EDQM Viewpoint on the Role of the Ph. Eur. in the Field of Biosimilars

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Outline

• Place of the Ph. Eur. within EU regulatory landscape
• Ph. Eur. and biosimilars
  - monographs for biologicals
  - Ph. Eur. Reference standards/preparations
  - bioassay
• Flexibility of monographs
  - case study: Ph. Eur. *Human coagulation factor IX (rDNA)*
• Concluding remarks
Lays down common, compulsory quality standards for all medicinal products in Europe.

Mandatory on the same date in 37 states (CoE) and the EU (European Union Directives 2001/82/EC, 2001/83/EC, and 2003/63/EC, as amended, on medicines for human and veterinary use).

The Ph. Eur. is legally binding, but the legislation foresees a mechanism to provide the pharmacopoeia authority with information on the quality of products on the market, an excellent tool to ensure that monographs are not cast in stone but routinely updated to reflect the state-of-the-art.

Needs to keep pace with the regulatory needs of licensing, control and inspection authorities in the public health area, with technological and scientific advances, and with industrial constraints.
Relation Ph. Eur. – EU Guidelines

✓ Ph. Eur. provides specifications, harmonised approach for similar products/product classes
→ single common quality standard for medicines throughout Europe

✓ Ph. Eur. sets quality standards for biologicals, whether or not such products were to be submitted/approved as biosimilars.

✓ Ph. Eur. monographs and chapters can be complemented by scientific guidelines
→ complementary instruments to ensure quality of medicinal products
Ph. Eur. public standards

Recombinant DNA proteins:
(examples)
- Human insulin
- Insulin analogues
- Glucagon
- Somatropin
- Filgrastim
- Molgramostim
- Interferon alfa-2, beta-1a
- Interferon gamma-1b
- Erythropoetin
- Follitropin
- Calcitonin

Human coagulation factors...

Ph. Eur. update 2013
Ph. Eur. standards – biologicals

**Classes of substances, dosage forms**
- Recombinant DNA technology, products of (784)
- Monoclonal antibodies for human use (2031)

**Standard analytical methods general requirements for equipment**
- Peptide mapping (2.2.55)
- Amino acid analysis (2.2.56)
- Glycan analysis of glycoproteins (2.2.59)
- Isoelectric focusing (2.2.54)
- Size-exclusion chromatography (2.2.30)
- Capillary electrophoresis (2.2.47)
Ph. Eur. standards – biologicals (cont’d)

- based on approved specification(s) backed up by batch data
- specifications for drug substance
- analytical procedures and acceptance criteria to demonstrate the substance meets required quality standards

<table>
<thead>
<tr>
<th>General monographs</th>
<th>Product specific monographs</th>
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<tr>
<td>Biological Reference Preparations (BRP)</td>
<td>Chemical Reference Substances (CRS)</td>
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</table>

**DEFINITION** (amino acid sequence, glycosylation site, assay limits)

**PRODUCTION**: instructions for manufacturers (*different host expression systems, truncated/PEG forms not covered*)

**IDENTIFICATION** (peptide mapping, bioassay, glycan analysis…) *cross-reference to the test section*

**TESTS (purity)** (physico-chemical / chromatographic methods)

**ASSAY** (physico-chemical assay methods, bio/immuno-assays)
Ph. Eur. standards – biologicals (cont’d)

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Ph. Eur. Chapter 5.12 *Reference standards*

- Officially, legally-binding standards
- Method-specific
- Integral part of the Ph. Eur. texts
- Guaranteed for the intended purpose
- Support comparability of results
"The similar biological medicinal product shall, with regard to the quality data, fulfil all requirements for Module 3 as defined in Annex I to Directive 2001/83/EC and satisfy the technical requirements of the monographs of the European Pharmacopoeia and any additional requirements, such as defined in relevant CHMP and ICH guidelines."

Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)

However, as stated Directive 2001/83/EC:

"The provisions of Article 10(1)(a) (iii) may not be sufficient in the case of biological medicinal products. If the information required in the case of essentially similar products (generics) does not permit the demonstration of the similar nature of two biological medicinal products, additional data, in particular, the toxicological and clinical profile shall be provided."
**Biosimilars: EU Guidelines and Ph. Eur.**

**✓ Overarching** Guideline (CHMP/437/04 Rev.1): “Guideline on Similar Biological Medicinal Products”

**✓ Quality** Guideline (EMA/CHMP/BWP/247713/2012)

**✓ Non-clinical/ Clinical** Guideline (EMEA/CHMP/BMWP/42832/2005 Rev. 1)

**✓ Product-class** specific Guidelines (Insulin, Somatropin, GCSF, Epoetin, LMWH, IFN-α and -β, mAbs)

**use of publicly available standards (Ph. Eur. Standards)**

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Biosimilars: Ph. Eur. expectations

✓ Ph. Eur. monographs play an important role as quality standards for biotech products, as they are considered
  • by manufacturers, during the development of the similar biological products as they should be used for method qualification and validation,
  • by regulators, during the assessment of the biosimilar application.

✗ But... compliance with the respective Ph. Eur. monograph does not imply that the product is comparable and hence acceptable as a biosimilar product without further clinical/non-clinical studies.

• **Blockbuster biotech products** – **priorities** for the Work Programme
• Need for **harmonised quality criteria**
• Feedback on the **need to update** the monograph

For example, in case of different impurity profile compared to the monograph, application of the EU directive 2001/83/EC Annex 1
<table>
<thead>
<tr>
<th>Product name</th>
<th>Drug substance</th>
<th>Year of approval</th>
<th>Ph. Eur. monograph</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omnitrope</td>
<td>somatropin</td>
<td>2006</td>
<td>Somatropin (951); Somatropin concentrated solution (950); Somatropin for injection (952)</td>
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<tr>
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<td>somatropin</td>
<td>2006, withdrawn in 2012</td>
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<tr>
<td>Retacrit</td>
<td>epoetin zeta</td>
<td>2007</td>
<td>Erythropoietin concentrated solution (1316)</td>
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<td>Silapo</td>
<td>epoetin zeta</td>
<td>2007</td>
<td></td>
</tr>
<tr>
<td>Abseamed</td>
<td>epoetin alpha</td>
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<td>Binocrit</td>
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<td>Epoetin alfa Hexal</td>
<td>epoetin alpha</td>
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<td>Biogrostim</td>
<td>filgrastim</td>
<td>2008</td>
<td>Filgrastim concentrated solution (2206)</td>
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<td>2008, withdrawn in 2011</td>
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<td>Filgrastim Hexal</td>
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<td>Zarzio</td>
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<tr>
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<td>filgrastim</td>
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<tr>
<td>Somatropin Biopartners</td>
<td>somatropin</td>
<td>2013</td>
<td>Somatropin concentrated solution (950); Somatropin for injection (952)</td>
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<tr>
<td>Inflectra</td>
<td>infliximab</td>
<td>2013</td>
<td>-</td>
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<td>Remsima</td>
<td>infliximab</td>
<td>2013</td>
<td></td>
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<tr>
<td>Grastofil</td>
<td>filgrastim</td>
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<td>Filgrastim concentrated solution (2206)</td>
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<tr>
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<tr>
<td>Bemfola</td>
<td>follitropin alfa</td>
<td>CHMP positive opinion 2014</td>
<td></td>
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</table>
Need for monographs to remain up to date

Annex 1 of Directive 2001/83/EC: “In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State 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.”

Feedback on the ability of the Ph. Eur. monograph to support the quality part in the comparability exercise is essential for the monograph to remain used and useful.
Compliance with the European Pharmacopoeia is, therefore, a necessary, but not sufficient requirement for a biosimilar application in the EU.

- quality standard for product characterisation
- product-specific requirements
- documentary (monographs/general chapters), reference (materials) standards

Biosimilars: Ph. Eur. supporting activities

Ph. Eur. Standards

- Quality
- Comparability

Reference Standard

Acceptance criteria for comparability vs reference medicinal product
Ph. Eur. Reference Standards

✓ Intended for use as stated in a monograph or general chapter of the Ph. Eur.

✓ Where a Ph. Eur. reference standard is referred to in a monograph or general chapter, it represents the official standard that is alone authoritative in case of doubt or dispute

Ph. Eur. General Chapter 5.12

✗ Reference standards for either biological or physico-chemical test methods are not reference (comparator) products
Types of Ph. Eur. Reference Standards

- Established and guaranteed for their intended purpose:
  - **Identification** (*e.g.* by LC)
  - **Purity testing** (*e.g.* impurity CRS)
  - **Assay** (assigned content/potency – CRS/BRP)
  - **Peak identification / system suitability** (one or more specified impurities)
    - to be located in the chromatogram or electropherogram
    - to enable verification of selectivity, sensitivity or other method attributes

- To be used with monographs: help users to make an unambiguous pass/fail decision on the batch being tested.
Assay CRS

✓ Verification of identity, structure, compliance with the monograph (when applicable)
✓ Determination of purity
✓ Confirmation of purity by alternative methods (e.g. quantitative NMR)
✓ Homogeneity verification
✓ Inter-laboratory study to assign a content:
  • based on the compendial method and compendial specifications
  • an assigned value is given on “as is” basis:
    \[ X \, (\% \, m/m) = \left(100 - (\% \, \text{water} + \% \, \text{inorganic compounds})\right) \times \% \, \text{purity} / 100 \]
    for lyophilised standards, exact quantity per vial is assigned (mg/vial)
  • measurement uncertainty associated to the content value of Ph. Eur. CRS is not stated since it is considered to be “negligible in relation to the defined limits of the method-specific assays for which they are used.” (ISO Guide 34, chapter 5.17)

Example: *Insulin glargine* (Ph. Eur. 2572)

*Content:* 94.0 per cent to 105.0 per cent (anhydrous substance).
Assay – recombinant DNA proteins

Protein content
usually by a comparative LC procedure against a defined CRS

Potency determination
Bioassay calibrated against WHO international standards/Ph. Eur. standards (BRPs) / in-house standards (in vivo assay / in vitro assay)

limits expressed as:
- an acceptable range for the labelled potency (e.g. 80-125 per cent of the stated potency)
- an acceptable range for the confidence limits of the estimated potency (e.g. 64-156 per cent of the stated potency)

Ph. Eur. General Chapter 5.3. Statistical analysis of results of biological assays and tests

“Guide for the elaboration of monographs on synthetic peptides and recombinant DNA proteins” (Edition 2010)
Bioassay – *Erythropoietin example* (1)

- Ph. Eur. *Erythropoietin concentrated solution* (1316)
  
  **ASSAY**
  
  The activity of the preparation is compared with that of *erythropoietin BRP* and expressed in International Units (IU).

- Ph. Eur. General Chapter 5.3. *Statistical analysis of results of biological assays and tests* ⇒ **parallel-line model**
**Bioassay – Erythropoietin example (2)**

**Erythropoietin concentrated solution** (Ph. Eur. 1316)

**ASSAY**

The activity of the preparation is compared with that of *erythropoietin BRP* and expressed in International Units (IU).

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency. The confidence limits of the estimated potency ($P = 0.95$) are not less than 64 per cent and not more than 156 per cent of the stated potency.
Bioassay in Ph. Eur. monographs

- *In vivo assay / in vitro assay* are described in monographs for **potency determination** of recombinant DNA products (analytical procedure, specifications).

**BUT**

- **A physico-chemical assay alone** may be employed (where the battery of physico-chemical tests has been shown to characterise adequately the molecule). However

**PRODUCTION**
During the course of **product development**, it must be demonstrated that the manufacturing process produces a product having a **biological activity** of at least 2.5 IU/mg, using a validated bioassay **based on growth promotion** and approved by the competent authority. (Ph. Eur. *Somatropin concentrated solution* (0950))

**PRODUCTION**
During the course of **product development** it must be demonstrated that the manufacturing process produces a product having a biological activity of not less than 1 IU/mg using a suitable validated bioassay. (Ph. Eur. *Glucagon, human* (1635))
Ph. Eur. monographs: one single quality

- **Test methods:**
  - valid analytical methods
  - sufficiently detailed for the user to be able to perform the test
  - suitability criteria (performance verification)

- **Specifications:**
  - derived from approved products
  - robust test procedures, validated analytical methods based on collaborative laboratory testing
  - common reference substances
  - acceptance criteria (e.g. peptide mapping, related proteins...)

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Flexibility of monographs

• **Alternative approaches** are possible:
  - concept of "alternative methods of analysis" (Ph. Eur. General Notices)
  - approved by competent authority
  - **monograph revision to include changes (if necessary)**

• **PRODUCTION section** in some monographs (e.g. glycan analysis, bioassay)
Case study: rFIX monograph (Ph. Eur. 2522) (1)

HUMAN COAGULATION FACTOR IX (rDNA) CONCENTRATED SOLUTION

Factoris IX coagulans humani (ADNr) solutio concentrata

- Monograph elaborated under P4Bio procedure
- Covers recombinant human coagulation factor IX (nonacog alfa) drug substance:
  - single-chain glycoprotein
  - 415 amino acids
  - multiple posttranslational modifications

**DEFINITION**

Solution containing closely related glycoproteins, which have the same amino acid sequence (415 amino acids) as the naturally occurring Ala 148 allelic form analogue (plasma-derived coagulation factor IX). It is a single-chain glycoprotein with structural and functional characteristics similar to those of the endogenous factor IX. It may contain buffer salts and/or non-proteinaceous stabilizers.

Content: minimum 150 IU per milliliter.

Potency: 200 to 360 IU per milligram of protein.
Case study: rFIX monograph (Ph. Eur. 2522) (2)

PRODUCTION
- **Host-cell-derived proteins**
- **Host-cell- and vector-derived DNA**
- **Glycan analysis**

IDENTIFICATION
A. Cross-reference to **Assay** (Potency)
B. **Peptide mapping** (2.2.55)
C. Polyacrylamide gel electrophoresis (2.2.31)

TESTS
- **Gamma-carboxyglutamic acid (Gla)**. LC (2.2.29)
- **Related proteins and impurities**. LC (2.2.29)
- **Impurities with molecular masses differing from that of human coagulation factor IX (rDNA)**. SDS-PAGE (2.2.31)
- **Impurities with molecular masses greater than that of human coagulation factor IX (rDNA)**. SEC (2.2.30)

ASSAY
- **Protein**. SEC (2.2.30)
- **Potency**. Assay of human coagulation factor IX (2.7.11)
## System suitability

**reference solution:**

*human coagulation factor IX (rDNA) CRS*

- The chromatogram obtained with the **reference solution** is qualitatively similar to the chromatogram supplied with *human coagulation factor IX (rDNA) CRS*

- All peaks identified in the chromatogram supplied with *human coagulation factor IX (rDNA) CRS* are visible in the chromatogram obtained with the **reference solution**
rFIX: Peptide mapping (2)

- The profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with the reference solution.

- No new major peaks are observed in the chromatogram obtained with the test solution in comparison to the chromatogram obtained with the reference solution.

Chromatogram of peptide mapping of human coagulation factor IX (rDNA)

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Mandatory requirement: Ph. Eur. *Glycan analysis* (2.2.59), Section 2.3 “Analysis of released glycans”

**Analytical procedure:**
- **release** of glycans
- **labelling** of the released glycans
- **analysis** of the labelled glycans

Requirements for how to carry out these steps are flexible in order to allow the user to use another method based on the principles stated in the Ph. Eur. General Chapter 2.2.59.

Thus, the user is able to adapt those requirements to its own equipment and approach.

An example is given of the method using liquid chromatography for the analysis of the labelled glycans, including sample preparation.
rFIX: Glycan analysis (2)

**Identification of peak groups:**

- **identify** the 5 groups of oligosaccharides
- **retention times** of the most prominent peaks in groups P0 to P4.
- **relative retentions** of the most prominent peaks in groups P0 to P3 with reference to the most prominent peak in group P4.

**Tetrasialylated peak area ratio:**  

\[
\frac{A_{P4}}{\sum_{i=0}^{3} A_{Pi}}
\]

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rFIX: Glycan analysis (3)

System suitability:

human coagulation factor IX (rDNA) CRS (reference solution a)
– the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with human coagulation factor IX (rDNA) CRS;
– …

Results:

suitable in-house reference preparation (reference solution b)
– the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);
– …
– the tetrasialylated peak area ratio for the test solution is within the limits authorised by the competent authority.
rFIX: Glycan analysis (4)

Glycan analysis is described in the PRODUCTION section of the monograph, according to the provisions given in the General Notices, as the test cannot be performed by an independent analyst for the following reasons:

- the glycan profile depends on the manufacturing process;
- the user needs acceptance criteria in form of numerical limits, which are not prescribed in the monograph;
- the respective specifications have to be set in agreement with the competent authority.
Concluding remarks (1)

✓ Ph. Eur. monographs – provide framework requirements for the quality of biosimilars,

**BUT**: biosimilarity requires **further comparison** between quality of the reference product and of the biosimilar, and clinical/non-clinical studies.

✓ Ph. Eur. reference standards are essential tools to determine the potency, content and assess the purity of biologicals/biotech products,

**BUT**: they are not reference products.
Concluding remarks (2)

- **Role of monographs:**
  - One single quality for everybody.
  - Protection of public health via a standard which represents one known quality.
  - Links between Ph. Eur. and authorities needs to be tighten – monographs need to remain up to date and reflect current marketing situation.

- **Flexibility of monographs** under well-defined conditions:
  - Ph. Eur. *Human coagulation factor IX (rDNA) (2522)* – example of flexibility between monograph requirements, specifications, regulatory expectations and industry resources (in-house standards).
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