European Pharmacopoeia – recent developments in the field of biopharmaceuticals

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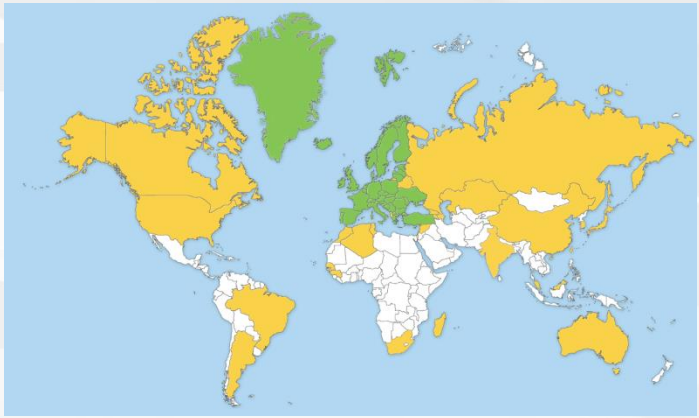
European Pharmacopoeia

- Protecting public health – one common compulsory standard
- Official pharmacopoeia in Europe (complemented by national pharmacopoeias)
- Legally binding quality standards for ALL medicinal products i.e. raw materials, preparations, dosage forms, containers…
- Mandatory at the same date for all Members

- 39 Members (38 Member States & EU)
- 30 Observers (6 European, 22 non-European countries, TFDA, WHO)
- Suppl. 9.8: 2406 monographs, 365 general texts, 2730 reagents



Structure of the Ph. Eur.

General notices

General chapters

General monographs

Individual monographs

Structure of the Ph. Eur.

- ✓ Apply to ALL texts
- ✓ Provide basic information, rules and conventional expressions
- ✓ Address general issues
- ✓ Essential reading

General notices

General chapters

General monographs

Individual monographs

- ✓ General methods & texts
- ✓ Editorial convenience
- ✓ Not mandatory "per se"
- ✓ Part of the standard when referred to in a monograph
- ✓ Can be used when there is no monograph → may need validation

- ✓ Classes of substances and dosage forms
- ✓ Mandatory to all substances/preparations within the definition scope
- ✓ Not cross-referenced in individual monographs

Reference standards

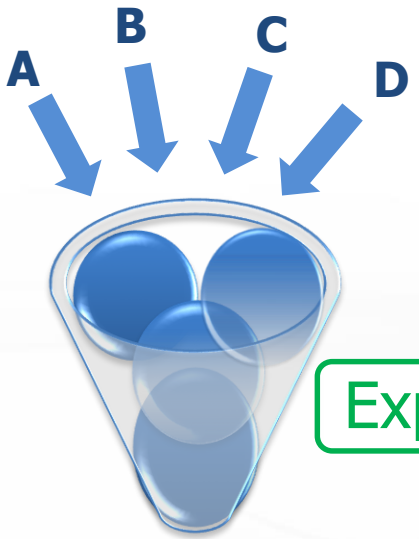
- ✓ Established specifically and exclusively for use in Ph. Eur. texts
- ✓ 5.12 Reference standards

- ✓ Specific
- ✓ Not stand-alone
- ✓ Based on approved specification(s) backed up by batch data
- ✓ Validated analytical procedures

Monographs elaboration procedures

PROCEDURE 1

Multi-source



Revision

MONOGRAPH
valid for A, B, C & D

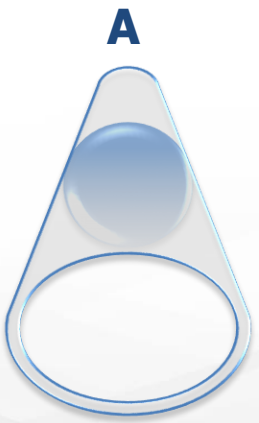
Group of Experts or Working Parties

On request, data handled confidentially

Experimental verification

Single-source

Direct cooperation with innovator



MONOGRAPH

Revision

applicable to
B, C, D ....

Working parties of regulators

Data handled confidentially by EDQM

PROCEDURE 4

Monograph elaboration – experimental verification

- **Robustness** and **transferability** of the methods to be introduced in the monograph
- **Method performance**
- **Sometimes** methods are out-of-date or not robust enough

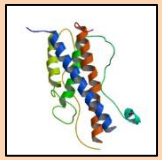
Multiple exchanges with the manufacturers

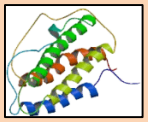
- ✓ Specific instructions added
- ✓ Strengthen verification of method performance (*e.g.* resolution solution for SST)
- ✓ Reference to existing pharmacopoeial methods/general chapters or to monographs on closely related substances
- ✓ For certain tests experimental verification may go beyond the monograph itself (*e.g.* peptide mapping by LC-MS to confirm marker peaks in complex peptide maps)
- – Validation needed for implementation of alternative methods

Consumes significant resources

Elaboration procedures – - monograph examples for biotherapeutics

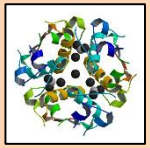
P1

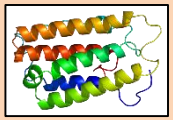

Somatropin (0950, 0951, 0952)

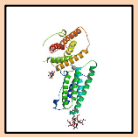

EPO (1316)

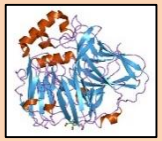

IFNβ-1a (1639)


Follitropin (2285, 2286)

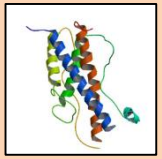

Insulin human (0838)

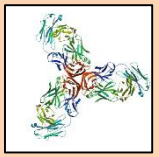

IFNα-2 (1110)


IFNγ-1b (1440)


Human coagulation factor VIII rDNA (1643)


Filgrastim (2206)

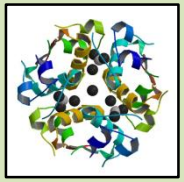

Somatropin soln. for injection (2370)


Infliximab (2928)

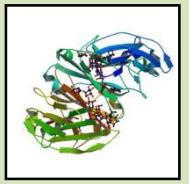

Filgrastim injection (2848)

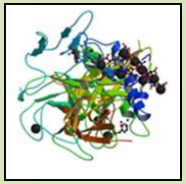
1990 2010 2019

P4


Insulin glargine (2571)

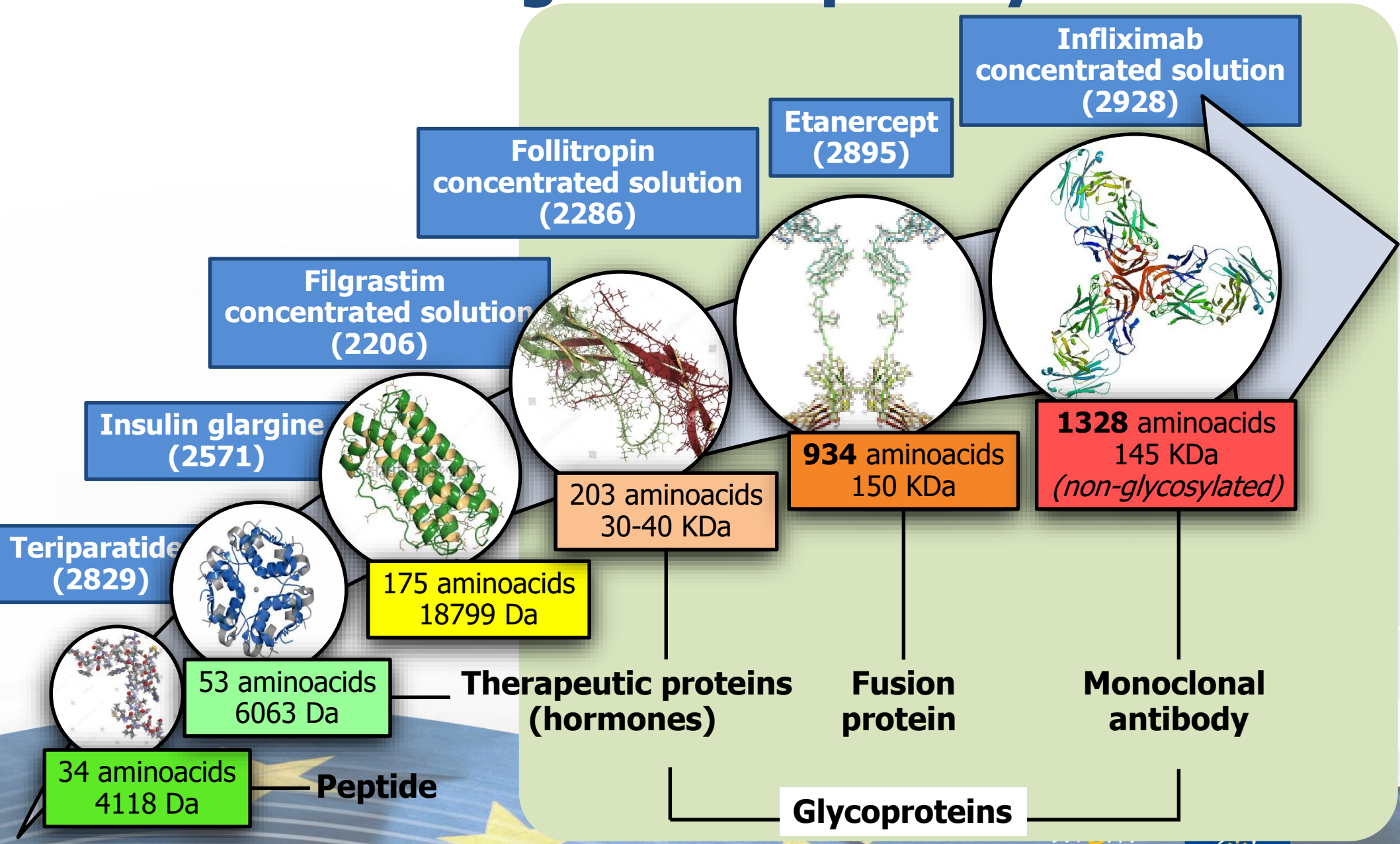

Human coagulation factor IX (rDNA) DS (2522) and DP (2994)


Etanercept (2895)


Human coagulation factor VIIa (rDNA) (2534)


Teriparatide (2829)

Evolution of Ph. Eur. monographs and biological complexity



for monograph elaboration

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

for monograph elaboration

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.'*

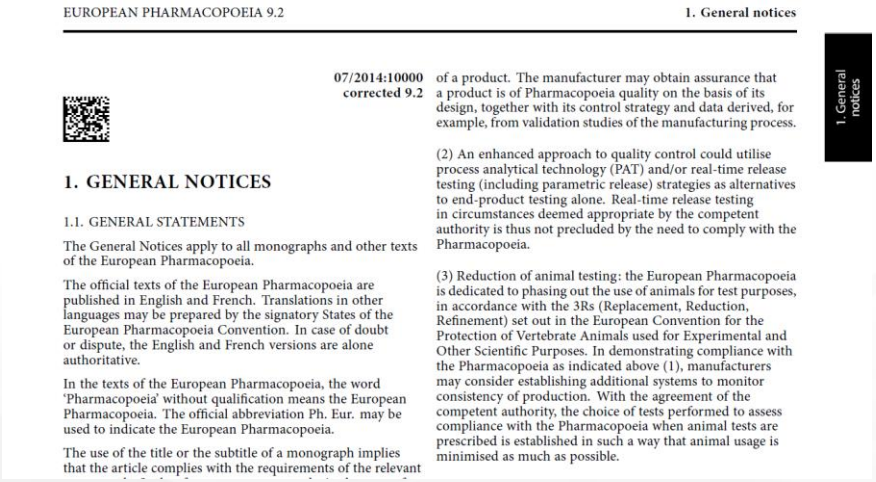
'**ASSAY**. *Carry out a suitable biological assay compared to the reference preparation.'*

How to transfer flexibility into a public standard?

Ph. Eur. flexibility #1: General Notices

- **Alternative methods (since 1997)**

allowed if lead to the same pass/fail results; subject to the agreement of the competent authority



EUROPEAN PHARMACOPOEIA 9.2 — 1. General notices

07/2014:10000 corrected 9.2

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.

The use of the title or the subtitle of a monograph implies that the article complies with the requirements of the relevant

of a product. The manufacturer may obtain assurance that 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 utilise process analytical technology (PAT) and/or real-time release testing (including parametric release) strategies as alternatives to end-product testing alone. Real-time release testing in circumstances deemed appropriate by the competent authority is thus not precluded by the need to comply with the Pharmacopoeia.

(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 as indicated above (1), manufacturers may consider establishing 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 minimised as much as possible.

1. General notices

- **Possibility to omit tests (since 1997)**

if assured that a product is of Pharmacopoeia quality on the basis of its design, together with its control strategy and relevant data

DEMONSTRATION OF COMPLIANCE ≠ TESTING

- **Enhanced approaches (since 2013)**

Use of PAT and/or real-time release testing (including parametric release) as alternatives to end-product testing acknowledged

Ph. Eur. flexibility #2: Production Section

- Introduced in 1991 in monographs for biological preparations (discussions in the 80s).
- Draws attention to particular aspects of the manufacturing process; not necessary comprehensive
- Mandatory requirements for manufacturers (unless otherwise stated)
- Incudes statements on e.g. source materials, process, validation and control, in-process testing or tests to be carried out on the final article prior to release
- Cannot necessary be verified by an independent analyst on the final article

Ph. Eur. flexibility #2: Production Section

07/2019:2206

FILGRASTIM CONCENTRATED SOLUTION

Filgrastimi solutio concentrata

(...)

PRODUCTION

Filgrastim concentrated solution is produced by a method based on recombinant DNA (rDNA) technology, using bacteria as host cells.

Prior to release, the following tests are carried out on each batch of the final bulk product, unless exemption has been granted by the competent authority.

Host-cell-derived proteins. The limit is approved by the competent authority.

Host-cell- or vector-derived DNA. The limit is approved by the competent authority.

(...)

07/2018:2571

INSULIN GLARGINE

Insulinum glarginum

(...)

PRODUCTION

Insulin glargine is produced by a method based on recombinant DNA (rDNA) technology under conditions designed to minimise the degree of microbial contamination.

Prior to release, the following tests are carried out on each batch of the final bulk product, unless exemption has been granted by the competent authority.

Host-cell-derived proteins. The limit is approved by the competent authority.

Single-chain precursor. The limit is approved by the competent authority. Use a suitably sensitive method.

(...)

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics - example methods

SUITABLE METHOD

- **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 METHOD

- **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."***

Technical Guide for the Elaboration of Monographs on Synthetic Peptides and Recombinant DNA Proteins (2018)

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – 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/charge variants	✓
Product-related impurities (e.g. HMW, LMW by SEC	✗
Related proteins	✗

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – example

PRODUCTION section:

- **general requirements for consistency of production:**

07/2019:2895

ETANERCEPT

Etanerceptum

(…)

PRODUCTION

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.

(…)

01/2019:2928

INFLIXIMAB CONCENTRATED SOLUTION

Infliximabum solutio concentrata

(…)

PRODUCTION

Infliximab 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 *N*-glycan occupancy and Fc-effector functions (antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC)) using suitably qualified assay(s).

(…)

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – example

PRODUCTION section:

- **Specific requirements related to process-dependent heterogeneity set in a flexible way:**

  - **Generic method of analysis**

ETANERCEPT 07/2019:2895

Etanerceptum

(…)

***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.

(…)

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – example

PRODUCTION section:

- **Specific requirements related to process-dependent heterogeneity set in a flexible way:**
  - Generic method of analysis
  - **Specific analytical procedure as example**

- detailed instructions

ETANERCEPT 07/2019:2895

Etanerceptum

(...)

N-Glycan analysis.

(...)

The following procedure is given as an example.

Test solution. To 4 µL of the preparation to be examined (about 25 mg/mL) add 21 µL of *water R*, 3 µL of *0.25 M sodium phosphate buffer solution pH 7.5 R* and 2 µL of a 500 000 U/mL solution of *peptide N-glycosidase F R*. Mix and incubate at 37 °C for 20-24 h. Label the released glycans with 2-aminobenzamide using a suitable procedure. The procedure employs a combination of reagents optimised and validated for the efficient labelling of glycans, and for the subsequent extraction and recovery of the labelled glycans from the reaction. Resuspend or dilute the labelled glycans in 100 µL of *water R*.

Reference solution (a). Dissolve the contents of a vial of *etanercept CRS* in *water R* to obtain a concentration of about 25 mg/mL. Carry out the release and labelling of glycans in the same manner as for the test solution. Resuspend or dilute the labelled glycans in 100 µL of *water R*.

Reference solution (b). Use a suitable etanercept in-house reference preparation shown to be representative of batches tested clinically and batches used to demonstrate consistency of production. Dilute, if necessary, with *water R* to obtain a concentration of about 25 mg/mL. Carry out the release and labelling of glycans in the same manner as for the test solution. Resuspend or dilute the labelled glycans in 100 µL of *water R*.

Blank solution. Prepare at the same time and in the same manner as for the test solution but using *water R* instead of the preparation to be examined.

Analyse the labelled glycans by liquid chromatography (*2.2.29*).

Column:

- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: an amide derivative of *silica gel for chromatography R* (5 µm);
- *temperature*: 35 °C.

Mobile phase:

- *mobile phase A*: mix 9.8 mL of *anhydrous formic acid R* and 500 mL of *water for chromatography R*, adjust to pH 4.0 with *ammonia R* and dilute to 1000 mL with *water for chromatography R*;
- *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	20 → 30	80 → 70
2 - 67.0	30 → 52	70 → 48
67.0 - 67.1	52 → 80	48 → 20
67.1 - 73.0	80	20

Flow rate: 0.4 mL/min.

Detection: fluorimeter at 330 nm for excitation and 420 nm for emission.

Autosampler: set at 2-8 °C.

Injection: 10 µL.

(...)

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – example

PRODUCTION section:

- **Specific requirements related to process-dependent heterogeneity set in a flexible way:**

  - Generic method of analysis
  - **Specific analytical procedure as example**

- detailed instructions

- method performance (system suitability) criteria

ETANERCEPT 07/2019:2895

Etanerceptum

(...)

***N*-Glycan analysis.**

(...)

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.

(...)

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – example

PRODUCTION section:

- **Specific requirements related to process-dependent heterogeneity set in a flexible way:**

  - Generic method of analysis
  - **Specific analytical procedure as example**

- detailed instructions

- method performance (system suitability) criteria

- Use of a Ph. Eur. Chemical Reference Standard to verify method performance

ETANERCEPT 07/2019:2895

Etanerceptum

(...)

***N*-Glycan analysis.**

(...)

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.

(...)

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – example

PRODUCTION section:

- **Specific requirements related to process-dependent heterogeneity set in a flexible way:**

  - Generic method of analysis
  - **Specific analytical procedure as example**

- detailed instructions
- method performance (system suitability) criteria
- Use of a Ph. Eur. Chemical Reference Standard to verify method performance
- **Results – comparison with an in-house standard**

ETANERCEPT 07/2019:2895

Etanerceptum

(...)

***N*-Glycan analysis.**

(...)

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).

(...)

Ph. Eur. flexibility #3: additional flexibility for complex biotherapeutics – example

PRODUCTION section:

- **Specific requirements related to process-dependent heterogeneity set in a flexible way:**

  - Generic method of analysis
  - Specific analytical procedure as example

- detailed instructions
- method performance (system suitability) criteria
- Use of a Ph. Eur. Chemical Reference Standard to verify method performance
- Results – comparison with an in-house standard

  - **Acceptance criteria – as approved by the competent authority**

ETANERCEPT 07/2019:2895

Etanerceptum

(...)

N-Glycan analysis.

(...)

Limits:

– *percentage of neutral N-glycans*: as approved by the competent authority;

– *percentage of sialylated N-glycans*: as approved by the competent authority.

(...)

Monograph for Biotherapeutics: Additional Flexibility

- **PRODUCTION section**
  - ✓ requirements related to **process-dependent heterogeneity**

MONOGRAPH FLEXIBILITY

- **Test procedures**
  - ✓ **complex (multi-step) analytical procedure(s)** given as **example(s)**
- **Reference preparations**
  - ✓ **Ph. Eur. CRS** to demonstrate **method performance** (system suitability)
  - ✓ in-house reference preparation – matching profiles
- **Acceptance criteria**
  - ✓ limits to be set in **agreement with the competent authority**

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

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

✓ **Address complexity**

Biotherapeutics – dedicated section on EDQM Website

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

COUNCIL OF EUROPE
CONSEIL DE L'EUROPE

Home | About us | European Pharmacopoeia | Patient & Consumer Health Protection

Home > European Pharmacopoeia > Focus > Biotherapeutics

Biotherapeutics

Topics covered

- **Biosimilars**
- **P4-Bio Pilot Phase**
- **MAB Pilot Phase**
- **Flexibility in Ph. Eur. monographs**

Last update: November 2018

Biotherapeutics – Ph. Eur. monograph portfolio
The list is not exhaustive and is for information only.

! General Notices apply to all Ph. Eur. texts!

General monographs

- Dosage form monographs
- Monoclonal antibodies for human use (2031)
- Pharmaceutical preparations (2619)
- Products with risk of transmitting agents of animal spongiform encephalopathies (1483)
- Recombinant DNA technology products of (0784)
- Substances for pharmaceutical use (2034)

Individual monographs

- Alteplase for injection (1170)*
- Calcitonin salmon (0471)
- Erythropoietin concentrated solution (1316)§
- Etanercept (2895)
- Filgrastim concentrated solution (2206)
- Filgrastim injection (2848)*
- Follitropin (2285)
- Follitropin concentrated solution (2286)
- Glucagon, human (1635)
- Human coagulation factor IX (rDNA) powder for solution for injection (2994)*
- Human coagulation factor IX rDNA concentrated solution (2522)
- Human coagulation factor VIIa rDNA concentrated solution (2534)
- Human coagulation factor VIII rDNA (1643)*§
- Infliximab concentrated solution (2928)
- Insulin aspart (2084)
- Insulin glargine (2571)
- Insulin lispro (2085)
- Insulin preparations injectable (0854)*
- Insulin, human (0838)
- Interferon alfa-2 concentrated solution (1110)
- Interferon beta-1a concentrated solution (1639)
- Interferon gamma-1b concentrated solution (1440)
- Molgramostim concentrated solution (1641)
- Somatropin (0951)§
- Somatropin concentrated solution (0950)§
- Somatropin for injection (0952)*§
- Somatropin solution for injection (2370)*§
- Teriparatide (2829)

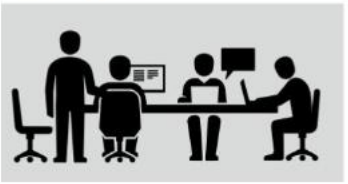
New monographs in preparation

- *Pegfilgrastim (2889)*
- *Darbepoetin alfa (3009)*
- *Golimumab (3103)*
- *Insulin glargine injection (3129)**
- *Teriparatide injection (3130)**

** finished product monographs; § under revision*

In addition to general and individual monographs, the Ph. Eur. contains a number of general chapters, of which ***Glycan analysis of glycoproteins (2.2.59)*** and ***Host-cell protein assays (2.6.34)*** could be of particular interest in reference to biotherapeutics.

Work programme



Consult the Ph. Eur. biotherapeutics portfolio

To consult the complete W… rogramme, search the Knowledge Database

Search Knowledge

Acknowledgements

Many thanks to:

Mihaela Buda

Gwenaël Ciréfice

Emmanuelle Charton

...

Thank you for your attention!