European Pharmacopoeia and Pharmacopoeial Discussion Group (PDG) update

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Content

1. Background: The Council of Europe and EDQM
2. Is There a Need for A Pharmacopoeia? – Scope
3. Challenges of Globalisation – What Can Pharmacopoeias Contribute?
4. International Harmonisation
The Council of Europe

- Founded in 1949
- Development of European common and democratic principles
- 47 member countries
- Headquarters in Strasbourg

Core values:
Protection of human rights (European Convention on Human Rights & Fundamental Freedoms), pluralist democracy & the rule of law
The EDQM

The European Directorate for the Quality of Medicines & HealthCare (EDQM), a Directorate of the Council of Europe (DG Democracy)

Our vision is to be a leader in protecting public health by

- establishing high quality standards for human and veterinary medicinal products, for blood transfusion and organ transplantation,

and for the safe and appropriate use of medicines;

and by

- participating in consumer health protection programs.

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The mission statement needs to be updated; we are now part of DG Democracy

Susan KEITEL, 11/6/2011
From the European Pharmacopoeia....

- 1964: Activities based on an International Convention of the Council of Europe to promote free movement of medicines in Europe
- Mandatory status reinforced in 1975 in the EU pharmaceutical legislation – with relevance for the EEA
- 1994: EU signs the Ph.Eur. Convention
- 1994: creation of the European Network for Official Medicines Control Laboratories
..... To the EDQM

- 1994: creation of the procedure of certification for active substances
- 2007: transfer of activities on blood transfusion and organ transplantation
- 2008: transfer of activities on combating counterfeits and healthcare activities
- 2009: transfer of activities on cosmetics and food-packaging
Member States and Observers
The role of Pharmacopoeias is to Guarantee the Quality of Medicines

- Harmonised specifications for substances of different origin (worldwide trade)
- Transparent monographs (impurity profile)
- Specifications and valid analytical working methods
- Common Reference Substances
Why a Monograph?

- A public standard, an independent evaluation
- One single quality for everybody
- Protection of public health via a standard which represents one known quality
- Simplifies the compilation of dossiers for industry and the evaluation of marketing authorisation applications
What Type of Monograph?

- All active ingredients and excipients of general interest
- Priority: therapeutic interest, number of patients treated, number of countries where the product is approved, mandatory quality
Fields Covered

• Active substances (organic, inorganic)
• Excipients
• Substances of biological and biotechnological origin (insulin, somatropin…)
• Herbal drugs and preparations, essential and fatty oils
• Radiopharmaceuticals
• Vaccines, sera (human, veterinary), blood derivatives
• Homoeopathic preparations
• …
The European Pharmacopoeia is...

- A public health instrument
- A source of standardisation
- A reference and a model for quality in the field of medicines
- The result of harmonisation by 36 European countries, ensuring the possibility for free movement of medicines
- A means to ensure competition of industry at « eye level » as everybody is bound by the same health standards
- Based on an international Convention under the aegis of the Council of Europe
Impact of Globalisation

- The chemical and pharmaceutical industry are – to a large extent – working globally
- Fragmentation of the supply chain can make tracing the quality of a substance difficult
- New routes of API synthesis may result in different impurity profiles
- Cost pressure in public health systems may cause frequent changes in suppliers
- A globally acting industry needs harmonised regulatory requirements
General Principles in Elaborating Monographs

• **SAFETY FIRST!**
  • Products of proven safety
  • Products evaluated and approved by competent authorities of Member States
  • Impurity profiles for existing, approved synthetic routes
  • Robust, validated analytical methods based on collaborative laboratory testing
3.2 Content: basic principles and requirements

“The monographs of the European Pharmacopoeia shall be applicable to all substances, preparations and pharmaceutical forms appearing in it. In respect of other substances, each Member State may require observance of its own national pharmacopoeia..."
Directive 2003/63/EC

...However, where a material in the European Pharmacopoeia ... has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described....
Directive 2003/63/EC

In cases where a specification contained in a monograph of the European Pharmacopoeia ... might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation holder. The competent authorities shall inform the authorities responsible for the pharmacopoeia in question. The marketing authorisation holder shall provide the authorities of that pharmacopoeia with the details of the alleged insufficiency and the additional specifications applied.”
Need to Stay Up-Dated

• To serve its purpose, the pharmacopoeia has to stay up-dated with changes in medical practice and technological developments, for example:
  – The significant growth of biotechnologically manufactured API
  – The growing importance of ethnic medicines, e.g. Traditional Chinese Medicines
Need to Stay Up-Dated

• To follow developments in the pharmaceutical industry (change in paradigm introduced by the ICH guidelines Q8, Q9, Q10), while taking into consideration the specific needs of the globally acting industry and small and medium-sized enterprises

• In 2010, 177 monographs and 16 general chapters were revised to ensure standards and methods are state-of-the-art
How Quality Standards Are Regularly Reviewed and Revised To Stay ‘State of The Art’

Developments in Regulatory Environment
- e.g. Guidelines, ICH Q8/Q9/Q10/Q11, REACH

Increased demand for Generic and Biosimilar products
- e.g. New sources

Scientific / technical evolutions
- e.g. Fast LC, NIR, PAT, new molecules, new therapies
- e.g. CT

Need to regularly review and update Ph Eur texts
- need to create new texts

New risks to Public Health
- e.g. Genotoxic impurities, TSE, contamination/ falsification (heparins)

Developments in Manufacture and Globalisation
- e.g. continuous manufacturing, changed routes of synthesis

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Pharmacopoeial Harmonisation - PDG

• Informal initiative between Ph.Eur., JP and USP with WHO as observer
• Focussed on general chapters and excipients
• Harmonisation of long-existing texts has proven to be:
  – difficult due to different approaches / traditions
  – slow to take account of stakeholders’ needs in the different regions who need to adapt
• At present
  – 28 of the 35 General Chapters
  – and 43 of the 62 excipient monographs have been harmonised.
Pharmacopoeial Harmonisation - PDG

• Met in parallel with ICH since its beginning in 1990 until 2010
• Following a decision of the ICH Steering Committee in Nov. 2010 to discontinue ICH Q4B (assessment of regulatory interchangeability of harmonised texts), separate meetings
**API Pilot Project Ph.Eur./USP**

- Common initiative of 2 manufacturers, Ph.Eur. and USP in 2008 to work on API monographs
- JP has been informed and observes process and outcome, with a view to potentially joining at a later stage
- Main idea: harmonise _prospectively_ based on EDQM “P4” procedure for substances still under patent
Pilot Procedure

1. Submission of identical data packages to EDQM and USP
2. After paper review, a common list of questions is sent to the manufacturer
3. EDQM reviews the replies and prepares a draft to a joint EDQM-P4/USP expert group
4. The draft is verified in parallel in laboratories of EDQM, USP, national authorities (OMCLs) or FDA.
Pilot Procedure (2)

5. The manufacturer may test in parallel

6. All labs reports are exchanged

7. The P4 Rapporteur co-ordinates the discussion on the reports and proposes potential changes of the first draft to the manufacturer

8. A consensus draft is published in Pharmeuropa and Pharmacopoeial Forum
Pilot Procedure (3)

• Review of public comments coordinated by the P4 Rapporteur in consultation with the joint expert group
• Common version of the final draft must be agreed by all parties
• Sent for adoption by Ph.Eur. Commission and USP committee
Pilot Procedure (4)

• Any changes during the approval process must be notified to all parties
• Target: identical implementation date
• From the first evaluation of pilot process (June 2011):
  – Prolongation of pilot phase to cover first revisions
  – Consideration of life-cycle mechanism for harmonised monographs.
Where Do We Stand Today?

- 4 dossiers from 2 manufacturers received 08-10/2008
- Reviewed by EP and USP
- Joint list of questions sent (10-11/2008)
- Answers from manufacturers received 02/2009-03/2009
- All 4 monographs (rizatriptan benzoate, montelukast sodium, celecoxib and sildenafil) are now adopted
Potential Problems

- Non-harmonised general chapters such as chromatography, heavy metals, water determination etc.
- Establishment of reference substances e.g. availability of sufficient amounts of impurity samples
Outlook API Pilot Program

- Communication worked well so far
- All parties committed to progress
- Final decision on a future extension to be taken based on life-cycle experience
- JP voiced interest in joining the activity
Ph.Eur. Current Issues and Priorities

- Adapting to globalisation and new sources of active ingredients and excipients:
  - IMPURITIES CONTROL
  - Arrival of generic biotechnological products (biosimilars)
  - Standardisation of advanced therapy products
  - Evaluating the impact of “Quality by Design” on monographs, PAT
  - Monographs on herbals
Current issues and priorities (2)

- New biological therapies (cell therapy, gene therapy products)
- Traditional herbal medicines (Chinese, Ayurvedic etc.)
- International Harmonisation
- Modern methods in microbiology
New topic under discussion

- In addition to Finished Product monographs existing in other fields, the Ph. Eur. Commission agreed on a pilot phase for Finished Product Monographs for chemically defined APIs

- In close collaboration with regulators
  - define desired scope and format of monographs
  - examine feasibility of monograph development for single-source as well as for multi-source products
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