THE EUROPEAN DIRECTORATE FOR THE QUALITY OF MEDICINES & HEALTHCARE (EDQM)

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COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Ph. Eur. Monographs on Biotherapeutics

European Pharmacopoeia Training Session on Biologicals
4-5 February 2020

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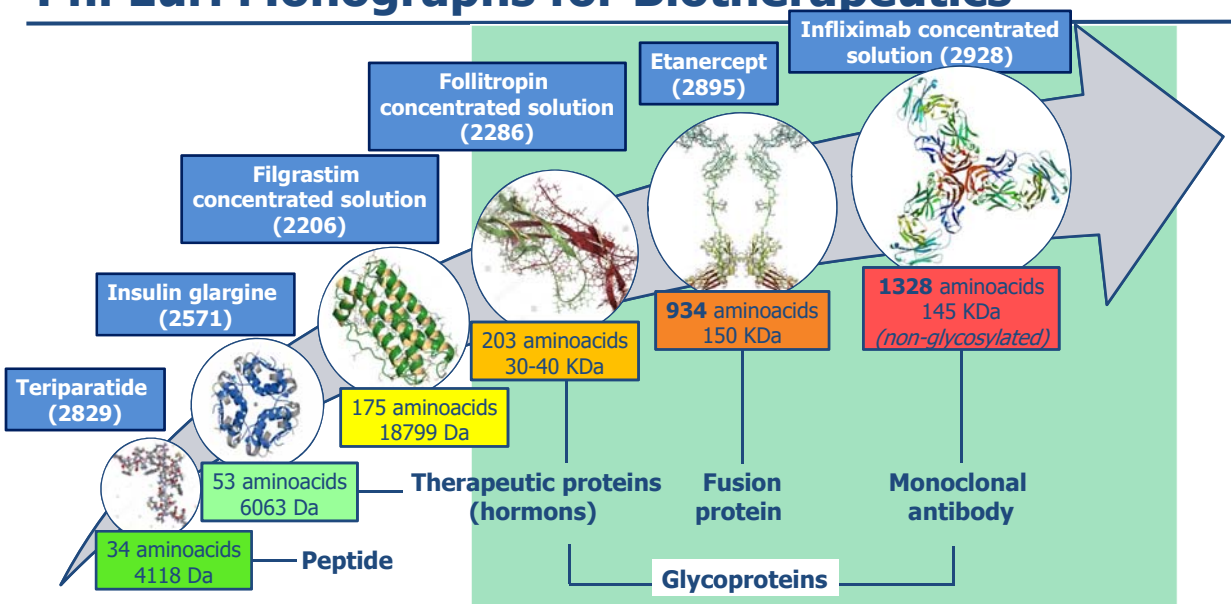
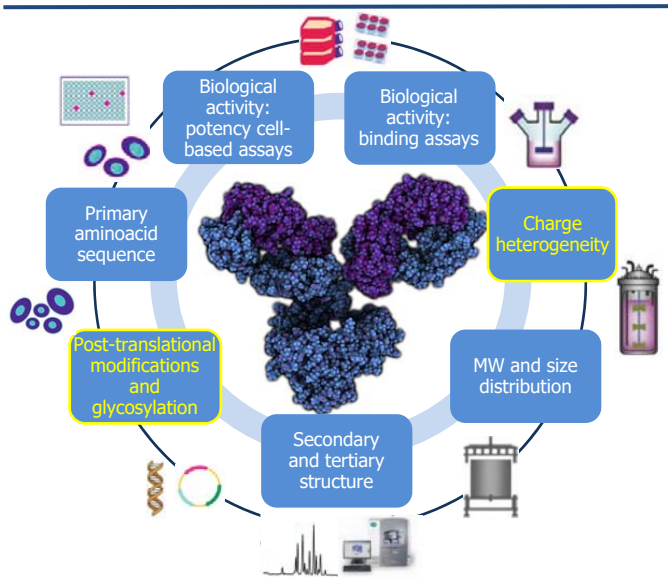
Presentation Outline

- **Introduction**: **Ph. Eur. and flexibility**: the case of biotherapeutic product monographs (**etanercept and infliximab case studies**)
- **Monograph elaboration/revision process:**
  - participation and role of stakeholders
- **Monograph implementation** – impact on already approved products:
  - **Infliximab case study**
- **Ph. Eur. and biosimilars**

Ph. Eur. Monographs for Biotherapeutics



Complexity of Biotherapeutics



Challenge for setting monograph specifications

Specific Monographs 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

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

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

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

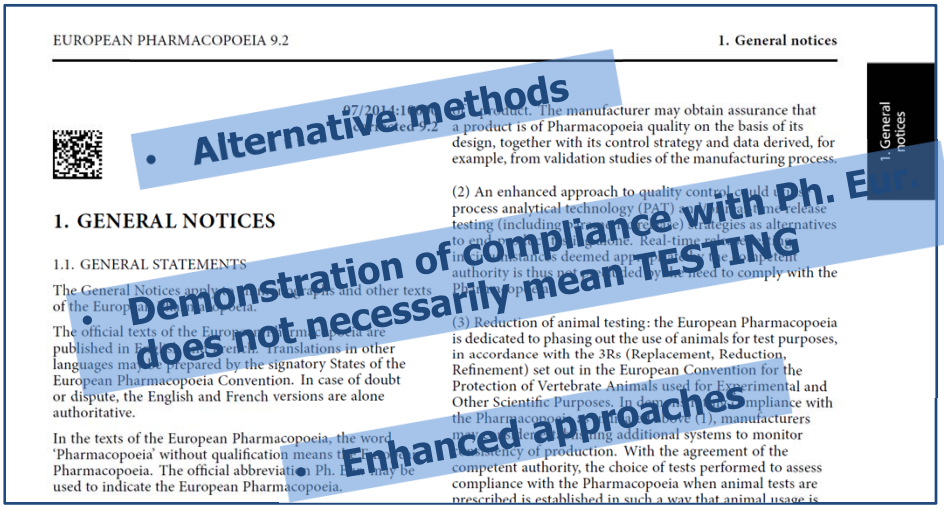
Too much flexibility leads to a meaningless standard

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.'*

Flexibility from the General Notices



EUROPEAN PHARMACOPOEIA 9.2 — 1. General notices

1. GENERAL NOTICES

1.1. GENERAL STATEMENTS

The General Notices apply to all monographs and other texts of the European Pharmacopoeia.

The official texts of the European Pharmacopoeia are published in English and French. Translations in other languages may be prepared by the signatory States of the European Pharmacopoeia Convention. In case of doubt or dispute, the English and French versions are alone authoritative.

In the texts of the European Pharmacopoeia, the word 'Pharmacopoeia' without qualification means the European Pharmacopoeia. The official abbreviation Ph. Eur. may be used to indicate the European Pharmacopoeia.

a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and data derived, for example, from validation studies of the manufacturing process.

(2) An enhanced approach to quality control could use process analytical technology (PAT) and real-time release testing (including parametric release) strategies as alternatives to end-product testing. Real-time release testing is deemed appropriate when the competent authority is thus persuaded that the need to comply with the Pharmacopoeia is fulfilled.

(3) Reduction of animal testing: the European Pharmacopoeia is dedicated to phasing out the use of animals for test purposes, in accordance with the 3Rs (Replacement, Reduction, Refinement) set out in the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. In demonstrating compliance with the Pharmacopoeia, manufacturers may develop additional systems to monitor consistency of production. With the agreement of the competent authority, the choice of tests performed to assess compliance with the Pharmacopoeia when animal tests are prescribed is established in such a way that animal usage is

1. General notices

- Alternative methods
- Demonstration of compliance with Ph. Eur. does not necessarily mean TESTING
- Enhanced approaches

Flexibility in Ph. Eur. – Monograph Section on Production

"***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. They may relate, for example, to source materials; to the manufacturing process itself and its validation and control; to in-process testing; or to testing that is to be carried out by the manufacturer on the final article, either on selected batches or on each batch prior to release. 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."* (**Ph. Eur. General Notices**)

Ph. Eur. Monographs for Biotherapeutics

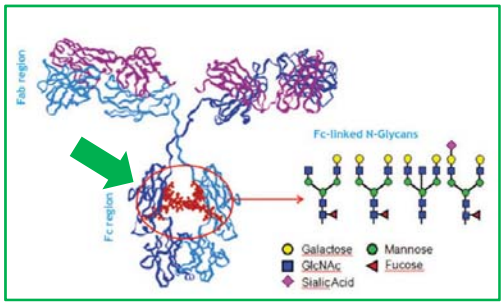
Monograph specifications

- Flexibility of expectations, so that they apply to a large variety of products:
  - **Ph. Eur. General Notices** (alternative methods; waiving of tests; enhanced approaches);
  - **"Additional" flexibility**
- Prescriptive requirements so that the respective test procedures can be applied successfully in a control laboratory/allow independent testing:
  - **method performance (system suitability) criteria**; qualification of analytical methods using Ph. Eur. standards;
  - acceptance criteria; standardisation of potency/functionality.

Ph. Eur. Monographs for Biotherapeutics: Flexibility (1)

Production section

- **general requirements** for consistency of production;
- **specific requirements** related to process-dependent heterogeneity (*e.g.* glycosylation, charged variants profile) **set in a flexible way**:



- generic methods of analysis: **suitable method** developed according to general chapter *Glycan analysis of glycoproteins (2.2.59)*;
- specific analytical procedure as **example**, including:
  - **detailed instructions**;
  - **method performance** (system suitability) **criteria**;
  - use of a **Ph. Eur. Chemical Reference Substance (CRS)** to verify **method performance.**

Ph. Eur. Monographs for Biotherapeutics: Flexibility (2)

Test procedures: "Suitable" / "Example"

SUITABLE PROCEDURE

- **general indications** on the test procedure (main steps to be carried out, type of method, readout, cells, reagents…)
- the term "suitable" is a **conventional term:** '*In certain monographs […], the terms 'suitable' and 'appropriate' are used to describe a reagent, micro-organism, test method etc.; if criteria for suitability are not described in the monograph, suitability is demonstrated to the satisfaction of the competent authority.' (General Notices)*

EXAMPLE PROCEDURE

- **specific instructions**, quantities, concentrations, compositions of reagents/buffers, chromatographic conditions etc. together with **system suitability criteria**; method may be used as such but any other suitable validated procedure may be used without demonstrating its equivalence to the 'example' method (subject to approval by the competent authority);
- ***"The following procedure is given as an example."***

Ph. Eur. Monographs for Biotherapeutics: Flexibility (3)

Reference preparations

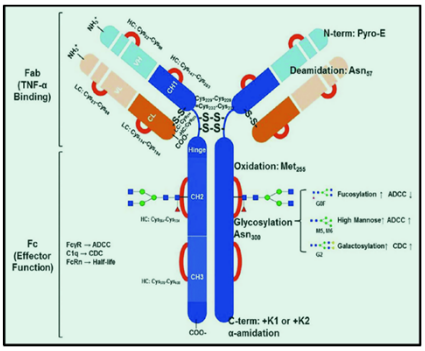
- Ph. Eur. reference standards to evaluate **method performance** (Chemical Reference Substance (CRS) for system suitability)
- *In-house reference preparation* (shown to be representative of batches tested clinically and batches used to demonstrate consistency of production) – for **comparative purpose** (*e.g.* matching LC profiles)

Ph. Eur. Monographs for Biotherapeutics: Flexibility (4)

Acceptance criteria:

- **numerical limits/ranges**
- **'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/charged variants	✓
Product-related impurities (e.g. HMW, LMW by SEC)	×
Related proteins	×

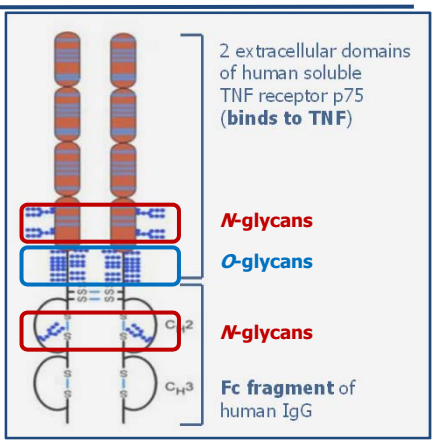


MONOGRAPH FLEXIBILITY

Case Study 1: Etanercept Monograph – Production (1/3)

Production section

General requirements for **consistency of production**	Specific requirements related to **process-dependent heterogeneity**
Etanercept is produced in a suitable mammalian cell expression system by a method based on recombinant DNA (rDNA) technology. During the course of product development, it must be demonstrated that the manufacturing process consistently produces a product with the expected *O*-glycan occupancy using a suitably qualified assay.	**Generic method** ***N*-Glycan analysis.** Use a suitable method developed according to general chapter *2.2.59. Glycan analysis of glycoproteins*, section 2-3: – release the glycans using one of the agents described in Table *2.2.59.*-1, for example peptide *N*-glycosidase F (PNGase F); – label the released glycans with one of the fluorescent labelling agents described in Table *2.2.59.*-2, for example 2-aminobenzamide; – analyse the labelled glycans by liquid chromatography (*2.2.29*) using fluorescence detection. **Specific procedure as example** *The following procedure is given as an example.*



$C_{2224}H_{3472}N_{618}O_{701}S_{36}$ (monomer)
M_r approx. 51 200 Da
(monomer without glycosylation)

Case Study 1: Etanercept Monograph – Production (2/3)

_N_-glycan analysis: specific procedure as example

- Detailed **description**:
  - **sample preparation**,
  - PNGase **digestion**;
  - **labelling** of released glycans and cleanup;
  - **LC analysis** (fluorescence detection): chromatographic system, mobile phase, gradient, separation conditions.
- ***Identification of peaks***: use the chromatogram shown in Figure 2895.-1 to identify the 2 groups of oligosaccharides corresponding to:
  - **neutral** (peaks 1 to 5) _N_-glycans;
  - **sialylated** (peaks 6 to 9) _N_-glycans.

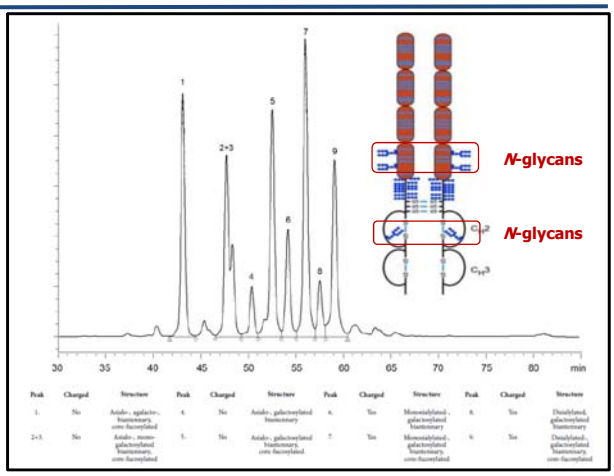


Figure 2895.-1. – Chromatogram for _N_-glycan analysis of etanercept (Ph. Eur. monograph for *Etanercept (2895)*)

Case Study 1: Etanercept Monograph – Production (3/3)

_N_-glycan analysis: reference preparations

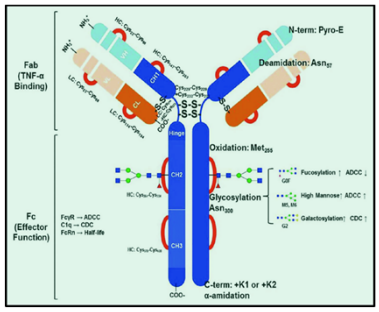
System suitability:
- the chromatogram obtained with reference solution (a) is qualitatively similar to the chromatogram supplied with *etanercept CRS* and peaks 1 to 9 are clearly visible;
- no significant peaks are observed in the chromatogram obtained with the blank solution.

Results:
- the profile of the chromatogram obtained with the test solution corresponds to that of the chromatogram obtained with reference solution (b);
- the retention times of the peaks in the chromatogram obtained with the test solution correspond to those in the chromatogram obtained with reference solution (b);
- no additional peaks are observed in the chromatogram obtained with the test solution in comparison with the chromatogram obtained with reference solution (b).

Reference solution (a): etanercept CRS

Reference solution (b): a suitable etanercept in-house reference preparation […]

Case Study 2: Infliximab Monograph – Acceptance Criteria

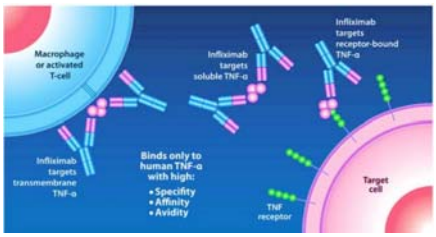


$C_{6462}H_{9960}N_{1728}O_{2036}S_{44}$
M_r approx. 145 kDa (without glycosylation)

Quality attribute	Monograph specifications	
	Test procedure	Acceptance criteria
Protein content	see Assay (protein)	✓
Potency (specific activity)	see Assay (protein and potency)	×
Host-cell-derived proteins	Ph. Eur. 0784; 2.6.34	✓
Host-cell- and vector-derived DNA	Ph. Eur. 0784; *2.6.35*	✓
Residual protein A	Ph. Eur. 2.7.1	✓
Glycan analysis	Ph. Eur. 2.2.59; Example method	✓
Charged variants (acidic and basic variants)	**A. IEF** (Ph. Eur. 2.2.54); Example method *Alternative method: capillary IEF*	✓
	B. CEX-HPLC	✓
Peptide mapping (primary structure)	Trypsin digestion	×
pH	Ph. Eur. 2.2.3	✓
Related proteins (fragmentation)	CE-SDS reducing and non-reducing	×
HMW and LMW species	SEC	×
Protein	UV determination	-
Potency (Fab-related) biological activity	TNF-α cell-based neutralisation assay Example method	- ×

Case Study 3: Infliximab Monograph – Potency (1/3)

Target Antigen	MOA
TNF-α	prevents TNF-α receptor activation by binding to TNF-α, thereby neutralising the biological activity of TNF-α



Biological activity evaluated in **cell-based potency assays** using different approaches for **TNF-α neutralisation**

DEFINITION

- Content;
- Potency (specific activity)

IDENTIFICATION

A. Complies with limits of **Assay (potency)**
B. Peptide mapping: compare with RS

PRODUCTION

During the course of product development, it must be demonstrated that the manufacturing process consistently produces a product with the **expected *N*-glycan occupancy and Fc-effector functions** ((ADCC), (CDC)) using suitably qualified assay(s).

ASSAY:

- **Protein**: UV determination
- **Potency**: suitable cell-based assay based on the inhibitory action of infliximab on the biological activity of TNF-α and a suitable readout for assessing this inhibitory effect.
  - **reference standard**: Infliximab BRP
  - example procedure: WEHI-164 cytotoxicity assay; WST-8 colorimetric readout.

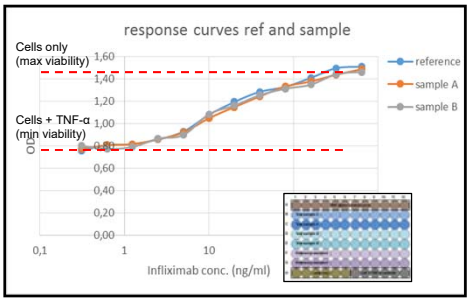
Case Study 3: Infliximab Monograph – Potency (2/3)

ASSAY. Potency:

- **Example procedure**: WEHI-164 cytotoxicity assay – **detailed instructions** for:
  - sample preparation; TNF-α solution
  - plate preparation
  - cell preparation
  - plating test solution, reference solution, controls and cells
  - addition of tetrazolium salt
  - colorimetric measurement (450 and 650 nm)
  - statistical analysis: 4-parameter logistic fit (Ph. Eur. chapter 5.3)

System suitability

- 'TNF-α control curve': shape; r^2
- **standard curve (infliximab BRP)**: shape; upper and lower plateaus corresponding to 'cell only control' and 'cell + TNF-α control' respectively; r^2
- maximum value (cell only) to minimum value (TNF-α control) ratio



WEHI-164 cytotoxicity assay: dose response curve of infliximab

Acceptance criteria

- **estimated potency** relative to the reference solution
- **confidence limits (P = 0.95)**

Case Study 3: Infliximab Monograph – Potency (3/3)

Ph. Eur. BRP for Infliximab batch 1

Assigned potency **500 IU/ampoule**

1st **WHO International Standard** for Infliximab

Biological Standardisation Programme

Funded by the European Union and the Council of Europe — EUROPEAN UNION

COUNCIL OF EUROPE — CONSEIL DE L'EUROPE

Implemented by the Council of Europe

World Health Organization

⇨ **Ph. Eur. Biological Reference Preparations (BRPs):** A substance or mixture of substances intended for use as stated in a monograph or general chapter of the European Pharmacopoeia. BRPs are either secondary standards calibrated in International Units or primary standards, which may be used to define a European Pharmacopoeia Unit (Ph. Eur. U.). Other assigned contents may also be used, for example, virus titre or number of bacteria. [Ph. Eur. General chapter on *Reference standards (5.12)*]

Monograph Flexibility: SUMMARY

Production section (Ph. Eur. General Notices)

- Requirements related to process-dependent heterogeneity (*e.g.* glycan profile, charged variants)

Test procedures

- Generic methods of analysis (*e.g.* developed according to general chapters) – **suitable** methods
- Specific analytical procedures – '**example**' method

Acceptance criteria for quality attributes

- Numeric limits/ ranges (specific activity; primary structure; related proteins; HMW species)
- 'As authorised by the competent authority' (process-dependent quality attributes)

Reference preparations

- Ph. Eur. reference standards to evaluate method performance (system suitability)
- *In-house reference preparation* – for comparative purpose (*e.g.* matching LC profiles)

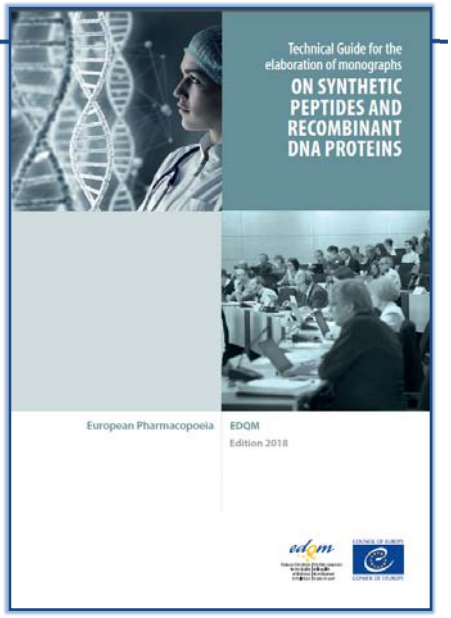
Monograph flexibility

Individual monographs can address complexity of biotherapeutics

Technical guide for the elaboration of monographs on recombinant DNA proteins and synthetic peptides (Edition June 2018):

- general update to take into account recent experiences on elaboration of monographs for complex proteins;
- new section '**Flexibility**'.

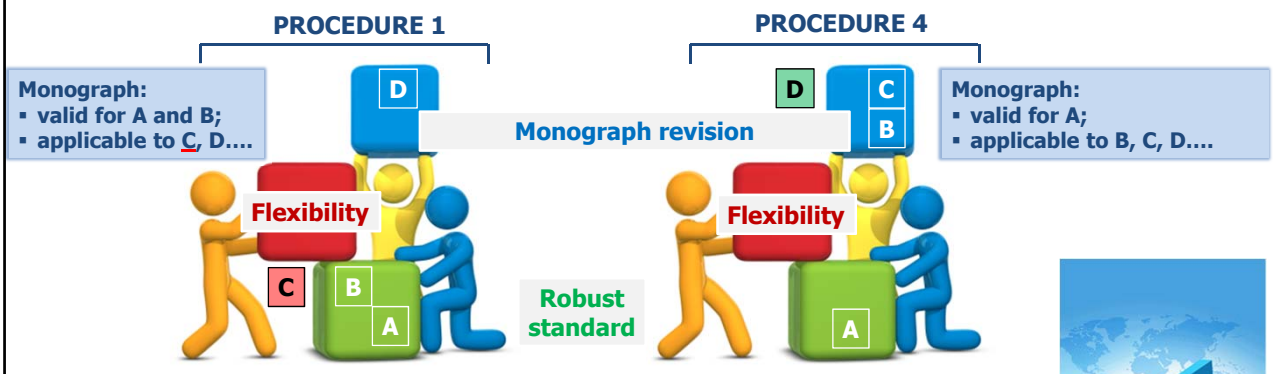
https://www.edqm.eu/en/biotherapeutics



Presentation Outline

- **Introduction**: **Ph. Eur. and flexibility**: the case of biotherapeutic product monographs (**etanercept and infliximab case studies**)
- **Monograph elaboration/revision process:**
  - participation and role of stakeholders
- **Monograph implementation** – impact on already approved products:
  - **Infliximab case study**
- **Ph. Eur. and biosimilars**

Ph. Eur. Monograph Elaboration/Revision: the Process



⇨ comparison of different products and test procedures provides a forum for consensus and leads to the elaboration of robust quality standards

⇨ suitable public standards are in place for biotherapeutics as they come off-patent, as well as to strengthen the quality of upcoming products

Ph. Eur. Monograph Elaboration/Revision: the Process

Monographs are based on quality described for **registered products**

Call for interest

Participation of interested parties

Responding to Pharmeuropa enquiry is a must

OMCLs, assessors, companies

1. Request for monograph elaboration/ revision
2. Endorsement by the Ph. Eur. Commission
3. Assignment to a Group of Experts
4. Creation/ revision of the text by the Group
5. Public enquiry in Pharmeuropa
6. Text adopted by the Ph. Eur. Commission
7. Publication in the Ph. Eur.

survey among NPAs

- **Data package** (current specifications, analytical procedures; validation data; batch and stability data)
- **Material** for testing
- *Candidate material for RS establishment*

- **Review of data package**
- **Draft monograph development**
- **Laboratory study/ collaborative testing – all preparations** (protocol preparation; method verification; data analysis)

- **Draft published for comments** (testing of draft monograph) – 3 months commenting period
- **Evaluation of stakeholder feedback** (technical comments, data)

Once a monograph is published and implemented, MAH's of registered products have to assure their product meets the requirements of the monograph

Example Infliximab: Design of the Study

⇨ Verify robustness, transferability and suitability of analytical procedures applied to infliximab for use as pharmacopoeial methods.

⇨ Decide on the choice of test procedures and way(s) to express acceptance criteria in the monograph.

Collaborative study: experimental verification of **physico-chemical** and **bioassay** tests used for infliximab

METHODS

Based on the **data package** submitted by **infliximab MAH** (specifications, SOPs, validation data)

MATERIAL

Innovator and biosimilar infliximab tested:

- **Six batches** (from drug substance and medicinal product approved in EU)
- **In-house RS**

PARTICIPATING LABORATORIES

- **Official Medicines Control Laboratories** (4)
- EDQM Laboratory

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Impact of Monographs on Already Approved Products

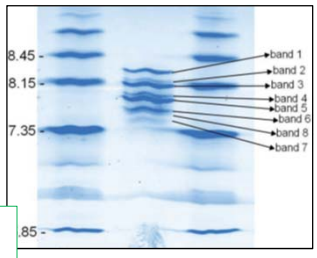
If a monograph is revised/published, what is the **impact** on the **already approved product(s)**?

- 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 company).
  → Company evaluates and secures compliance with the monograph within 6 months.
- This is why it is important that key stakeholders get involved in the monograph elaboration (revision) process as early as possible.
- This is why monographs are published for consultation.

Scenario 1: Charged Variants

Ph. Eur. Monograph

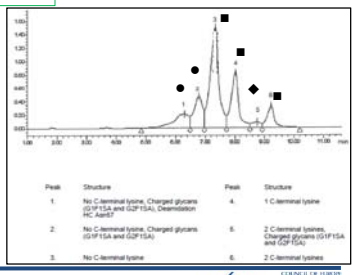
A. Isoelectric focusing – gel electrophoresis (Ph. Eur. 2.2.54)



- **test procedure**: example method
  - system suitability: pI markers; infliximab CRS
- **acceptance criteria (isoforms)**:
  - comparison with in-house RS profile

Alternatively, use a **suitable** capillary isoelectric focusing **method** developed according to general chapter 2.2.47. *Capillary electrophoresis*.

B. CEX-HPLC (Ph. Eur. 2.2.29)

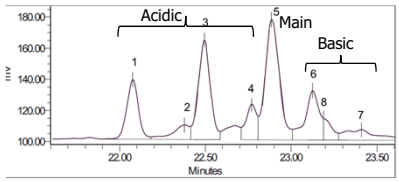


- **test procedure**: prescriptive requirements
  - system suitability: infliximab CRS
- **acceptance criteria (isoforms ●■◆)**:
  - in-house reference preparation
  - limits: 'as authorised by the competent authority'

Scenario 1: Charged Variants (cont'd)

"Company A" (registered product)

Capillary isoelectric focusing (cIEF)



- Specification limits for:
  main peak, **acidic** peaks and **basic** peaks

QUESTION: *Is my product compliant with the European Pharmacopoeia?*

RESPONSE: Ph. Eur. General Notices:

- **demonstration of compliance** with the Ph. Eur.
- **alternative methods** (*e.g.* demonstrate equivalence of alternative method to method B)

Scenario 2: Potency/Specific Activity

Ph. Eur. Monograph

Potency – TNF-alpha neutralisation

- suitable cell-based assay and a suitable readout for assessing the inhibitory effect of infliximab on the biological activity of TNF-alpha; infliximab BRP (assigned potency in IU)
- example method: WEHI-164 cytotoxicity assay; WST-8 colorimetric readout
  - **method performance**/system suitability: infliximab BRP
  - **estimated potency**: 80-120% relative to infliximab BRP (numeric range)

Specific activity*

- 8×10^3 to 12×10^3 IU per milligram of protein

** As indicated under section "Definition"*

Scenario 2: Potency/Specific Activity (cont'd)

"Company B" (registered product)

Potency – TNF-alpha neutralisation

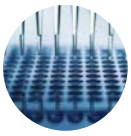
- **U937 apoptosis assay**;
  - **in-house RS**
  - estimated potency: x-y% (relative to in-house RS)

QUESTION: *Is my product compliant with the European Pharmacopoeia?*

RESPONSE:

☑ **Potency assay**: **choice of assay** model

☒ In-house RS (working standard) to be established by **comparison with infliximab BRP** to which it is traceable. (Ph. Eur. *Reference standards (5.12)*)



Protein content (mg/mL) (UV 280 nm)

Potency (IU/mL)

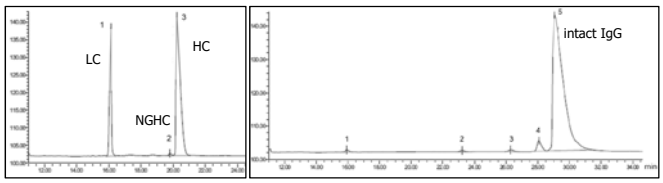
▪ **Specific activity (IU/mg)*:** fulfills pharmacopeia requirements

Scenario 3: Related Proteins by CE-SDS

Ph. Eur. Monograph

Capillary electrophoresis (2.2.47) under both reducing and non-reducing conditions

- **test procedure**: prescriptive requirements
  - system suitability: infliximab CRS
- **limits**:
  - reducing conditions: ∑peaks other than HC and LC: ≤ 2%
  - non-reducing conditions: ∑peaks other than IgG peak: ≤ 8%



LC: light chain; HC: heavy chain;
NGHC: non-glycosylated heavy chain

"Company C" (registered product)

Different CE-SDS method

QUESTION: *Is my product compliant with the European Pharmacopoeia?*

RESPONSE: Ph. Eur. General Notices:

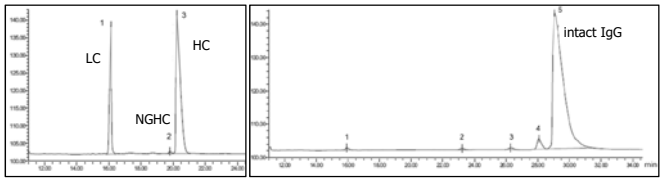
- **demonstration of compliance** with the Ph. Eur.
- **alternative methods** (equivalence testing)

Scenario 3: Related Proteins by CE-SDS (cont'd)

Ph. Eur. Monograph

Capillary electrophoresis (2.2.47) under both reducing and non-reducing conditions

- **test procedure**: prescriptive requirements
  - system suitability: infliximab CRS
- **limits**:
  - reducing conditions: ∑ peaks other than HC and LC: ≤ 2%
  - non-reducing conditions: ∑ peaks other than IgG peak: ≤ 8%



LC: light chain; HC: heavy chain;
NGHC: non-glycosylated heavy chain

"Company C" (registered product)

~~**Different CE-SDS method**~~

~~**Ph. Eur. General Notices:**~~
- ~~**demonstration of compliance** with the Ph. Eur.~~
- ~~**alternative methods** (equivalence testing)~~

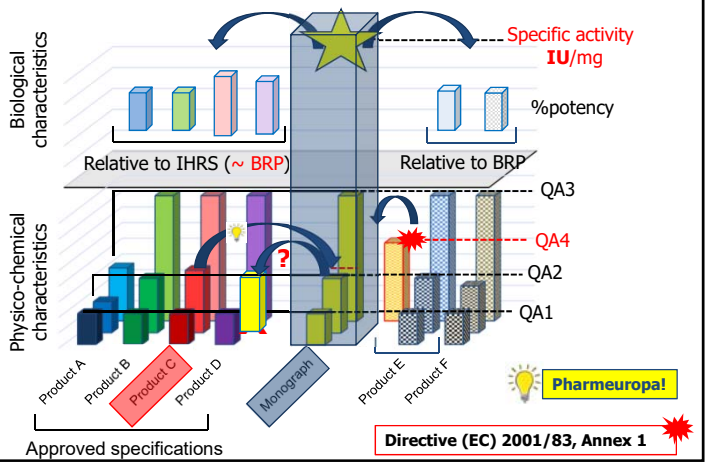
Higher limits

Ph. Eur. Monograph Elaboration/Revision:

Do not miss **Pharmeuropa!**

Ph. Eur. Monographs for Biotherapeutics: Other Cases...

Simulation of impact of a monograph – hypothetical situation



The Pharmacopoeia monograph ensures continuity of product quality

Presentation Outline

- **Introduction**: **Ph. Eur. and flexibility**: the case of biotherapeutic product monographs (**etanercept and infliximab case studies**)
- **Monograph elaboration/revision process:**
  - participation and role of stakeholders
- **Monograph implementation** – impact on already approved products:
  - **Infliximab case study**
- **Ph. Eur. and biosimilars**

Biosimilars and the Ph. Eur.

- **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.*"

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

*"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."*

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

- **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. (…)

  Extensive state-of-the-art characterisation studies should be applied to the biosimilar and reference medicinal products in parallel, to demonstrate with a high level of assurance that the quality of the biosimilar is comparable to the reference medicinal product.

  It is the responsibility of the applicant to demonstrate that the selected methods used in the biosimilar comparability exercise would be able to detect slight differences in all aspects pertinent to the evaluation of quality (e.g. ability to detect relevant variants with high sensitivity). Methods used in the characterisation studies form an integral part of the quality data package and should be appropriately qualified for the purpose of comparability. If applicable, standards and reference materials (e.g. from Ph. Eur., WHO) should be used for method qualification and standardisation."

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

QUESTION: What is the role of pharmacopoeial monographs in the evaluation of biosimilars?

RESPONSE: Pharmacopoeial monographs are public standards which include quality requirements for medicinal products and their constituents. A biosimilar should show the same level of compliance with a pharmacopoeial monograph as the reference product. However, since pharmacopoeial monographs provide only minimal requirements, **compliance with pharmacopoeial monographs will not be sufficient to demonstrate biosimilarity.**

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

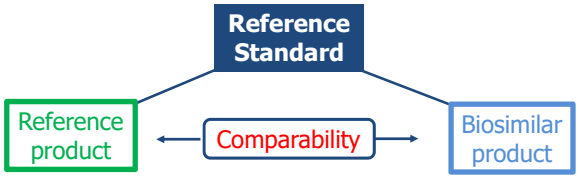
QUESTION: What is a reference product mentioned in the concept for licensing a biosimilar?

RESPONSE:

- A **reference product** is used as the comparator for head-to-head comparability studies with the biosimilar in order to show similarity in terms of quality, safety and efficacy. The term does not refer to measurement standards such as **Ph. Eur. reference standards.**

☒ **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** can be used during the development of biosimilars for method qualification and standardisation.



Need for Monographs to Remain Up-to-date

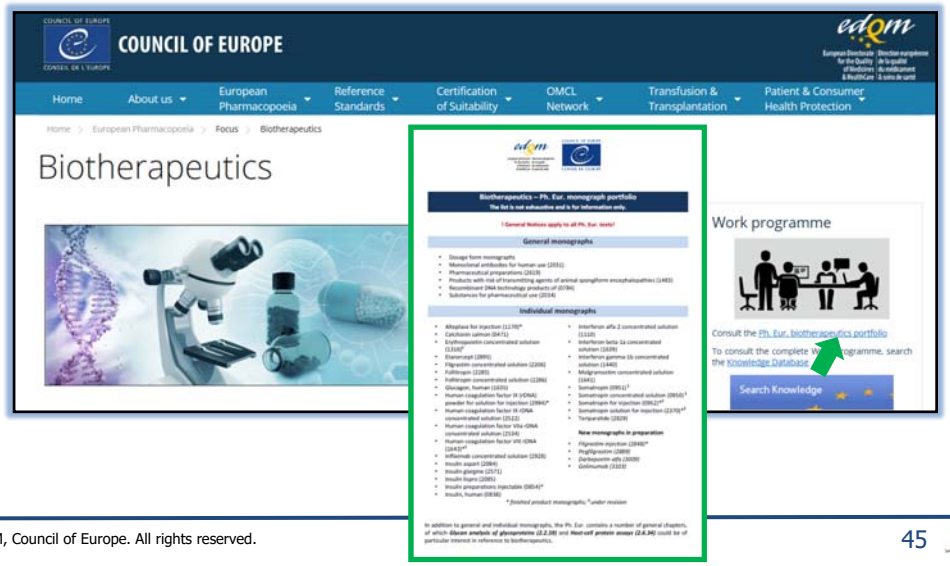
"*In cases where a specification contained in a monograph of the European Pharmacopoeia or in the national pharmacopoeia of a Member State might be insufficient to ensure the quality of the substance, the competent authorities may request more appropriate specifications from the marketing authorisation 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.*"

Directive (EC) 2001/83, Annex 1

MODULE 3: CHEMICAL, PHARMACEUTICAL AND BIOLOGICAL INFORMATION FOR MEDICINAL PRODUCTS CONTAINING CHEMICAL AND/OR BIOLOGICAL ACTIVE SUBSTANCES, 3.2 Content and Basic Principles

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 useful.

Section Dedicated to Biotherapeutics on EQDM Website



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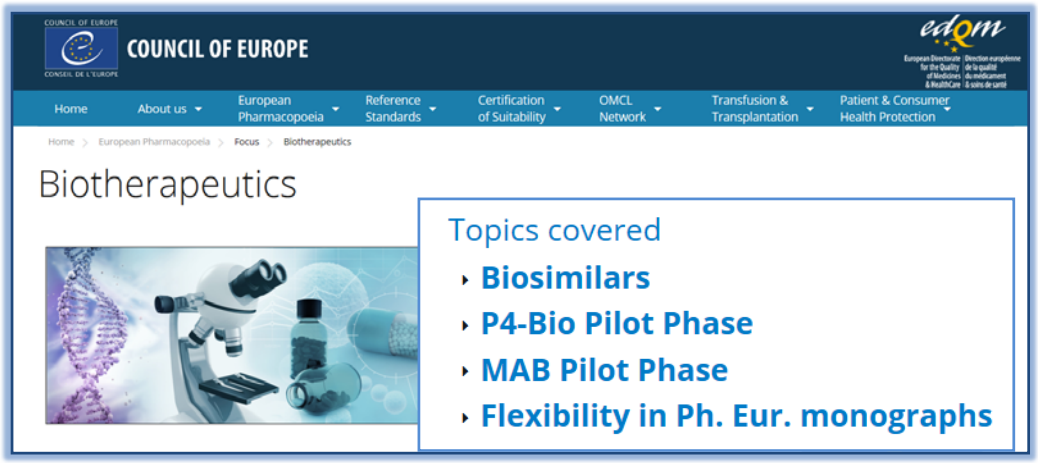
Section Dedicated to Biotherapeutics on EQDM Website



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