
Technical Officer - Quality Assurance and Safety: Medicines
The International Pharmacopoeia – Ph.Int

- Content & Scope
- WHO Expert Committee on Specifications for Pharmaceutical Preparations - Consultative procedure
- 4th Edition – Update
Pharmacopoeias

Quality control specifications:

- Medicines for a specific market
- Legally binding "official"
- Prepared by a national/regional authority
The history of the *Ph.Int* dates back 1874...
Monographs and requirements (1)

- Active Pharmaceutical Ingredients (APIs)
- Finished dosage forms
- General methods/texts

Completed with:

- General notices
- Supplementary information
- Infrared reference spectra
Monographs and requirements (2)

- **APIs/Excipients (441)**
- **FPPs (141)**
- **Radiopharmaceuticals (27)**
- **General monographs (9)**
- **General methods (73)**
- **Supplementary Information (14)**
- **IR spectra (154)**

Total: 892 items
International Chemical Reference Substances (ICRS)

Primary reference standards

Identification, Quantification, Qualification of analytical instruments

Establishment of secondary standards

WHO Custodian Organization for ICRS

The European Directorate for the Quality of Medicines & HealthCare – EDQM

Council of Europe (France)
Scope since 1975

WHO Model Lists of Essential Medicines

*Essential medicines selected with due regard to disease prevalence, evidence on efficacy and safety, and comparative cost-effectiveness*

Priority medicines recommended and specifications needed by WHO Programmes

- treatment guidelines for *Malaria, TB, HIV/AIDS*…
- medicines for *Children, Maternal Health*…
Special features

….when complex, technically demanding methods are described (e.g. HPLC),

--> a less sophisticated analytical method (e.g. TLC) is proposed as an alternative (if possible), or is primarily considered during development.

…. minimum use of reference substances preferred (e.g. in situ preparation of impurities considered during development…)

Ph.Int
Implementation

→: “ready for use” by Member States

"The Ph.Int […] is intended to serve as source material for reference or adaptation by any WHO Member State wishing to establish pharmaceutical requirements. The pharmacopoeia, or any part of it, shall have legal status, whenever a national or regional authority expressly introduces it into appropriate legislation."

[Reference to World Health Assembly resolution WHA3.10, WHO Handbook of Resolutions and Decisions, Vol. 1, 1977, p. 12]
How does it function?

- The Ph.Int is based on the work and decisions of the WHO Expert Committee on Specifications for Pharmaceutical Preparations.

- Aim over the last 60 years:

  "to promote quality assurance and quality control of pharmaceuticals"
WHO Consultative procedure

- This process is designed to ensure **wide consultation** and **transparency** during monograph development and to make the adopted texts available in a timely manner.
Annex 1

Process: Phases in the development of new monographs,
WHO Technical Report Series, No. 970, 20

- **Phase 1:** Identify specific pharmaceutical products for which quality control (QC) specifications need to be developed, following confirmation by all WHO parties concerned (including the Department of Essential Medicines and Health Products, specific disease programmes and the Prequalification of Medicines Programme). Establish whether monographs also need to be developed for the active pharmaceutical ingredients (APIs) contained in the pharmaceutical products identified. Update the current plan on The International Pharmacopoeia website.

- **Phase 2:** Obtain the contact details for the manufacturers selected APIs and pharmaceutical products, as applicable collaboration with all parties concerned.

- **Phase 3:** Contact manufacturers for provision of QC specifications and samples.

- **Phase 4:** Identify and contact QC laboratories for collaboration (the number of laboratories will depend on how many and pharmaceutical products have been identified in Phase 1).

- **Phase 5:** Make arrangements with the collaborating laboratories for drafting the specifications and undertaking the laboratory work.

- **Phase 6:** Search for information on QC specifications available in the public domain.

- **Phase 7:** Perform laboratory testing, development and validation of QC specifications.

- **Phase 8:** Follow the WHO Expert Committee consultative meeting guidelines for providing the first feedback to the Expert Advisory Panel and start to finalize the draft specifications on the website.

- **Phase 9:** Contact collaborating manufacturers to ascertain the availability of the respective substances to establish International Chemical Reference Substances (ICRS), as necessary.

- **Phase 10:** Support the WHO host organization (European Director for the Quality of Medicines and HealthCare, Council of ICRS) responsible for the establishment of ICRS.

- **Phase 11:** Collect and collate the comments received during the global consultative process.

- **Phase 12:** Discuss comments received during the consultation process with contract laboratories, WHO collaborating centres, and if relevant with the ICRS host organization; conduct additional laboratory testing to add, verify and/or validate specifications.

- **Phase 13:** Discuss the comments received during the consultation process and test results received as feedback from the collaborating laboratories in an informal consultation with experts and specialists.

- **Phase 14:** Recirculate draft monograph extensively for comments.

- **Phase 15:** Repeat Phases 8–15, until the agreed draft is suitable for adoption.

- **Phase 16:** Present the drafts to the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSP) for possible formal adoption. If not adopted, repeat Phases 8–14 as often as necessary. If the draft is adopted, proceed to Phase 17.

- **Phase 17:** Incorporate all changes agreed during the discussion leading to adoption together with any editorial corrections.

- **Phase 18:** Where necessary, also take account of any further comments that may be received due to comment deadlines for recirculated texts (Phase 12 and subsequent) falling shortly after the relevant consultation or ECSP meeting.

- **Phase 19:** In all cases, confirm the amended text by correspondence with the relevant experts and/or contract laboratory before making it available on The International Pharmacopoeia website.

- **Phase 20:** Make “final texts” available on The International Pharmacopoeia website to provide users, such as prequalification assessors and manufacturers, with the approved specifications in advance of the next publication date.

- **Phase 21:** Include in The International Pharmacopoeia.
WHO Procedure
...or why it takes so long... (1)

- **WHO priority diseases**

Identification of priorities

Step 1

- **Letters
  - Briefings
  - Workshops**

Invitation to manufacturers involvement

Steps 2, 3

- **WHO laboratories network**

Identification of collaborating laboratories

Steps 4, 5

- **Public/New specifications reviewed**

Analytical work carried out

Steps 6, 7

WHO Systematic Review Process

- ...or why it takes so long... (1)

Ph.Int
WHO Procedure
...or why it takes so long... (2)

- Wide circulation Web posting
- Draft mailing Comments compilation
  Steps 8,11

- WHO Expert Panel Specialists
- Consultations/Meetings
  Steps 12,13

- Inclusion of comments
- Draft revision
  Step 14

- Obtention of consensus
- Draft recirculation as many times as required ...

Additional analytical work if required
WHO Procedure
...or why it takes so long... (3)

Experts and/or contract laboratory confirmation

1. Once a year
   Discussion / Adoption
   - Expert committee
   - Step 16
2. EC decisions
   - Editorial changes
   - If adoption
   - Text finalization
   - Steps 17, 18, 19
3. Posting of final texts
   - Web
   - Step 20
4. Compilation (CD-rom, online, ...)
   - Publication in Ph.Int
   - Step 21

Ph.Int. - Mumbai, September 2012
WHO Procedure
...or why it takes so long... (4)

- Once a year Discussion / Adoption
- Need for revision/inclusion of important points
  - If non adoption Back to Steps 8 to 15 as many times as required...
  - Agreed revised draft suitable for adoption
- Major issues reviewed
- Presentation for adoption

If non adoption
Back to
Steps 8 to 15
as many times as required...

Additional analytical work if required

Expert Committee

Step 15

Expert Committee

Ph.Int.

World Health Organization

Ph.Int. - Mumbai, September 2012
Scheme and interactions

Monograph development

21 steps

Extensive network

Partners

WHO
Expert Committee
on Specifications
for Pharmaceutical
Preparations

WHO priorities

WHO Secretariat

Public inquiry

Collaborating laboratories

Industry

Partners*
WHO Partners (1)

Within WHO…

- **WHO disease programmes** (*Stop TB, Roll-Back Malaria, HIV/AIDS, Tropical Neglected Diseases, programmes on Children, Women's Health…*)

- **Prequalification Programme** – A United Nations Programme, managed by WHO

With Regulatory Bodies…

- National/Regional regulatory authorities

- Regional/Interregional regulatory groups (*ASEAN, ICH…*)
WHO Partners (2)

With Organizations and Associations…

- International organizations (UNAIDS, UNICEF, IAEA, World Bank…)

- International professional and other associations, NGOs (incl. industry, consumer associations: IFPMA-IGPA-WSMI, IPEC, FIP, WMA, MSF…)

With Standard-setting Bodies…

- Pharmacopoeia Commissions and Secretariats (e.g. Brazilian, BP, IP, JP, Ph.Eur, Ch.P, USP, and PDG)
WHO Partners (3)

With "recognized" Experts…

- WHO Expert Panel on The International Pharmacopoeia and Pharmaceutical Preparations (official nomination process)
- Specialists from all areas for specific projects (regulatory, university, industry…)

With "recognized" Laboratories…

- National/Regional Quality control laboratories
- WHO Collaborating Centres (official nomination process)
Briefing sessions organized by the WHO Quality Assurance Programme for interested parties

Opportunity to meet the Ph.Int Secretariat:
- raise technical and general questions/issues on texts
- express interest for collaboration on specific projects

possibility to send points of particular interest beforehand
Second Supplement

New!

→ 34 New monographs for medicines for HIV/AIDS, TB and Malaria, incl. Paediatric formulations

→ About 30 New monographs for Radiopharmaceuticals (new section)

→ 18 Revisions, 29 new IR reference spectra

Available in CD-ROM and Online
WHO Medicines web pages

- **Texts adopted** in 2010 and 2011 + **revisions** to date
- **Drafts texts** proposed for comment
- **Work plan** as adopted by the Expert Committee

⇒ **Important updates**
New trends (1)

- Slow shift towards **more sophisticated methods** to allow a better control of quality, e.g. related compounds detection

- Revision of no longer adequate methods considering common analytical practices worldwide
  
  e.g. - artemisinin derivatives with TLC related substances test,
  - antibiotics with microbiological assay

  ➔ to revise without compromising current policy to keep analytical methods at a reasonable level of sophistication and cost
New trends (2)

Use of Chemical Reference Substances

Specifying individual impurities in monographs requires, and is facilitated, by the use of corresponding reference standards.

- usually increases the cost of analyses
- close collaboration with manufacturers enhanced to obtain candidate material for establishment of ICRS
New trends (3)

Harmonization

In response, notably, to requests from industry for globally harmonized pharmacopoeial requirements

- Enhanced collaboration with other national/regional standard setting bodies, through:
  - WHO Consultative procedure
  - Special agreements for specific projects
New trends (4)

Harmonization

WHO participate, as an observer, to international initiatives for harmonization initiated by European Pharmacopoeia (Ph.Eur), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP):

- Pharmacopoeial Discussion Group (PDG)
- International Conference on Harmonization (ICH)

➤ suitability of 11 internationally harmonized texts for the Ph.Int reviewed and adopted in 2011 by WHO EC
WHO’s strategy for quality control

→ **Step-wise approach:**

- Basic tests (identification)
- Screening tests (TLC)

- *The International Pharmacopoeia*
- *International reference materials (ICRS and IR reference spectra)*
The International Pharmacopoeia's advantages (1)

1. Specifications validated internationally, through an independent scientific process

2. Input from WHO Collaborating Centres, National Drug Quality Control Laboratories

3. Collaboration with manufacturers around the world

4. Development considering the costs of analysis, i.e. using as few ICRS as possible
5. Collaboration with standard-setting organizations and parties, including regional and national pharmacopoeias

6. Networking and close collaboration with WHO Member States, Drug Regulatory Authorities

7. Links with other WHO activities

8. FREE FOR USE by all Member States
Supplement 3

- There are a number of monograph changes under review at the present time.

- The outcome of this discussions can not be guaranteed but the final step (Expert Committee) occurs in October.

- Some notable changes that may be of interest follow.
Supplement 3

Abacavir Sulphate

- Change to solubility specification from “freely soluble in water” to “soluble in water”.

Nevirapine

- Corrections to the monograph transparency
Supplement 3

Tenofovir disoproxil fumarate

- New limits for optical rotation are proposed.

Cycloserine

- A lowering of the system suitability criteria for peak resolution.
Supplement 3

Mefloquine

- Introduction of a monograph for mefloquine.

Artemisinin

- Revision of the method for related substances to adopt those specified in the recommendation for artemisinin as a starting material.
- Removal of the monographs for artemisinin tablets and artemisinin capsules.
Thank you!
For further information
or, in case of questions
contact

Dr Herbert Schmidt

schmidth@who.int