The International Pharmacopoeia

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Technical Briefing Seminar 04 October 2018
The International Pharmacopoeia

• Brief Introduction
• Monograph development process
• Work Programme
• International Chemical Reference Substances
• The Role of The International Pharmacopoeia in Public Health
  • Monograph on Dextromethorphan HBr
The International Pharmacopoeia
Brief Introduction
The Constitution requires WHO

• “to develop, establish and promote international standards with respect to biological and pharmaceutical products”

this has been done for more than 60 years now

Norms and standards are established by Expert Committees

• official advisory bodies to Director-General of WHO
• established by World Health Assembly or Executive Board

What is a pharmacopoeia?

• compendium describing medicinal products, issued by an officially recognized authority and serving as a standard
The International Pharmacopoeia
Brief Introduction

contains analytical methods and specifications for

• active pharmaceutical ingredients (API)
• finished pharmaceutical products
• excipients
• radiopharmaceuticals

focuses on medicines

• Model List of Essential Medicines
• Invitations to submit EOI for product evaluation to Prequalification Team - Medicines
• WHO/UN specific disease programmes
The International Pharmacopoeia
Brief Introduction

is ready to use

• “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.”

is free for use by WHO Member States

• [http://apps.who.int/phint/en/p/about/](http://apps.who.int/phint/en/p/about/)
main areas of work

• medicines for maternal, newborn, child and adolescent health
• antimalarial medicines
• antiviral medicines including antiretrovirals
• antituberculosis medicines
• medicines for tropical diseases

provides public standards for major public health needs

• Ph.Int. monographs are often the only publicly available compendial standards for priority medicines
It should be understood that a distinction exists between pharmacopoeial standards and manufacturers' release specifications.

Pharmacopoeial standards are publicly-available compliance specifications and provide the means for an independent check of the quality of a product at any time during its shelf life.

Although release specifications must be compatible with pharmacopoeial specifications, they may differ in several respects.

In order to ensure compliance with the pharmacopoeia the manufacturers' specifications may need to be more exacting than corresponding pharmacopoeial requirements.
The International Pharmacopoeia

Brief Introduction

applies current international standards

• aligned with harmonized regulatory standards

focus on technical aspects most relevant for LMIC

• Ph.Int. aims at global applicability of its methods/specifications
  • for complex, technically demanding methods less sophisticated tests are given as an alternative, if equally satisfying
  • "These strategies shall be applied when, during the elaboration of the methods, evidence could be obtained that the intended measures are equally satisfying to conclusively demonstrate conformance to the applicable standards!"
8th Edition 2018

- will be available online on the WHO website in October and on CD-ROM
- New and revised texts introduced for
  - 40 monographs on pharmaceutical substances
  - 13 monographs on dosage forms
  - 1 method of analysis
- based on the decisions taken at the meeting of the ECSPP 2017
8th Edition 2018

- Replacement of mercury salts in volumetric titration
  - As part of the activities to replace mercury salts in titrations of halide salts of weak bases, alternative titrations either with perchloric acid in anhydrous acetic acid or with sodium hydroxide in alcoholic media were introduced in 31 monographs.
- New harmonized text on Capillary electrophoresis
  - The new text on Capillary electrophoresis is based on the internationally-harmonized texts developed by the Pharmacopoeial Discussion Group (PDG). It has been developed and amended in line with the style and requirements of The International Pharmacopoeia.
- Various new and revised monographs
NEW TEXTS

Pharmaceutical substances

- Clindamycin palmitate hydrochloride, Ganciclovir, Clavulanate potassium

Dosage forms

- Amoxicillin and clavulanic acid tablets, Clindamycin palmitate powder for oral solution, Ganciclovir for injection, Protionamide tablets

Methods of analysis

- Capillary Electrophoresis
8th Edition 2018

- REVISED TEXTS

- Pharmaceutical substances

  - Amiloride hydrochloride, Amitriptyline hydrochloride, Amoxicillin trihydrate, Atazanavir sulfate, Atenolol, Biperiden hydrochloride, Capreomycin sulfate, Chlorhexidine dihydrochloride, Chlorpromazine hydrochloride, Ciclosporin, Dacarbazine, Dopamine hydrochloride, Edrophonium chloride, Ephedrine hydrochloride, Ethambutol hydrochloride, Fluphenazine hydrochloride, Homatropine hydrobromide, Homatropine methylbromide, Ketamine hydrochloride, Lidocaine hydrochloride, Loperamide hydrochloride, Metoclopramide hydrochloride, Morphine hydrochloride, Naloxone hydrochloride, Neostigmine bromide, Pilocarpine hydrochloride, Procarbazine hydrochloride, Proguanil hydrochloride
• REVISED TEXTS

• Pharmaceutical substances (cont.)
  • Propranolol hydrochloride, Protonamide, Pyridostigmine bromide, Pyridoxine hydrochloride, Quinine dihydrochloride, Quinine hydrochloride, Suxamethonium chloride, Thiamine hydrochloride, Verapamil hydrochloride

• Dosage forms
  • Atazanavir capsules, Capreomycin for injection, Efavirenz, emtricitabine and tenofovir disoproxil fumarate tablets, Emtricitabine and tenofovir disoproxil fumarate tablets, Ethinylestradiol and levonorgestrel tablets, Mebendazole tablets, Protonamide tablets, Sulfamethoxazole and trimethoprim oral suspension, Tenofovir disoproxil fumarate tablets
### 8th Edition 2018

- **OMITTED TEXTS**
  - Thiamine hydrobromide

- **IN TOTAL**
  - Pharmaceutical substances 372
  - Specific dosage forms 142
  - General dosage forms 8
  - Methods of analysis 72
The International Pharmacopoeia
Monograph Development Process
The International Pharmacopoeia
Monograph development process

- elaboration
- verification
- validation

Laboratory

- comments
- style
- consistency

Secretariat

- comments
- guidance
- adoption

Experts/Public
The International Pharmacopoeia Monograph development process

Main features of the process

• Process designed to ensure wide consultation and transparency

• is governed by publicly available rules and procedures
  • "schedule for the adoption process" outlining the development history is included in each working document

• allows participation of all interested parties

• applies conflict of interest and confidentiality rules

• is based on the work and decisions of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP)
  • texts and reference standards are approved/revised/suppression by EC
The International Pharmacopoeia Monograph development process

Partners

- organizations and associations
  - International organizations:
    - UN Commission on Life-Saving Commodities
    - UNAIDS, UNICEF, IAEA, World Bank
  - international professional and other associations, non-state actors
    - IFPMA-IGPA-WSMI, IPEC, FIP, WMA, MSF
  - standard-setting bodies...
    - pharmacopoeia commissions and secretariats
      - e.g. Brazilian, BP, IP, JP, Ph.Eur, Ch.P, USP, and PDG
The International Pharmacopoeia
Monograph development process

Partners

• experts
  • WHO Expert Panel on The International Pharmacopoeia and Pharmaceutical Preparations (official nomination process)
  • specialists from all areas for specific projects (regulatory, university, industry...)

• laboratories
  • national or regional quality control laboratories
  • WHO Collaborating Centres (official nomination process)
The International Pharmacopoeia
Work Plan 2018-2019
revised work plan is submitted to the EC on a biannual basis

Ph.Int. focuses on medicines

• Model List of Essential Medicines
• Invitations to submit EOI for product evaluation to Prequalification Team - Medicines
• WHO/UN specific disease programmes
• preferably not already described in pharmacopoeias

How do these priorities translate into a work plan?

• acknowledging available resources
• aiming to meet expectations of Member States, WHO programmes and other partners
Which of the medicines listed on

- WHO Model List of Essential Medicines (EML) or
- Invitations to submit EOI for product evaluation to PQ Team

are not yet subject to a monograph in Ph.Int.?

Results

- 140 monographs already published in the Ph.Int.
- 548 monographs identified as candidate monographs
Which of the candidate monographs are of particular interest for WHO and the PQ Programme?

• Which of the missing medicines are listed on
  • WHO Model List of Essential Medicines (EML) and
  • Invitations to submit EOI for product evaluation to PQ Team
• and are not subject to a monograph in the current
  • British Pharmacopoeia, United States Pharmacopeia, European Pharmacopoeia or Japanese Pharmacopoeia?

• Result
  • 38 monographs identified to be developed with high priority
The International Pharmacopoeia
Work programme

Monographs to be elaborated with high priority

- Antiviral medicines including antiretrovirals
- Antituberculosis medicines
- Antimalarial medicines
- Medicines for maternal, newborn, child and adolescent health
- Medicines for tropical diseases
- Medicines for anesthesia, pain and palliative care
- Other medicines for infectious diseases
The International Pharmacopoeia
ICRS
primary reference standards

• established by
  *European Directorate for the Quality of Medicines & HealthCare (EDQM)*

• under the authority of
  *WHO Expert Committee on Specifications for Pharmaceutical Preparations*
Purpose of ICRS

• to provide users of *The International Pharmacopoeia* with authenticated substances for reference

• for those analytical tests and assays that are based on comparison of physical or chemical properties of a sample with those of a reference standard

  • for identification, for quantification, to assess system suitability, to calibrate analytical instruments

• applicable in quality control of

  • active pharmaceutical ingredients and

  • finished dosage forms
Policy on ICRS

- rational use of International Chemical Reference substances (ICRS)
  - in situ preparation of impurities for identification purposes
  - quantification of impurities by comparing their responses with the response of the parent compound in a diluted sample solution along with the establishment of correction factors to compensate for differences in the responses of the impurity and the parent compound
  - provision of International Infrared Reference Spectra for use in identification tests
Policy on ICRS

• rational use of International Chemical Reference substances (ICRS) (cont.)
  • Provision of assay methods not requiring reference substances, like titrations and UV spectrophotometry using absorptivity values. These methods shall be provided as alternatives in particular to chromatographic assays in monographs for pharmaceutical substances.
The International Pharmacopoeia
Its Role in Public Health
The International Pharmacopoeia
Dextromethorphan HBr
new and revised Dextromethorphan (DMX) monographs in the Sixth Edition, 2016

• Dextromethorphan hydrobromide (revised)
• Dextromethorphan oral solution (new)
• Levomethorphan limit test for dextromethorphan-containing finished products (new, Supplementary Information)

revised following severe incidents with contaminated cough syrups in 2013

example of how compendial texts translate into protection of patients
January 2013 – WHO Drug Alert No. 126

• death of 50 persons following consumption of two locally produced dextromethorphan containing cough syrup in Pakistan

• a national quality control laboratory revealed that API and medicines were contaminated with varying levels of levomethorphan (LVM) (10% – 23%)

October 2013 – WHO Drug Alert No. 129

• drug intoxications involving 44 patients in Paraguay (in the age from 5 months to 48 years), 1 fatality

• all patients consumed locally manufactured medicines containing DXT

• investigations indicated the source of the API to be same as for the medicines in Pakistan
WHO strongly advised

- that extreme caution should be exercised by importing countries and manufacturers in determining that DXM is carefully tested for the presence of LVM

specific optical rotation (SOR) to test for LVM

- all API samples tested in both incidents failed to comply with compendial requirements for SOR

- estimated sensitivity of SOR test corresponds to about 2% LVM in DXM

- determination of the OR is not specific for LVM; thus not suitable to determine LVM in DXM containing oral solutions
development of a sensitive and specific assay for LVM

- to be used as
  - routine test for the release of DXM API
  - compliance test for suspicious DXM products

- scientific assessment of LVM toxicity
  - "a “safe” limit for human exposures through contaminated DXM can be estimated at an impurity concentration of about 0.1 %”
development of specific assay for LVM

- chiral separation of LVM and DXM based on Tedesco et al.
  - Journal of Pharmaceutical and Biomedical Analysis, 81-82 (2013), 76-79
- sufficient selectivity to allow determination of LVM in an excess of DXM
  - stationary phase: Chiralcel OJ-H column
  - mobile phase: n-hexane, 2-propanol and diethylamine (940:60:1)
- LVM limit test MONOGRAPH ON DXM HBR (6th edition)
- reference to the Supplementary Information section in the MONOGRAPH ON DXM ORAL SOLUTION (6th edition)
Dextromethorphan for system suitability ICRS

- containing a mixture of levomethorphan and dextromethorphan
- available since March 2016
“No family should endure financial hardship for out-of-pocket payments for the purchase of medicines to treat their loved ones, and no man, woman or child should die simply because they cannot access the life-saving medicines they need.”

Dr Tedros Aghanom Ghebreyesus