The International Pharmacopoeia

Dr Herbert Schmidt

Technical Briefing Seminar 04-08 November 2019
Outline

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 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
contains analytical methods and specifications for

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

focuses on priority 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/
The International Pharmacopoeia
Brief Introduction

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
quotes from the preface

• It should be understood that a distinction exists between pharmacopoeial standards and manufacturers' release specifications. Although release specifications must be compatible with pharmacopoeial specifications, they may differ in several respects.

• 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.

• 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!"
The International Pharmacopoeia

9th Edition 2019

• available online on the WHO website
• will be available on USB sticks
• new and revised texts introduced for
  • 7 monographs on pharmaceutical substances
  • 3 monographs on dosage forms
  • 2 method of analysis
• based on the decisions taken at the meeting of the ECSPP 2018
NEW TEXTS

• Pharmaceutical substances
  • Daclatasvir dihydrochloride, Estradiol valerate, Ivermectin, Moxifloxacin hydrochloride

• Dosage forms
  • Daclatasvir tablets, Ivermectin tablets, Moxifloxacin tablets

REVISED TEXTS

• Pharmaceutical substances
  • Atazanavir sulfate, Ethinylestradiol, Tetracycline hydrochloride

• Methods of analysis
  • Limit test for heavy metals (2.2.3)
  • Dissolution test for solid oral dosage forms (5.5)
IN TOTAL

• 371 monographs on pharmaceutical substances (including excipients)
• 142 monographs on specific dosage forms
• 8 monographs on general dosage forms
• 72 methods of analysis
The International Pharmacopoeia
Monograph Development Process
The International Pharmacopoeia
Monograph development process

- elaboration
- verification
- validation

Secretariat
- comments
- style
- consistency

Laboratory

Experts/Public
- comments
- guidance
- adoption
Main features of the 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 2020-2021
Optimal use of available resources

• by avoiding duplication of work

Survey to set up Ph.Int. work-plan 2020-2021

• 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 subject to a monograph in the current
  • BP, Ph.Eur., Ph.Int., JP or USP?
• These monographs will be developed with PRIORITY.
Pharmacopoeias considered by PQ Team Medicines

  - focus on medicines commonly used in the countries where the pharmacopoeias are legally binding, i.e. high income countries
- International Pharmacopoeia (Ph.Int.)
  - focus on priority medicines recommended by WHO
    - that satisfy the priority health care needs of the population
    - that are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness
The International Pharmacopoeia
Work Plan 2020-2021

Monographs to be developed with priority

- Antiviral: 23%
- Antituberculosis: 20%
- Antineoplastics: 17%
- Chronic diseases: 11%
- Tropical diseases: 8%
- Antimalarial: 7%
- Maternal, child health: 7%
- Other: 7%
The International Pharmacopoeia
ICRS
International Chemical Reference Substances (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
The International Pharmacopoeia
Dextromethorphan HBr

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