# Ph. Eur. monographs and biosimilars

Emmanuelle Charton, Ph. D.

European Pharmacopoeia Department

European Directorate for the Quality of Medicines & HealthCare





# Place of the Ph. Eur. within the EU regulatory framework

- Lays down common, compulsory quality standards for all medicinal products in Europe.
- Mandatory on the same date in 37 states (CoE) and the European Union
- The Ph. Eur. is legally binding.
- The European Pharmacopoeia needs to keep pace
  - with industrial constraints,
  - with technological and scientific advances,
  - with the regulatory needs of licensing, control and inspection authorities in the public health sector

.

# Dilemma faced by the European Pharmacopoeia:

- ✓ Provides legal requirements for the quality of medicinal products and their components: test procedures and acceptance criteria: SPECIFICATIONS
- ✓ Keeps pace with current thinkings and concepts, allows for the use of modern technologies -> FLEXIBILITY is needed!





# Monographs and licensing process

- ➢ Monographs are **public standards**
- ➢ However, a licencing authority **may accept a product in spite of this**, provided that the quality, safety and efficacy of the product have been demonstrated. In such cases, the authority must request a revision of the monograph as per EU 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." EU Directive 2001/83/EC

# Structure of the Ph. Eur.

**General notices** (essential; applicable to all texts)

| General chapters | Individual monographs | General monographs |
|---|---|---|
| ➢ analytical methods<br>➢ editorial convenience<br>➢ mandatory <u>when referred to</u> in a monograph | ➢ based on approved specification(s) backed up by batch data<br>➢ validated analytical procedures and acceptance criteria:<br>**SPECIFICATIONS** | ➢ classes of substances or products, dosage forms;<br>➢ mandatory for all the products within the scope of definition section |





# Public standards for biotherapeutics

➡**The setting process is a complex and challenging exercise**

**Public standard**

One part of a total control strategy designed to ensure product quality and consistency

It is not its aim to go beyond to characterisation that includes determination of physicochemical and immunochemical properties, biological activity, purity and impurities, an extensive program conducted by a combination of orthogonal methodologies

A set of relevant quality attributes, in order to confirm the quality of the active substance/medicinal product in question

# Specifications

**How to define the information needed for a public standard for biotherapeutic products?**

"Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product." ICH Q6B *Specifications: test procedures and acceptance criteria for biotechnological/biological products*

"The tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to fully characterise it." ICH Q5E *Comparability of biotechnological/biological products subject to changes in their manufacturing process*

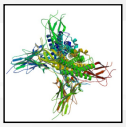




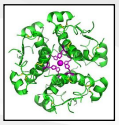
# Monograph elaboration: procedure P1

- Ph. Eur. monographs are based on specifications approved by licensing authorities
- Monographs in a **multi-manufacturer situation**: comparison of different products and test procedures provides a forum for consensus and leads to the elaboration of robust quality standards - all manufacturers invited to participate (whether biosimilar or innovator)

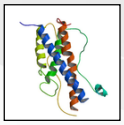

*Filgrastim concentrated solution* (2206)



*Insulin, human* (0838)



*Somatropin* (0952, 0952, 0838)

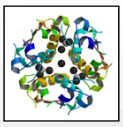


.....

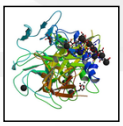
# Monograph elaboration: procedure P4

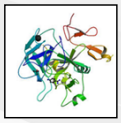
- Ph. Eur. monographs are based on specifications approved by licensing authorities
- **P4 Procedure**: applied to substances still under patent protection; based on collaboration with the Innovator, before patent expiry

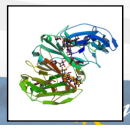
when new products (biosimilars) are approved → Monograph revision



*Insulin glargine* (2571)


*Teriparatide* (2829)


*Human coagulation factor VIIa (rDNA)* (2534)


*Human coagulation factor IX (rDNA)* (2534)


*Etanercept* (2895)





# Flexibility in the Ph. Eur. – Alternative methods

- Ph. Eur. tests are **reference methods**, essential in cases of dispute.
- Compliance is required, but **alternative methods** may be used as long as they lead to the same pass/fail result.
- It is the responsibility of the user to demonstrate their suitability. Approval of the competent authority is necessary in many cases.

# Flexibility in the Ph.Eur. – Waiving of tests

- **Compliance** to the Ph. Eur. is a **prerequisite**
- Testing might be omitted based on
  - product design
  - control strategy
  - process validation

*As a consequence: Tests for process-specific impurities may be omitted if it is demonstrated that they will not occur with the particular process used.*




# Challenge for setting monograph specifications

To find the **appropriate equilibrium** between:

- flexibility of expectations, so that they apply to a large variety of products
- detailed (prescriptive) requirements so that the respective analytical procedures can be performed successfully in a control laboratory

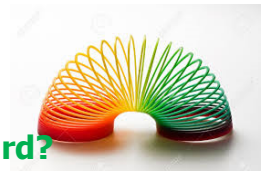
**Too much flexibility leads to a meaningless standard**


**Ph. Eur. General monograph** *Monoclonal antibodies for human use* (2031)

*'**Purity**. Tests for process- and product-related impurities are carried out by suitable validated methods.'*

*'**ASSAY**. Carry out a suitable biological assay compared to the reference preparation.'*

# Monograph flexibility



**How to transfer flexibility into a public standard?**

**Ph. Eur. biotherapeutic product monographs** are:

→ adapted to **biomolecule complexity**, **potential diversity** in **biosimilar compounds**, and different **manufacturing processes;**

→ **flexible**, while being comprehensive and **sufficiently prescriptive.**

use of the **PRODUCTION section** of the monograph

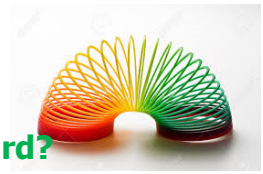




# Production section

**Ph. Eur. General Notices**: "*Statements under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute* ***mandatory requirements for manufacturers****, unless otherwise stated. These statements cannot necessarily be verified on a sample of the final article by an independent analyst. The* ***competent authority*** *may establish that the instructions have been followed, for example, by examination of data received from the manufacturer, by inspection of manufacture or by testing appropriate samples.*"

# Monograph flexibility



**How to transfer flexibility into a public standard?**

**PRODUCTION section** of the monograph adapted to**:**

- ✓ reflect **process-dependent heterogeneity** (*e.g.* glycosylation);
- ✓ include requirements for **consistency of production.**
- ✓ **Generic method of analysis** (Ph. Eur. *Glycan analysis of glycoproteins* (*2.2.59*); specific **analytical procedure** given as **example**
- ✓ **Acceptance criteria** to be set in **agreement with the competent authority**

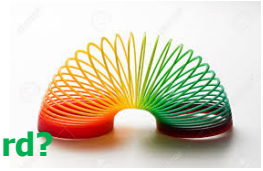
**Glycan analysis approach:**

✓ Means of improving **monograph flexibility** under **well-defined conditions**

✓ **Compatible** with development of **biosimilars**

✓ **Addresses complexity**

# Monograph flexibility



**How to transfer flexibility into a public standard?**

**Remove acceptance criteria**

# Limit(s): 'as authorised by the competent authority'

| Quality attribute | Flexibility? |
|---|---|
| Potency (specific activity) | × |
| Protein concentration | ✓ |
| Host-cell-derived proteins | ✓ |
| Host-cell-derived DNA | ✓ |
| Primary structure (Peptide mapping) | × |
| Glycan profile | ✓ |
| Isoforms/charge variants | ✓ |
| Product-related impurities (*e.g.* HMW, LMW by SEC) | × |
| Related proteins | × |

.....





# Monograph specifications (SWOT)

- Provides information on quality requirements for approved products, ICHQ2(R1) validated methods including tools for verification of method performance and, thus, leading to robust standards;
- Standards for assays provide assurance of continuity of content and therefore patient safety;
- Only publicly-available source of information.

# Monograph specifications (SWOT)

- The methods described in monographs may not detect new impurities/adulterants (*e.g.* heparins);
- Analytical methods based on older files might be outdated.

**S** STRENGTHS | **W** WEAKNESSES | **O** OPPORTUNITIES | **T** THREATS



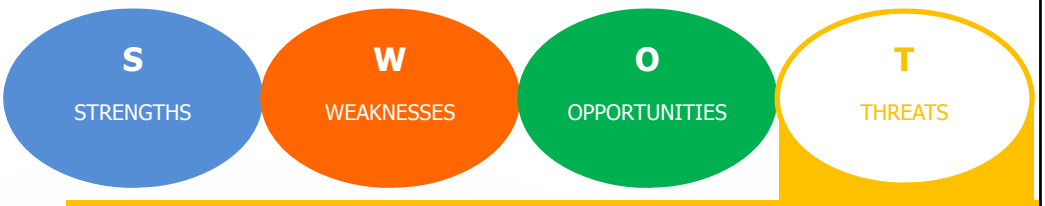


# Monograph specifications (SWOT)

**S** STRENGTHS | **W** WEAKNESSES | **O** OPPORTUNITIES | **T** THREATS

- The methods described in monographs do provide standardised methodologies that have undergone extensive laboratory verification – guarantee of robustness and transferability;
- Examples of analytical procedures to be followed
- Availability of a method including a reference standard for the "independent analyst";
- Method + reference standard: allow for the comparison of products and may detect differences in quality;
- The availability of a monograph may support the development of biosimilars.

# Monograph specifications (SWOT)



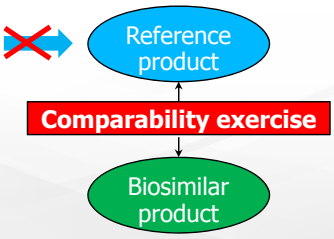

- Monograph methods may be perceived as the sole methods and prevent innovation;
- May provide false perception that meeting the requirements of the acceptance criteria means demonstration of biosimilarity;
  - ➢ A comparison of the biosimilar to a publicly available standard, *e.g.* a pharmacopoeial monograph, is not sufficient for the purposes of comparability (EMA/CHMP/BWP/247713/2012)
- Potential use of reference standards for head to head comparison in the comparability exercise – not appropriate.





# Ph. Eur. Reference Standards

➢ Ph. Eur. reference standards are intended to be used within the scope of Ph. Eur. monographs (Ph. Eur. General Chapter on *Reference standards* (5.12))


➢ Ph. Eur. reference standards are not intended to be used as reference (comparator) products in the context of applications for biosimilars!

# Ph. Eur. Reference Standards

- The **only requirement** is that they be suitable for the intended purpose.
- The monograph intent is not to lockout the quality of a product but to ensure that there is a public standard to assess that the quality corresponds to the quality that has been approved
  → consequence: any material approved in Europe is in principle OK as candidate for RS establishment





# Biosimilars and Ph. Eur.

- ✓ **European Pharmacopoeia monograph**: a public standard providing harmonised **quality requirements for medicinal products** throughout Europe: used by all.
- ✓ Monographs **are established, whether or not the products** are to be submitted/approved as **generics/biosimilars**.

## Biosimilars and Ph. Eur. (cont'd)

- ✓ **Biosimilars**: a class of products that was established to avoid unnecessary pre-clinical and clinical studies. The regulatory pathway to be followed is given in appropriate **guidelines.**
- ✓ **Biosimilars** are developed by companies and evaluated by licensing **authorities, while** 18 of the 21 biosimilar products approved in Europe are covered by a monograph: ➡ there is nothing to suggest that the monographs delayed authorisation of these biosimilar products.





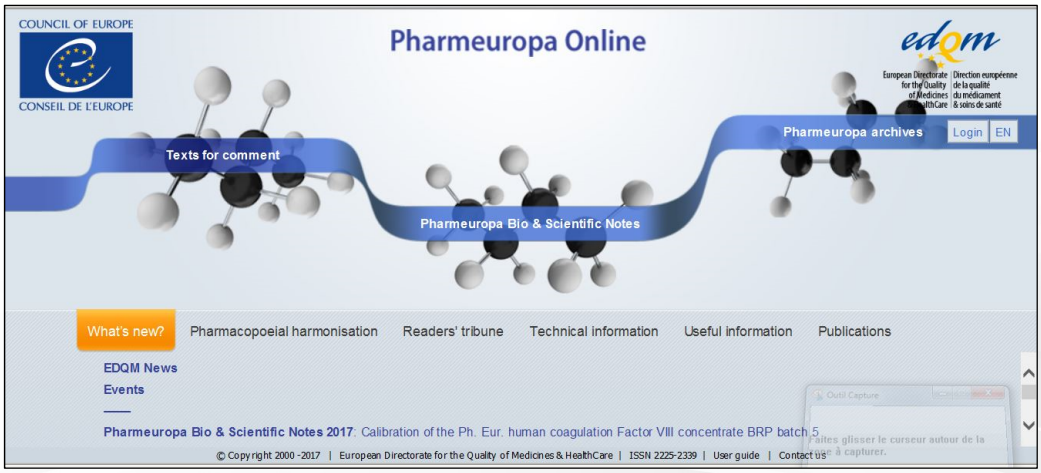
## Impact of monographs on already approved products

If a monograph is revised/published, what is the impact on the already approved product(s)?

- ❑ Compliance with the Ph. Eur. monograph is mandatory, manufacturers have to meet the requirements of the (revised) pharmacopoeial text at the date of its implementation (6 months after publication of the new/revised text);


- ❑ This is why monographs are published for consultation

# Stakeholders contribution: Pharmeuropa consultation

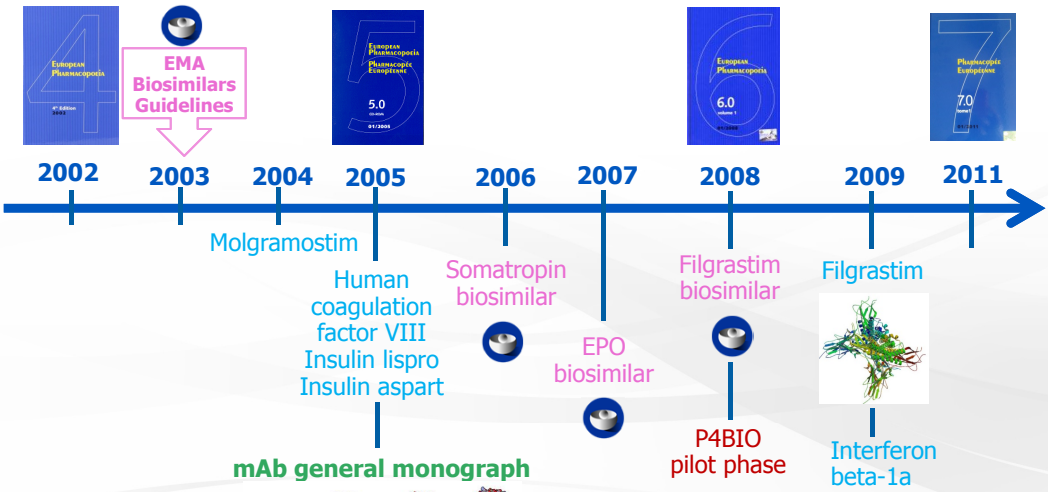







# European Pharmacopoeia and Biologicals

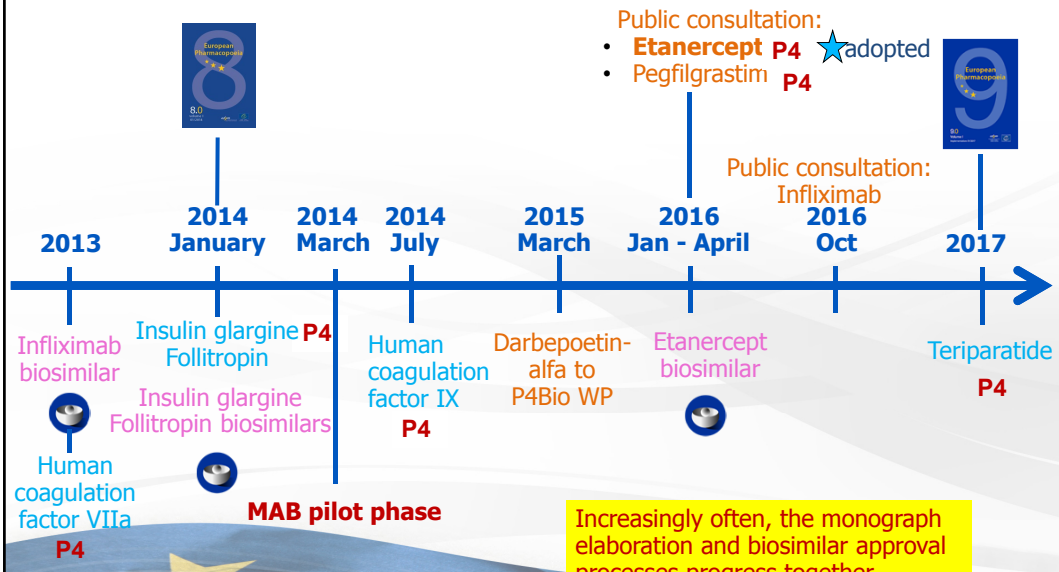
## rDNA products in the Ph. Eur. (2002-2011)




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

# European Pharmacopoeia and Biologicals

**rDNA products in the Ph. Eur. (2013-2017)**








# Biosimilars and Ph. Eur. (cont'd)

- Ph. Eur. is referred to in EU directives and guidelines:
  - Directive 2001/83/EC
  - Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)
  - Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (EMA/CHMP/BWP/247713/2012)
- However, biosimilars are not referred to in Ph. Eur.
  - The quality of a biotherapeutic product can be defined regardless of the regulatory pathway used for its authorisation

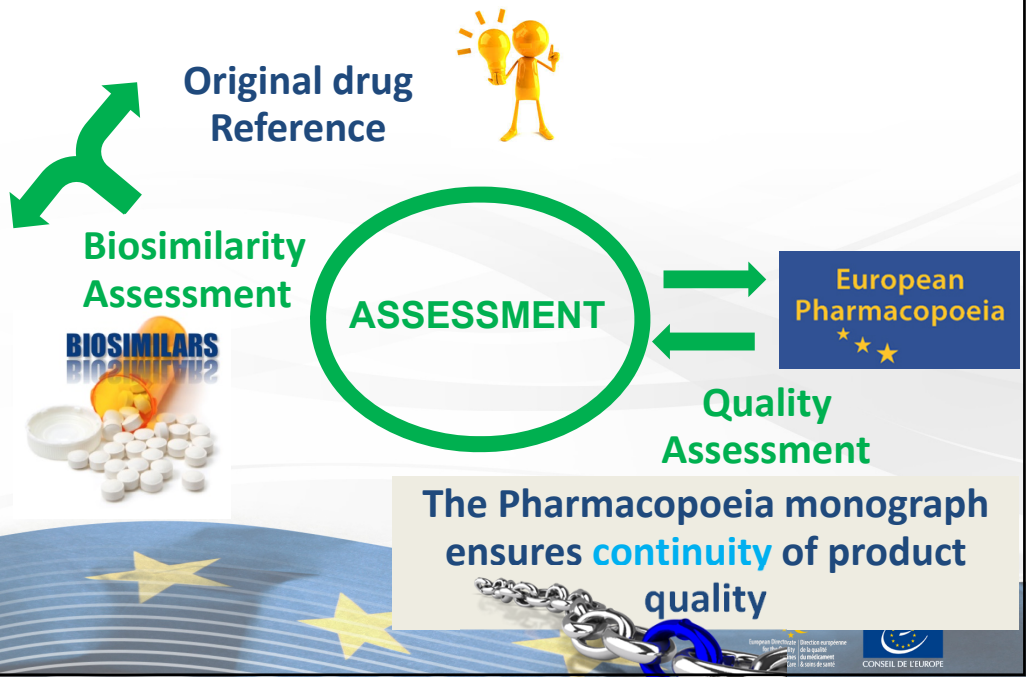
# Conclusions

- Individual monographs play a major role in ensuring a standardised level of quality for medicinal products, thus contributing to patient safety.
- Elaboration of monographs for biotherapeutic products present a number of challenges due to their complexity.
- The latter challenge has proven to be more difficult to overcome since the advent of biosimilars, probably due to misunderstandings about the role of Ph. Eur. monographs in European legislation on biotherapeutic products.





# Biosimilars and Ph. Eur.



# Further reading…

- M. Buda, S. Wicks, E. Charton. Elaborating European Pharmacopoeia monographs for biotherapeutic proteins using substances from a single source Pharmeuropa Sci. Notes, November 2016, 129-134
  https://www.edqm.eu/sites/default/files/article_elaborating_pheur_monographs_biotherapeutics_proteins_2016.pdf
- E. Charton. The role of European Pharmacopoeia monographs in setting quality standards for biotherapeutic products. Special report. GaBi Journal, Vol. 5, issue 4, 2016, 174-179 http://gabi-journal.net/the-role-of-european-pharmacopoeia-monographs-in-setting-quality-standards-for-biotherapeutic-products.html?utm_source=GOCC6+V16L16&utm_campaign=5d8c252b89-GJ+2016-4+anmt+V16L16-1&utm_medium=email&utm_term=0_88b14c86c6-5d8c252b89-136225325





# *Thank you for your attention!*