The role of European Pharmacopoeia monographs in setting quality standards for biotherapeutic products

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Place of the Ph. Eur. within EU regulatory network (1/2)

- Lays down common, compulsory quality standards for all medicinal products in Europe.

**Article 1 – CONVENTION on the elaboration of a European Pharmacopoeia (1964)**

*The Contracting Parties undertake:*

a- progressively to elaborate a Pharmacopoeia which shall be common to the countries concerned and which shall be entitled «European Pharmacopoeia»;

b- to take the necessary measures to ensure that the monographs which will be adopted by virtue of Articles 6 and 7 of the present Convention and which will constitute the European Pharmacopoeia shall become the official standards applicable within their respective countries.

- **Mandatory** on the same date in 37 states (CoE) and the European Union

- The Ph. Eur. is **legally binding**. The legislation also includes a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market;
The European Pharmacopoeia needs to keep pace

- with the regulatory needs of licensing, control and inspection authorities in the public health area,
- with industrial constraints,
- with technological and scientific advances.
Structure of the talk

- Part I: Feed-back from industry
- Part II: The Ph. Eur. approach to individual monographs
PART I: FEED-BACK FROM INDUSTRY
Concerns raised by industry associations
“Due to their inherent complexity and interdependence with their manufacturing processes, the quality and consistency of biologics can only be defined and ensured through individual and comprehensive process-and product-specific control strategies.”

- We fully agree!
- Complexity of biologicals acknowledged
  - Vaccines
  - Production section
  - Monographs on biologicals: same structure but different content!

**BUT...**

“Biotherapeutic products are well defined molecules that can be fully characterised using state of the art physico-chemical technologies and therefore do not necessitate standards for potency assays” (WHO consultation on the need for International Standards for biotherapeutics, Geneva, Sept 2015)
“The EU legislation itself (and even the EDQM certification procedure) excluded biological products from their scope because of the complexity of the molecules”

- The Marketing Authorisation Holder needs to have access to all information about the production of a biological product: this is necessary to allow the applicant to take the responsibility for the medicinal product. (CHMP/QWP/227/02 Rev3/Corr).

- This is not comparable to the use of a monograph.
MONOGRAPHS AND BIOSIMILARS

“Some biologicals have been rejected by licensing authorities as being acceptable as biosimilars although they met all requirements of monographs”

- A comparison of the biosimilar to a publicly available standard, e.g. a pharmacopoeial monograph, is not sufficient for the purpose of comparability (EMA/CHMP/BWP/247713/2012)
- The role of the monograph is to set the quality requirements

“Ph. Eur. reference preparations used in individual monographs are inappropriate since they do not reflect the quality of the approved innovator product”

- Ph. Eur. reference standards are intended to be used within the scope of Ph. Eur. monographs (Ph. Eur. Chapter 5.12)

Should we deny public standards just because they are mis-used?
“Elaborating a monograph based on several products lead the Ph. Eur. to establish a standard of the lowest quality, without consideration of criticality of the quality attribute and pre-clinical/clinical evidence”

- Monographs in a multi-manufacturer situation lead to stronger standards, examples are the insulins and somatropin
  - From human growth hormone (labelled in International Units) to rDNA somatropin (labelled in mg)
- Monographs reflect cumulative knowledge from regulatory authorities with regard to quality
PART II: PH. EUR. APPROACH TO INDIVIDUAL MONOGRAPHS
Why we are... where we are...


- Human insulin
- Somatropin
- Hepatitis B vaccine
- Interferon alfa-2, Alteplase
- EPO
- Interferon gamma-1b

Products of recombinant DNA technology
Why we are... where we are...
rDNA products in the Ph. Eur. (2003-2010)

Individual monographs have not blocked the licensing approval of these biosimilars!

2003  2004  2005  2006  2007  2008  2009  2010

- Human coagulation factor VIII
- Insulin lispro
- Insulin aspart

- Molgramostim

- Somatropin biosimilar
- EPO biosimilar

- Filgrastim biosimilar
- Interferon beta-1a

- mAb general monograph

- EMA Biosimilars Guidelines

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Where to go?
Recommendations from industry associations

- **Focus on classes of products**
- **Analytical testing strategies**
- **General analytical tools**
- **System suitability tools**
Example: Human coagulation factor VIIa (rDNA) (2534)

PRODUCTION

Host-cell proteins

Limit approved by the competent authority

To be released soon:

New Chapter 2.6.34 : Host-Cell Protein Assays (tentative publication date: Supplement 9.1, Oct. 2016)
Example: Human coagulation factor VIIa (rDNA) (2534) –continued

PRODUCTION: Glycan analysis (2.2.59)

✓ General (mandatory):
  ➢ desalting
  ➢ selective release of glycans
  ➢ labelling of glycans
  ➢ liquid chromatography (2.2.29) with fluorometric detection - ion exchange chromatography

✓ Detailed SOP-like instructions (given as an example): non-mandatory
Example: Human coagulation factor VIIa (rDNA) (2534) –continued

PRODUCTION: Glycan analysis

System suitability (reference):
- peaks 1-12
- peak width at half-height

Limit: percentage of charged glycans as authorised by the competent authority

From single to multisource
Availability of candidate reference material?

2013
- Infliximab biosimilar

2014
- Insulin glargine Follitropin
- Human coagulation factor IX
- Follitropin biosimilars
- Infliximab (start work)

2014-2017
- Darbepoetin-alfa (start work)

2015
- March

2016
- January
- April

2017
- Teriparatide

Public consultation:
- Human coagulation factor IX powder for injection
- Public consultation:
  - Etanercept
  - Pegfilgrastim

From single to multisource
Availability of candidate reference material?

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Conclusion

• **Individual monographs play a major role in assuring a standardised level of quality for medicinal products and therefore contributing to patient safety**

• The Ph. Eur. has to and will continue to fulfill its mission as regards setting quality standards for biologicals, the question is **HOW** this role can be played

• The Ph. Eur. needs collaboration with all players
Recommendations for further debates

- The question of the role of monographs should be separated from the regulatory approval status
- Biotherapeutic products should be seen from a quality and standardisation point of view and should not be viewed differently than other molecules for which monographs exist
- We wish to focus on scientifically-based discussions
Call for candidates 2016

- The Ph. Eur. Commission has opened up the nomination process of experts to non Ph. Eur. members.
  - Until 2015 only candidatures proposed by National Pharmacopoeia Authorities (NPA) and by Observers to the Ph. Eur. Commission were considered by the Ph. Eur. Commission.
  - From November 2016 (new cycle of experts nominations), experts from non Ph. Eur. member states will be able to participate to Ph. Eur. activities upon appointment by Ph.Eur. Commission.
Thank you for your attention!
Guideline on similar biological medicinal products
CHMP/437/04 Rev 1
The biosimilar shall, with regard to the quality data, fulfil all requirements for Module 3 as defined in Annex I to Directive 2001/83/EC, as amended and satisfy the technical requirements of the European Pharmacopoeia and any additional requirements, such as defined in relevant CHMP and ICH guidelines.

Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1)
EMA/CHMP/BWP/247713/2012

A comparison of the biosimilar to a publicly available standard, e.g. a pharmacopoeial monograph, is not sufficient for the purpose of comparability.

The results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, when available and appropriate. These assays should comply with appropriate European Pharmacopoeia requirements for biological assays, if applicable.
Non applicability of Active Substance Master File (ASMF) concept to biological active substances

Marketing Authorisation Holders (MAH) and Applicants are advised that the concept of Active Substance Master Files, as laid down in Directive 2001/83/EC and Directive 2001/82/EC, as amended, cannot be applied in the context of biological medicinal products.

The characterisation and determination of biological active substances’ quality requires not only a combination of physico-chemical and biological testing, but also extensive knowledge of the production process and its control. The MAH/applicant for a biological medicinal product could therefore not comply with the requirement to ‘take responsibility for the medicinal product’ without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and should therefore not be allowed for biological active substances.