

# **Modern European Pharmacopoeia Future Trends**

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Commission**

# Agenda

- Ph Eur strategy in the Biological field
- Ph Eur and “QbD”
- P4 procedure: a success story!
- “Heavy Metals”
- WFI by RO?
- Ph Eur and anti-counterfeiting activities
- Pharmacopoeial Harmonisation
- *REACH*

# **FUTURE IN THE FIELD OF BIOLOGICALS**

# Biosimilars: Ph. Eur. expectations

Biosimilarity relies on a combination of 3 pillars: quality, safety and efficacy.

Ph.Eur. monographs play an important role during the development of similar biological products as they should be used for method qualification and validation, even if *compliance to the Ph. Eur. is not sufficient to define/confirm the concept of biosimilarity.*

# Introduction

- In February 2011, EDQM organised a workshop on Biological products to gather the feed-back from European assessors in the field of biologicals with regard to Ph. Eur. monographs
- Concrete output highlighted in next slides

# Creation of new working parties

- *RCG working party:*
  - Creation of a new general text (e.g. monograph) to provide recommendations on raw materials for the production of cellular and gene transfer products
  - Scope: antibodies, basal media (for cell culture), serum/serum replacements, growth factors and cytokines
- *HCP working party:*
  - Provision of recommendations with regard to the development, validation and use of in-house or commercial kits or test methods for the detection and quantification of host-cell proteins.

# Development of finished product monographs

- Not new in the biological field (e.g. vaccines, blood products, insulin preparations)
- Need for further monographs to be assessed on a case by case basis
- Commission gave its green light (141<sup>st</sup> Session) to start **a pilot phase**, using filgrastim as case study



# P4Bio working party (pilot phase)

- Based on the P4 procedure
- The procedure applies to substances for which a **single** manufacturer has been identified. It is usually applied to substances **still under patent protection** where there is potential for future production of generics. The monograph draft is based on substances which are used in medicinal products that have been authorised by the competent authorities of Parties to the European Pharmacopoeia convention, normally in the EU.



# Timelines: Ongoing projects

- Insulin glargine:
  - Adopted: 11/2011
- rFVIIa:
  - Pharmeuropa 24.1: 01/2012
  - Proposed for adoption: Winter 2012
- rFIX
  - First draft: 09/2011 – end of 2011
  - Pharmeuropa 24.3 foreseen

# Expansion of the P4Bio pilot phase

One from each of the following categories

- Monoclonal antibodies
- Pegylated proteins

One finished product monograph (rFIX)

# BUT ALSO

# **“The consistency approach”**

- Concept already exists (implicitly) in General Notices
- Need for a clear definition in the General Notices
- Reflection on-going in the different Ph Eur Groups e.g. how to apply it in the context of the 3R's

**AND**

# The 3R's

- New Directive 2010/63/EU, Article 13

## Choice of methods

Without prejudice to national legislation prohibiting certain types of methods, Member States shall ensure that a procedure is not carried out if another method or testing strategy for obtaining the result sought, **not entailing the use of a live animal, is recognised under the legislation of the Union.**

# Foreseen in 2012

- Review of all monographs prescribing animal tests
- Continue efforts to remove/replace/refine
- Organisation of a 3R Workshop with EU specialist and Ph Eur Experts in June
- For presentation of a concrete work programme to the Ph Eur Commission



# PH. EUR. AND QBD

# Ph.Eur. activities to enable Implementation of QbD (1)

- Establishment of a PAT Working Group based on a request from EMA
- Review of General Notices and General Chapters

Update General Notices to take account of real time release testing

→will be updated once the EMA Guideline is adopted

# Additional Ph.Eur.activities to enable Implementation of QbD (2)

-New optional **general chapter 2.9.47** « Demonstration of Uniformity of Dosage Units based on large sample sizes » adopted at the last Commission session:

- recognises
  - that chapter 2.9.40 Uniformity of Dosage Units is harmonised by PDG (EP/JP/USP) and will continue to exist
  - that chapter 2.9.40 is needed when samples are tested in a market surveillance situation or when applicant does not use PAT tools
- intends not be a disincentive to make use of PAT-generated data
- should ideally been internationally harmonised
- has therefore been shared with ICH IWG

# **Additional Ph.Eur.activities to enable Implementation of QbD (3)**

- Reflection on the need for new general chapters, e.g. NIR-imaging, tera hertz spectroscopy, acoustics
- Development on an information chapter concerning chemometric methods applied to analytical data

# Additional Ph.Eur. activities to enable Implementation of QbD (4)

## Revision of chapter 2.2.40 NIR Infrared Spectroscopy

- to accommodate changes from « bench-top » to « in-line » measurements
  - Prepared in close consultation with Joint CHMP/CVMP Quality working Party
  - to be aligned with the ongoing revision of the Note for guidance on NIR from EMA (e.g. delete validation requirements)
- Pharmeuropa 23.3 under review, will be adopted in parallel with the revised version of the EMA Note for Guidance on NIR

# P4 PROCEDURE

# A success story!

- Already 59 P4 monographs adopted by the Ph. Eur. Commission
- Wish to have the submissions earlier [ideally 5 years after the 1<sup>st</sup> approval] to have enough time for technical work and to be ready by end of data exclusivity (ideally)



# **ELEMENTAL IMPURITIES**

## **(Heavy Metals chapter)**

# Objective:

- To draft a general chapter considering:
  1. first the EMA guideline on Metal catalysts and metal reagent residues
  2. and then the future ICH Q3D guideline.
- general chapter 5.20 (using the 5.4 Residual Solvent as a model), reproduction of the EMA guideline, adopted at the 142<sup>nd</sup> session along with method 2.4.20 ,
- Cross referenced in the general monograph 2034 Substances for pharmaceutical use? Will be published soon in Pharmeuropa for public enquiry

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# **USE OF REVERSE OSMOSIS (RO) FOR PRODUCTION OF WATER FOR INJECTION (WFI).**

# Main monographs on water

- Purified Water (Ph. Eur. N°0008)
- Water for injections (Ph. Eur. N°0169)
- Water highly purified (Ph. Eur. N°1927)
- *These 3 monographs are listed in the EMA Note for guidance on quality of water for pharmaceutical use.*

# History (1/2)

Ph. Eur. 1st edition  
1973 supplement:  
Water for injection  
1st publication –  
Distillation only

1983 - Ph. Eur. 2nd edition 5th Addendum:  
Water for injection, Revised monograph  
Distillation only, but first discussions about  
RO – RO discarded not enough experience  
and concerns with biological quality of water

1969

Ph. Eur. 1st edition:  
Purified water  
Prepared by distillation,  
ion exchange or  
suitable method

1999 – Preparation of Ph. Eur 4th Edition:  
Water for injection, Revised monograph  
under discussion.

Distillation only, but renewed discussions  
about RO – International seminar organized

# History (2/2)

Jan 2002 - Ph. Eur. 4th edition: Highly purified water is introduced

Production by RO coupled with UF and deionisation is allowed

March 1999  
International seminar  
Conclusion: Need for data and guidance

May 2002 – Adoption by CPMP/CVMP of Note for guidance on quality of water for pharmaceutical use

# Current position of the Ph. Eur. Commission

- Progress in the field of pharmaceutical water production acknowledged and considered.
- Request from Ph. Eur. COM to WAT working party to review the current situation and to propose action plan. See *November 2011 Ph. Eur. Commission press release*



# Work within the WAT WP

Point to be answered by the expert group based on the data gathered

- **WFI monograph (0169):**
  - » Evaluation whether RO would be appropriate or not,
  - » Current parameters: Adapted to non-distillation techniques?
  - » Change/Update limits for existing parameters?
  - » Add new parameters?
  - » Include new control methods?
  - » Modify/Update existing control methods?
- **Impact on other water monographs**
  - Ph. Eur. 0008 – Purified water
  - Ph. Eur. 1927 – Highly purified water
- **Impact on non-Ph. Eur. texts**

# **IMPURITIES: PGI** (Potentially genotoxic Impurities)

# Ph Eur approach (reminder)

- See PharmEuropa July 2008
- The policy developed reflected in:
  - the general monograph Substances for Pharmaceutical Use (2034);
  - general chapter 5.10. Control of impurities in substances for pharmaceutical use;
  - the Technical Guide.

# Revised general monograph 2034

- § PRODUCTION

*The manufacture of active substances must take place under conditions of good manufacturing practice.*

- § TEST / Related substances

*For all active substances included in a new application for a medicinal product for human use, the requirements of the guideline on the limits of genotoxic impurities and the corresponding questions and answers documents published on the website of the European Medicines Agency (or similar evaluation principles for non-European Union member states) must be followed.*

# Technical Guide

- New monographs:
  - evaluation for the presence of PGIs during marketing authorisation
- Before application of the CHMP guideline:
  - specifications as described in the dossier for marketing authorisation followed.
  - Action only where study data demonstrating genotoxicity of the impurity.

# PH EUR & ANTICOUNTERFEITING

Customs

Medicrime

CoE/EDQM Anti-  
counterfeiting  
activities

Inspection  
Testing

eTACT



# Role of the Ph Eur?

- New version of General Notices:

## POTENTIAL ADULTERATION

Due to the increasing number of fraudulent activities and cases of adulteration, information **may be made available** to Ph. Eur. users to help detect adulterated materials (i.e. active substances, excipients, intermediate products, bulk products and finished products).

To this purpose, a method for the detection of potential adulterants and relevant limits, together with a reminder that all stages of production and sourcing are subjected to a suitable quality system, may be included in this section of monographs on substances for which an incident has occurred or that present a risk of deliberate contamination. The frequency of testing by manufacturers or by users (e.g. manufacturers of intermediate products, bulk products and finished products, where relevant) depends on a risk assessment, taking into account the level of knowledge of the whole supply chain and national requirements.

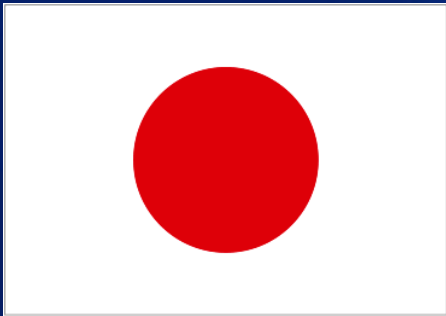
This section constitutes requirements for the whole supply chain, from manufacturers to users (e.g. manufacturers of intermediate products, bulk products and finished products, where relevant). **The absence of this section does not imply that attention to features such as those referred to above is not required.**

# PHARMACOPOEIAL HARMONISATION

# PDG (Pharmacopoeial Discussion Group)

# PDG

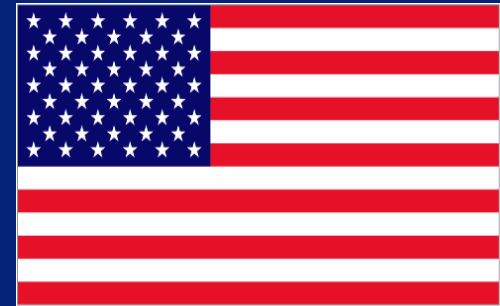
## Three major pharmacopoeias



Japanese  
Pharmacopeia  
Governmental



Ph. Eur.  
EDQM,  
Council of Europe  
Inter-governmental



US Pharmacopoeia  
Independent of  
Government

# The PDG & Harmonisation

- Pharmacopoeial Discussion Group (PDG) set up in 1990
- Drives international harmonisation of pharmacopoeial requirements among the world's three major pharmacopoeias, the Ph. Eur., JP and USP - a single set of global specifications.
- Aims:
  - Avoid redundant testing by suppliers and pharmaceutical industry to meet different standards
  - Reduce the overall cost of pharmaceutical research world-wide by avoiding duplication of work (preparation of dossiers and studies)
  - Reduce the time required for medicines to be made available to patients

# Pharmacopoeial Harmonisation

- Monographs and general methods of analysis proposed by national associations of manufacturers of pharmaceutical products
- To ensure rapid publication of signed-off texts, the PDG procedure has been woven into the Ph. Eur. procedure
- Texts are published in Pharmeuropa and approved by the Ph. Eur. Commission
- Priority of pharmacopoeias according to EU legislation  
Ph. Eur. > national pharmacopoeia > third country pharmacopoeias, e.g. USP, JP

# Status update

- 28 of the 35 General Chapters and 41 of the 61 excipient monographs of the current work programme have been harmonised.
- 17 General Chapters published in the chapter 5.8 and considered interchangeable



# Uniformity of dosage units

- 2% RSD exemption (May 2010) :
  - not acceptable for FDA
  - accepted by JP for item (4) only
  - accepted by Europe for all dosage forms subject to CU
- Future of the « old » methods 2.9.5 & 2.9.6 ?
  - Q&A under finalisation by QWP \_ will be published soon



# Other International Initiatives

# Prospective harmonisation

- Harmonisation of API monographs out of scope of PDG
- Bilateral initiative between EP and USP
- Pilot phase included four monographs\*, all adopted by the Ph Eur Commission
- Expansion of the pilot phase to cover the first revision request on these monographs before enlarging it to new candidate molecules

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# International meetings of pharmacopoeias

- First Global Summit of Pharmacopoeias
  - 17 & 18 November 2011, Beijing, China
  - Hosted by Chinese Pharmacopoeia and co-hosted by USP
  - Main proposal made:
    - Creation of an Index compiling all APIs monographs existing in Pharmacopoeias worldwide which might be extended to FPs

# International meetings of pharmacopoeias

- International Meeting Of World Pharmacopoeias
  - 29 February and 1-2 March 2012, WHO, Geneva
  - Hosted by WHO
  - Main proposal made:
    - Elaboration of « *Good Pharmacopoeia Practices* » to favour prospective harmonization, which procedure WHO could facilitate

# **REACH**

**(Registration, Authorisation and Restriction of Chemicals)**

## **Regulation EC N° 1907/2006**

### **Impact of REACH on European Pharmacopoeia**

# Which substances are concerned:

## Role of the different annexes

- REACH objective: Control and progressively replace substances of very high concerns (SvHC) – Annex XIV (SvHC requiring authorisation)
- Criteria for SvHC – Annex XIII: PBT (persistent, bioaccumulative and toxic) or vPvB (very persistent and very bioaccumulative) or wide dispersive use or high volumes
- Other substances with restricted use: Annex XVII
- Exemption: Specific uses or categories of uses – To be specifically asked to ECHA (Art. 58 §2 and 4)

# How is European Pharmacopoeia impacted?

- Substances described in monographs:
  - No impact (as long as the substances is solely used for pharmaceutical purposes)
- Laboratory reagents or substances limited to specific levels by monographs.
  - REACH has to be considered and might generate serious issues for methods to be applied.



# Conclusions (1/2)

- Small number of substances concerned (6) for the time being => about 100 texts concerned.
- Actions have already been initiated for 4 of these substances covering 20 texts, 80 texts remain but:
  - Arsenious trioxide used to prepare arsenic standard solutions covers 65 texts (monographs with arsenic limit test).
  - Acrylamide: Used for electrophoresis (replacement or deletion appears difficult) – 10 texts



# Conclusions (2/2)

- Annex XIV to be expanded in the 2 forthcoming years
  - Objective more than 150 substances
- Annex XVII will be the basis for inclusion of future substances (but not only) => Need to be proactive
- Blacklist of substances combining the different existing international legislation/conventions:  
<http://echa.europa.eu/web/guest/candidate-list-table>