The International Pharmacopoeia

Dr Sabine Kopp
Quality Assurance and Safety: Medicines
World Health Organization
The International Pharmacopoeia – Int.Ph.

1. Introduction
2. Int. Ph. - historical overview
3. Int. Ph. - scope
4. WHO consultative procedure
5. Types of monographs
6. Special features
7. Example of a monograph
8. WHO’s strategy in QC
9. WHO’s related activities
Who is WHO?

- 192 Member States
- Two governing bodies:
  - World Health Assembly
  - Executive Board
- WHO Secretariat:
  - headquarters (HQ)
  - six regional offices (RO)
  - WHO expert panels
    (e.g... on The International Pharmacopoeia and Pharmaceutical Preparations)

Constitution 1946, *in force since 7 April 1948 (World Health Day)*
The International Pharmacopoeia – myth, mystery or revival

- Myth


  "traditional narrative usu. involving supernatural or fancied persons etc. and embodying popular ideas in natural or social phenomena etc.; such narratives collectively; allegory (Platonic); fictitious person or thing or idea; .. [f. Gk mythos]"
The International Pharmacopoeia – myth, mystery or revival

- mystery

- Oxford Dictionary 7th ed. 1989:

  1 "1. hidden or inexplicable matter..2. secrecy, obscurity..; (practice of) making a secret of (unimportant) things. 3. religious truth divinely revealed, esp. one beyond human reasons; religious rite. 4. (in pl).. 5. miracle play. ..... [ME, f. AF misterie, OF mistere or f.L.f.Gk mysterion,..]

  2 "(arch.) handicraft, trade [ME, f. med. L "mi(ni)sterium.. ]
The International Pharmacopoeia – myth, mystery or revival

• Revival

• Oxford Dictionary 7th ed. 1989:

  "1. bringing or coming back into use or vogue,
  2. reawakening of religious fervour,
  3. restoration of bodily or mental rigour or to life or consciousness .."
The International Pharmacopoeia  
– myth, mystery or revival

- Pharmacopoeia

- Oxford Dictionary 7th ed. 1989:

  "book (esp. one officially published) containing list of drugs with directions for use; stock of drugs [mod. F Gk pharmakopiia (pharmakopoios drug-maker...)]"
The International Pharmacopoeia – myth, mystery or revival

- Pharmacopoeia
- The International Pharmacopoeia, preface
- "collection of recommended procedures for the analysis and specifications for the determination of pharmaceutical substances, excipients and dosage forms"
- Requirements implemented by legislation
International Pharmacopoeia
Historical overview

→ 1874 Discussion on Unification of terminology and composition of drugs
→ 1902 First Conference organized by the Government of Belgium
→ 1906 Agreement on Unification of the Formulae of Potent Drugs ratified by 19 states
→ 1925 Brussels agreement (signed 1929)
→ League of Nations: “international pharmacopoeia”
International Pharmacopoeia
Historical overview - 2 -

→ **1937** First meeting (experts from B, CH, DK, F, NL, UK, USA) - *League of Nations*

→ **1947** Interim Commission of WHO takes up health related work of League of Nations

→ **1948** First *World Health Assembly* established
    Expert Committee on Unification of Pharmacopoeia
International Pharmacopoeia
Historical overview - 3 -

→ **1950** WHA approved publication of *Pharmacopoeia Internationalis*

**WHO Expert Committee:**

→ **1951** *named:* Expert Committee on *International Pharmacopoeia*

→ **1959** *named:* Expert Committee on Specifications for Pharmaceutical Preparations --> *to date*
International Pharmacopoeia

→ implementation: “ready for use” by Member States
→ Scope since 1975:
  → Model List of Essential Medicines and
  → Drugs recommended by WHO Specific disease programmes, e.g. Malaria, TB, HIV/AIDS
WHO Procedure for the preparation of drug Quality Control specifications (1)
.....or why it takes so long....

- Preliminary consultation and drafting
- Draft Quality Control specifications
- Method development + validation: WHO Collaborating Centres and experts, contracted laboratories
- Circulation for comments + testing of samples
- Revision process, additional studies, contacts with manufacturers for queries and additional samples as needed

.........
WHO does the work … with Partners

- National and regional authorities
- International organizations (UNAIDS, UNFPA, UNICEF, World Bank, WIPO, WTO, WCO, etc.)
- International professional and other associations, NGOs (including consumer associations, MSF, industry: IFPMA-IGPA-WSMI, FIP, WMA, etc.)
- WHO Expert Panels (official nomination process)
- Specialists from all areas, regulatory, university, industry ……..
- WHO Collaborating Centres (official nomination process)
- Pharmacopoeia Commissions and Secretariats, national institutions and institutes ..
- Regional and interregional groups (ICH…)
WHO Procedure for the preparation of drug Quality Control specifications (2)

- ..........
- Adoption by WHO Expert Committee on Specifications for Pharmaceutical Preparations
- Presentation to WHO Governing Bodies
- Recommendation to governments for implementation
  → publication in Technical Reports and
  → The International Pharmacopoeia and Basic Tests series
What is a WHO Expert Committee?

- Official advisory body to Director-General of WHO
- Governed through rules and procedures (Ref. WHO Manual)
- Participation in Expert Committee (EC) meetings:
  - **Voting members** ("Expert") selected from WHO Panel of Experts
  - **Technical advisers**
  - **Observers**: - *international organizations*, - *NGOs*, etc.
- Report of EC (including adopted guidelines) presented to WHO Governing Bodies for final comments, endorsement and implementation by Member States
- → WHO technical guidance
How to become a "WHO Expert"?

- Official nomination process

- Upon proposal to WHO in consultation with:
  - Member State/national government (citizenship)+
  - WHO Regional Office (in accordance with Member State) +
  - WHO headquarters

- Period of maximum 4 years

- Possibility to renew
Type of monographs

→ Drug substances
→ Excipients
→ Finished dosage forms
→ General methods and requirements:
  → oral sold dosage forms, e.g. tablets
  → dissolution testing…
Some Figures

→ **Volume 1:**
  42 General methods and requirements

→ **Volume 2:**
  88 Active pharmaceutical ingredients

→ **Volume 3:**
  100 Active pharmaceutical ingredients
Some Figures

→ Volume 4:

  23  Active pharmaceutical ingredients
  65  Excipients
  25  Oral dosage forms
  14  Injectables
  11  General methods and requirements
Some Figures

Volume 5:
20 Oral dosage forms
39 Active pharmaceutical ingredients
9 General methods and requirements

Special section on antimalarial agents, artemisinin derivatives:
5 Active pharmaceutical ingredients
8 Oral dosage forms

+ General guidance texts on INNs, graphic formulae, establishment of RS...
Specifications adopted by WHO Expert Committee – status March 2006

Monographs for Antiretrovirals (API):

- abacavir sulfate
- didanosine
- efavirenz
- indinavir sulfate
- nelfinavir
- nevirapine
- lamivudine
- ritonavir
- saquinavir
- saquinavir sulfate
- stavudine
- zidovudine
Specifications adopted by 40th WHO Expert Committee (status March 2006)

Antiretrovirals (finished dosage forms):

- nelfinavir mesilate tablets
- nelfinavir mesilate oral powder
- saquinavir mesilate capsules

... More to come...
Specifications adopted by 40th WHO Expert Committee (status March 2006)

Fixed-dose antituberculosis medicines:

- rifampicin tablets
- rifampicin capsules
- rifampicin + isoniazid tablets
- rifampicin + isoniazid + pyrazinamide + ethambutol HCl tablets
- isoniazid + ethambutol HCl tablets
- rifampicin + isoniazid + pyrazinamide tablets
International Pharmacopoeia
Special features:

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

   --> a less technically demanding analytical method (e.g. TLC) proposed as alternative (if possible).

2. ..... international validation - impurity profile can vary from country to country!!
Example of monograph - didanosine

- **DIDANOSINE**
- **C$_{10}$H$_{12}$N$_{4}$O$_{3}$**
- **Relative Molecular Mass. 236.2**
- **Chemical name.** 9-[(2$R$,5$S$)-5-(hydroxymethyl)tetrahydrofuran-2-yl]-1,9-dihydro-6$H$-purin-6-one; 9-(2,3-dideoxy-$\beta$-D-glycero-pentofuranosyl)-1,9-dihydro-6$H$-purin-6-one; 2',3'-dideoxyinosine (DDI); CAS Reg. No. 69655-05-6.
- **Description.** A white to almost white powder.
- **Solubility.** Sparingly soluble in water; slightly soluble in methanol R and ethanol (95 per cent) R
- **Category.** Antiretroviral (Nucleoside Reverse Transcriptase Inhibitor).
- **Storage.** Didanosine should be kept in a tightly closed container.
Didanosine monograph: Requirements

- Identity test
- Specific Optical Rotation
- Heavy metals
- Sulfated ash
- Loss on drying
- Related Substances
- Assay
- Impurities
- Reagents
Didanosine - Assay

- Dissolve about 0.200 g, accurately weighed, in 50 ml glacial acetic acid R1 and titrate with perchloric acid (0.1 mol/l) VS as described under “Non-aqueous titration”; Method A (Vol. 1, p.131) determining the end-point potentiometrically.

- Each ml of perchloric acid (0.1 mol/l) VS is equivalent to 23.62 mg of C$_{10}$H$_{12}$N$_4$O$_3$. 
Note: Prepare fresh solutions and perform the tests without delay.

Carry out the test as described under “High-performance liquid chromatography” (Vol. 5, p. 257), using a stainless steel column (25cm x 4.6mm), packed with octadecylsilyl base-deactivated silica gel for chromatography R (5µm)[1].

Maintain the column temperature at 20 – 25°C.

The mobile phases for gradient elution consist of a mixture of aqueous phase (Mobile phase A) and methanol (Mobile phase B), using the following conditions:

- Mobile phase A: A 0.05 M solution of ammonium acetate R adjusted to pH 8.0 using a 20% v/v ammonia (∼260 g/l) TS.
- Mobile phase B: Methanol.

1 Hypersil BDS is suitable.
Didanosine- Impurities

- The following list of known and potential impurities that have been shown to be controlled by the tests in this monograph is given for information.

- A. 1,7-dihydro-6H-purin-6-one (hypoxanthine)
- B. 9-β-D-ribofuranosyl-1,9-dihydro-6H-purin-6-one (inosine)
- C. 9-(2-deoxy- β-D-erythro-pentofuranosyl)-1,9-dihydro-6H-purin-6-one (2'-deoxyinosine)
- D. 9-(3-deoxy-β-D-erythro-pentofuranosyl)-1,9-dihydro-6H-purin-6-one (3'-deoxyinosine)
- E. 9-(2,3-anhydro-β-D-ribofuranosyl)-1,9-dihydro-6H-purin-6-one (2',3'-anhydroinosine)
- ....
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)
Establishment of monographs for antiretrovirals

- collaboration Ph.Eur. USP, JP, IP, Chinese Pharmacopoeia, Brazilian Pharmacopoeia ...
- collaboration with manufacturers
- links with WHO-UNICEF project on prequalification of suppliers for HIV drugs
Int. Ph. and links with other programmes and organizations

→ Monographs for antimalarials, anti-TB drugs (different clusters in WHO)

→ General requirements for products derived from plant materials (WHO Traditional Medicines Programme)

→ Monographs for radiopharmaceuticals (with International Atomic Energy Agency - IAEA)

→ Monographs for excipients (with Pharmacopoeial Discussion Group - PDG)
WHO’s related activities (1)

→ International Chemical Reference Substances (ICRS)
→ International IR reference spectra
→ Good Practices for National Pharmaceutical Control Laboratories
→ Model Certificate of Analysis
→ Considerations for requesting analysis of drug samples
→ Basic and screening tests
WHO’s related activities (2)

- WHO good manufacturing practice (GMP) for pharmaceutical products and starting materials (active ingredients and excipients)

- Good Trade and Distribution Practices for Pharmaceutical Starting Materials and Good distribution practices for medicines

- WHO Good Storage Practices (GSP)

- WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce and WHO Pharmaceutical Starting Materials Certification Scheme (SMACS)

- ..............
INNs
What needs to be kept in mind!!

1. Quality cannot be tested into the product!
What needs to be kept in mind!!

2. Specifications in national and regional pharmacopoeias are:

- based on manufacturers' specifications

- specific for the product(s) marketed in its legislative territory
3. Specifications should be used in a comprehensive way, i.e. including all tests listed

4. Specifications should be used intelligently, there is no guarantee that all (possible and impossible) impurities and alterations are covered!
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, especially for new projects
4. Collaboration with standard-setting organizations and parties, including regional and national pharmacopoeias

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

- 6. Links with other WHO activities

- 7. FREE FOR USE by all Member States
Further questions ???????
http://www.who.int/medicines