Quality of Medicines
in a globalised World
The European Pharmacopoeia
Is it prepared for the Future?

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Objectives of Pharmacopoeias

- **Aim of Pharmacopoeias**
  Harmonisation of requirements in the field of medicinal products within a region (political unit or international organisation)

- **Historically:**
  - 1871: Deutsches Reich
  - 1872: Pharmacopoeia Germanica, edition 1
  - 1963: First discussion EC about free circulation of medicinal product
  - 1964: European Pharmacopoeia
  - 1965: First EC directive 65/65
  - 1948: International Pharmacopoeia, WHO
  - 1990: ICH – PDG process
European Pharmacopoeia and Quality of Medicines

- 30-40 years ago: main requirements for MA application described in Pharmacopoeias
- Set of mandatory requirements (standards), described in
  - General monographs
  - General chapters
  - Specific monographs: mostly APIs, but also vaccines
- Advantages e.g.:
  - Regulators:
    - Important tool during assessment
    - OMCL: marketing control
  - Industry:
    - Predictable requirements
    - Collaboration Regulators - Industry

European Pharmacopoeia and challenges (1)

- Globalisation – multi source materials
  - Different impurity profiles
  - Transparency of monographs
  - Certification of suitability process
- ICH – process: new paradigm in pharmaceutical quality:
  - More emphasis on manufacturing process, more knowledge about material attributes,
    - Functionality testing
    - RTRT versus end product testing
    - RTRT and sample size e.g. UDU
    - Impurities controlled at an intermediate stage rather at final product (how to make in line two different manufacturing processes)
European Pharmacopoeia and challenges (2)

- Introduction of new technology: Raman, NIRS, Acoustics, .......
- Counterfeiting
- Revision of monographs to make them in line with new scientific progress
  - HPLC versus fast LC
  - ............... 
- To cope with new guidelines (CHMP)
  - Residual metals/solvents

European Pharmacopoeia and challenges (3)

- What is the future in pharmaceuticals?
  - Cell therapy
  - Gene therapy
  - Nanotechnology and associated technology
    - E.g. Transmission electron microscopy
  - Personalized medicines?
European Pharmacopoeia: Prepared for the future?

- Elements are so far in place: they need to be used appropriately (see also General Notices).
- Flexibility/adaptation requested without decrease in quality.
  - Ph. Eur. remaining the reference
- Close collaboration between European Pharmacopoeia and Competent Authorities and including Industry.
- Harmonisation of Pharmacopoeias
The European Pharmacopoeia – Is it Prepared for the Future?

EDQM Conference – Prague
14-15 October 2010

J. Mark Wiggins
Compendial Affairs
Merck/MSD

Whose future?

- Patients
- Practitioners
- Industry
- Pharmacopoeias
- Regulators

[Diagram showing relationships]
Shared Goals / Challenges

- To provide safe, effective, high-quality medicines to patients in an increasingly global environment.

- “The Need for International Harmonisation – Globalisation and expansion in international trade present a growing need to develop global quality standards for medicines… (these) standards are a vital instrument for registration, market surveillance, and free movement and trade of medicines among as many countries as possible…”

Ideal Pharmacopoeia* (1)

- The "Ideal Pharmacopoeia" would:
  - provide appropriate standardisation
  - to facilitate drug registration
  - and support regulatory agencies
  - through a single, global compendial standard.

* J. Mark Wiggins, et. al. (PhRMA Compendial Liaison Team), Pharmaceutical Technology, Vol. 32, No. 11, pp. 122-125 (November 2008)
Ideal Pharmacopoeia (2)

- Single, Global Compendial Standard
  - Ph. Eur. 6.0 Conference – Revelation
  - Harmonisation
    - PDG – ICH Q4B
    - Ph. Eur., USP, JP
    - Brasil, Russia, India, China, etc.
    - Ph. Int. – WHO
    - Prospective Harmonisation
- Mutual Acceptance
- Legislative Revision

Ideal Pharmacopoeia (3)

- PDG – ICH Q4B: Retrospective Harmonisation
  - General Chapters
  - Excipient Monographs
  - Gaps:
    - API / Product Monographs
    - "X"P (Non-PDG / Non-ICH Pharmacopoeias)
- Prospective Harmonisation Pilot Program
  - API Monographs
  - Ph. Eur. / USP
  - Gaps:
    - Product Monographs
    - JP / "X"P
Global Compendial Standards

Future Collaboration?

JP

USP

Ph. Eur.

Industry

IP

Ch. P

F. Bras.

WHO/Ph. Int.

RP

Ideal Pharmacopoeia (4)

- Provide appropriate standardisation
- Facilitate drug registration
  - General Notices
  - General Chapters
  - Ingredients
    - Excipients
    - Drug Substance
  - Products (Dosage Forms)
    - Pharmaceuticals
    - Vaccines
    - Therapeutic Proteins
Ideal Pharmacopoeia (5)

- Supports regulatory agencies
  - Needs and objectives aligned:
    - To provide safe, effective, high-quality medicines to patients in an increasingly global environment.
      - Glycerin / Heparin / Melamine
      - Residual Solvents
      - Metal Impurities
      - Related Substances
      - Uniformity of Dosage Units
      - Dissolution Calibration

Monographs / Reference Standards (1)

Practical Matters / Details
- Timing of Monograph Submissions
- Assay – APIs
  - Titration vs. HPLC
  - Certified Reference Materials
    - Interchangeability of Reference Standards
- Impurities / Related Substances (ICH Q3A, Q3B)
  - Quantitation vs. Limit Test
  - Impurities vs. Degradates (Product Monographs)
  - Impurity Reference Standards
- Metal Impurities (ICH Q3D)
  - Heavy Metals Test vs. ICP-MS/OES
Monographs / Reference Standards (2)

Practical Matters / Details
- ICH Q8, Q9, Q10 / QbD / PAT
  - QbD in manufacturing (UDU, NIR)
  - QbD in analytical methods
    Pharmaceutical Technology, Vol. 34, No. 2, pp. 52-59 (February 2010)
- Functionality-Related Characteristics – Excipients
- Acceptable, Equivalent, or Better (USP)
- Performance-Based Monographs (USP)
- Flexible Monographs (USP)
- Pending Standards (USP)
- Contamination / Adulteration / Counterfeiting
- Other considerations?

Is Ph. Eur. Prepared for the Future?
- Yes…
  - Already international
  - Effective collaborations
    - EC Pharmacopoeias / Observers
    - EU Regulators / OMCLs
    - Industry
  - Continue focus on harmonisation
  - Expand with WHO – Ph. Int.
  - Expand with Ch. P, IP, RP, F. Bras., etc.
  - Focus on details, e.g. impurity limits
Thank you
I look forward to the discussion…
The European Pharmacopoeia - Is it prepared for the future?

A Statement by the Pharmaceutical Industry

Dr. Bernhard Wolf
Merckle GmbH
A member of the ratiopharm group

Quality deficiencies

A long list of major quality deficiencies

- Gentamycin (CN)
- Heparin (CN)
- Clopidogrel (IN)
- Loperamid (IN)
- Oxytetracyclin (CN)
- etc.
The heparin case

- **End of 2007 - January /February 2008**
  US-case reports on hypotension, allergic reactions and even death after heparin administration

- **February 2008**
  FDA Alert on heparin from chinese origin

- **March 2008**
  similar case reports in Germany

- **Identification of OSCS as source of ADR (?)**

- **Publication of NMR- and CE-methods**

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The heparin case

- **August 2008:**
  **Revised Monograph in Ph.Eur., rapid implementation**
  Additional requirements:
  - Nuclear magnetic resonance spectrometry
  - Capillary electrophoresis

- **August 2010:**
  **Revised Monograph in Ph.Eur., rapid implementation**
  Identification: NMR and SAX-HPLC
  Related substances:
  - Chondroitin- + Dermatansulfate: $\leq 2.0\%$
  - any other impurity: no other peak than CS and DS
  Potency: $\geq 180$ IU / mg

... specifications approved by the competent authority
Potential for Improvements

- Monographs
- Certificates of Suitability
- Reference substances

Monographs

- Monographs should be updated periodically to represent and ascertain the available quality on the market (e.g. penicillins).
- To fix acceptable and realistic limits in monographs the cooperation of manufacturers, licensing authorities, and EDQM Certification Unit is needed.
- Harmonisation efforts of monographs and General Chapters with USP and JP should be intensified.
- Wording has to be unequivocally understandable for users (other impurities, any other impurity, specified impurities etc.).

- Include in the preamble of a monograph if a transition period for implementation is allowed (e.g. 2.9.40 Uniformity of dosage units).

- Indicate which impurities are degradation or by products. The latter do not have to be considered in the finished pharmaceutical products.

- Typical chromatograms using different brands of columns should be available on the knowledge database and not only in Pharmeuropa.
Certificates of Suitability

- The initiative to make GMP-inspections before granting a CEP should not only be limited to sterile APIs (without excluding the responsibility of the pharmaceutical companies for their products).

- Implement more transparency by publishing inspected companies and major deficiencies.

Reference substances

- Since the allocation of impurities is often problematic peak-identification mixtures in conjunction with sample chromatograms would be preferable.

- Impurities listed in the transparency list which are not specified are not available as CRS. Allocation of these impurities in sample chromatograms should be published in the knowledge database.

- CRS should be available before a new monograph comes into force to be able to implement the methods in the labs.
Thank you

for your time and attention!
Is Ph. Eur. prepared for the Future?

The Perspective of an OMCL

Dr. Philippe Girard
Head of OMCL (Swissmedic)

14/15 October 2010

Table of Contents

- OMCL
- What we appreciate…
- Challenges
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Official Medicines Control Laboratory

- Part of Swissmedic
- Experimental control of the quality of medicines
  - Market surveillance
  - Authorization
  - Pharmacopoeia (Helv. and Eur.)
  - Official batch release (OCABR)
  - Other sectors of Swissmedic (legal)
  - Third parties (states, justice)
  - > 40 Collaborators
- > 1500 m² of laboratory
- > 250 analytical devices
- > 3000 mandates and reports/releases
- Accreditation ISO 17'025

What we appreciate…

- A set of rules defining a legally binding standard of quality
- Robust and validated methods
- SST
- Suitable reference materials
- Definition of the range of validity of the method (2.2.46), certain flexibility
- A knowledge database in case of difficulties
- Possibility to get advice (i.e. FAQ and EDQM HelpDesk)
- P4 procedure
- Adoption by consensus
Challenges

• Detailed method descriptions
  • Freedom of the users versus foolproof methods
  • Generic versus brands (i.e. specific columns)
  • One method for all manufacturers

• Integration of technical improvements
  • UHPLC
  • Methods relying on chemometrics (e.g. RAMAN)
  • State of the art methods (e.g. 254 nm, antibiotics)

• Fast integration of regulatory needs (reaction time)
  • Genotoxic impurities
  • Substandard, counterfeit, fraud API (e.g. Heparin)

What we would like to have…

• Monographs for finished products
  • Frequent in national pharmacopeias
  • Effort versus benefit
  • Generic testing
  • Reduction of hurdles for MA

• Reference materials
  • Uncertainties of assigned values (CRS)
  • Calculation of measurement errors
  • More impurities, purity of impurities…

• Faster adaptation of changes (technical and regulatory)
• Equivalents to regulatory frameworks (e.g. equivalent to ICH Q3B)
What we would like to avoid...

One Method Pharmacopoeia

- ‘Analyze a suitable sample with an adequate method using qualified equipment in order to generate compliant results’
- OMCL with access to the methods of the MAH...
- …but why do we need an pharmacopoeia ?
- …users don’t all have access to methods...

- Excessive costs to obtain standards and the Pharmacopoeia

Ph. Eur. prepared for the Future?

Yes !

( … but …with some revisions, a little improvement and continuous evolution)