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

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European Directorate for the Quality of Medicines & HealthCare | Direction européenne de la qualité du médicament & soins de santé

COUNCIL OF EUROPE

CONSEIL DE L'EUROPE

- Chemist with a PhD in pharmaceutical chemistry from the Ruprecht-Karls University of Heidelberg, Germany
- Post-doctoral research in the Institute for Pharmacy and Molecular Biotechnology at the University of Heidelberg
- Scientific/Technical Officer at the Institute for Reference Materials and Measurement (IRMM) of the Joint Research Centre, a Directorate-General of the European Commission:
  - responsibilities for the development and certification of reference materials for quality control and calibration in bioanalysis
- **Since 2013: Scientific Programme Manager in the European Pharmacopoeia Department, Biologicals Division**, with responsibilities for a number of Expert Groups including:
  - Group 6B (Human Plasma and Plasma products), P4Bio (single-source biotherapeutics)-, Monoclonal Antibodies-, mRNA vaccines- and AQbD Working Parties.

Dr Mihaela Buda

Ph. Eur. Texts on Biologicals: Now and in the Future

Finnish Pharmacopoeia Webinar
8 November 2023

Mihaela Buda, PhD
European Pharmacopoeia Department
EDQM, Council of Europe

Presentation Outline

- **The European Pharmacopoeia (Ph. Eur.):**
  - Key figures. Expert Network
- **Ph. Eur. Texts for Monoclonal Antibodies**:
  - "Horizontal standards" (general chapters)
  - Product class-based standards
  - Performance-based standards
  - Concluding remarks
- **What's in the pipeline?**
  - An overview of current and future activities related to biologicals

European Pharmacopoeia

Binding in the **39** signatory states of the Ph. Eur. Convention and used as a reference worldwide; **31** observers from all continents

► More than **2 800 documentary standards** for the quality control of medicines

- Cover the whole manufacturing process (*e.g. excipients, medicinal products*)
- All stages of the **life cycle** of a medicine from development through to production and market surveillance
- Methods verified & standardised

► **About 3000 reference standards shipped to 132 countries**

European Pharmacopeia Commission - treaty-based body - and its expert groups

Biological Standardisation Steering Committee

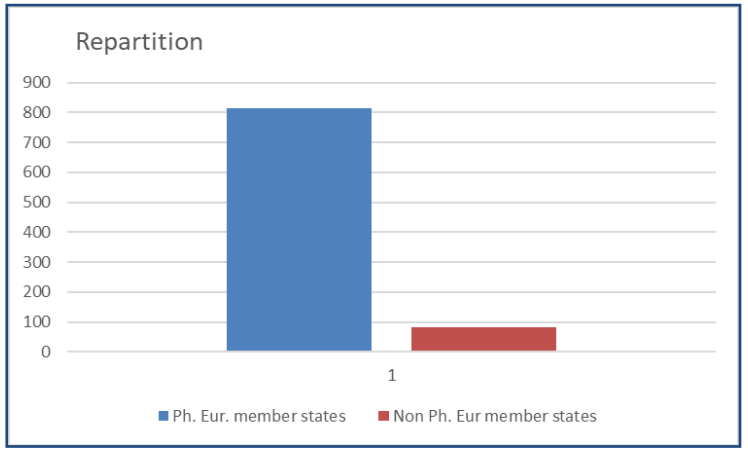
Laboratory, production, storage and distribution

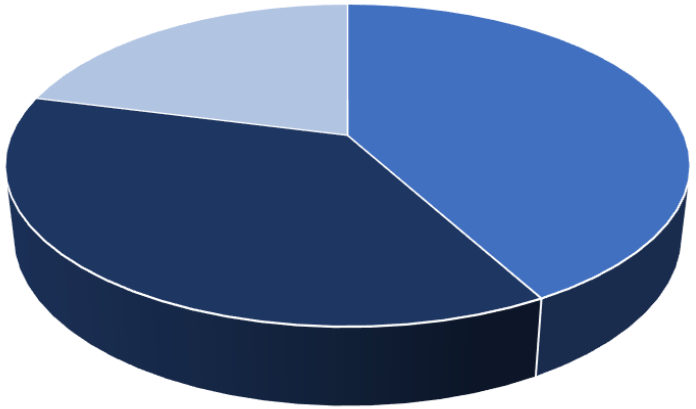
PUBLIC HEALTH IMPACT

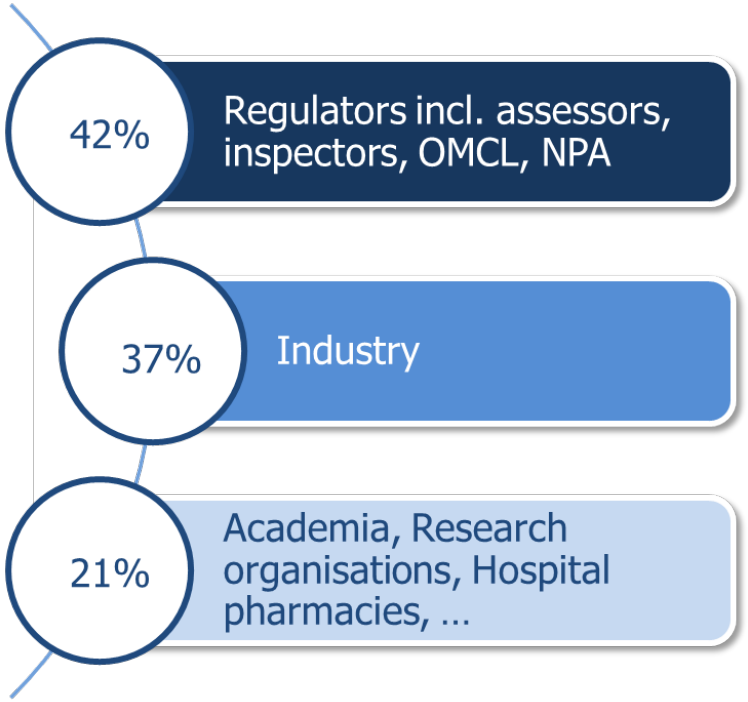
- **Ensure equivalent quality and safety of medicinal products throughout Europe and facilitate their free movement in Europe and beyond**

… relying on nearly 900 experts[1] working together …

[1] This number does not include:
- Chairs of Groups
- ad hoc specialists (around 100/year)
- Members of the Ph. Eur. Commission







In the field of biologicals:
- Groups of Experts: 6, 6B, 15, 15V
- Working parties: ALG, BACT, CTP, GTP, HTS, MAB, mRNAVAC, P4Bio

Ph. Eur. Texts for Monoclonal Antibodies

Ph. Eur. Standards for MAbs: Development Approaches

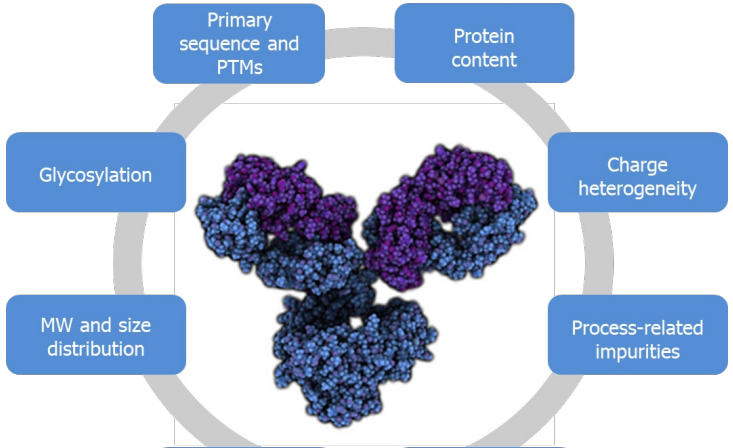
- **Expand** the portfolio of quality standards for mAbs:
  - Target **product classes** and specific drug substance; evaluate new opportunities on a case-by-case basis with support from key stakeholders
  - Develop **general methods of analysis** to support analytical testing → broad applicability, performance characteristics; multi-laboratory collaborative studies
- Explore **flexible concepts** and **new types of standardisation**:
  - Focus on key quality attributes and associated testing strategies
  - Establish suitable common expectations and general methodologies with broad applicability

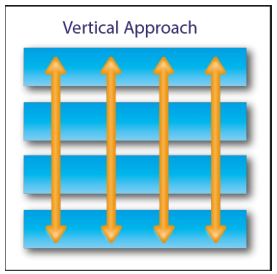
MAbs: Approaches to Public Standard-Setting

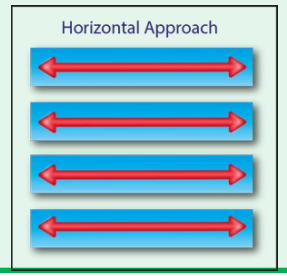
- Ustekinumab (3165)*
- Adalimumab (3147)*
- Golimumab concentrated solution (3103)*
- Infliximab concentrated solution (2928)
- Etanercept (2895)

Definition
Production
Identification
Tests
Assay/Content
Assay/Potency

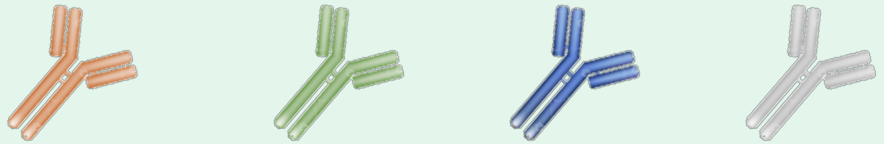
Monographs







Horizontal standards (general chapters)



Product-class standard

Cell-based assays for potency determination of TNF-alpha antagonists (2.7.26)

Performance-based standards

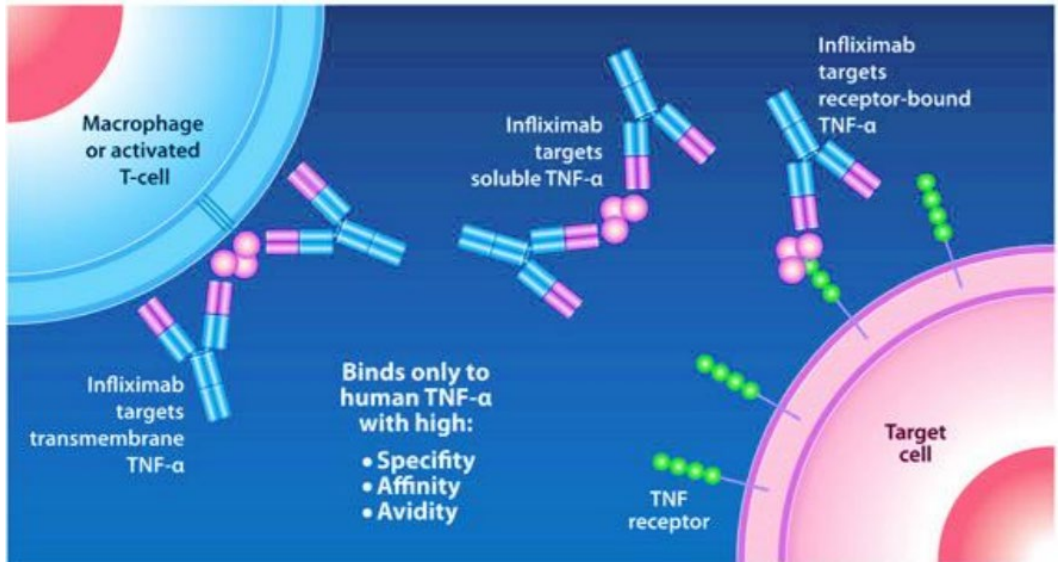
- Size-exclusion chromatography for recombinant therapeutic monoclonal antibodies (2.5.43)*
- Capillary isoelectric focusing for recombinant therapeutic monoclonal antibodies (2.5.44)*

*under elaboration

Standardisation of TNF-alpha Bioassays

- **Rapidly growing number** of TNF-alpha antagonists on the market
- **Increased variety of approaches** to bioassay selection for assessing and comparing potencies
- Questions raised concerning the **appropriate choice of potency assays** for particular products and how they should be designed, conducted, analysed and applied

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



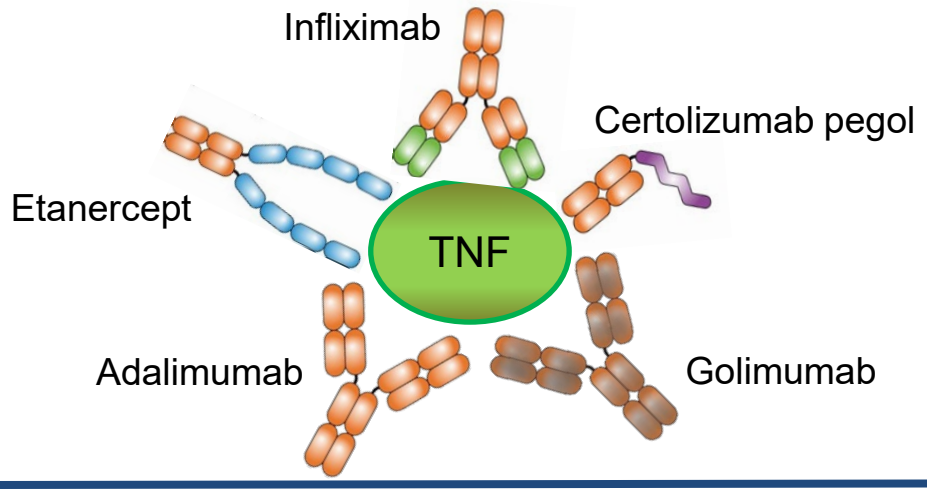
Biological activity evaluated in **cell-based potency assays** using different approaches for **TNF-alpha neutralisation**

Standardisation of TNF-alpha Bioassays

Cell-based assays for potency determination of TNF-alpha antagonists (2.7.26)

➢New **general chapter** providing: **common expectations** and **general methodologies** for potency determination, widely applicable to the class of **TNF-alpha antagonists**

Bioassay "Horizontal Standard"



➢ Choice of the assays and scope of validation/verification

TNF-alpha antagonist	U937 apoptosis assay - Procedure A -	WEHI-164 cytotoxicity assay - Procedure B -	NF-κB-inducible reporter gene assay - Procedure C -	L929 cytotoxicity assay - Procedure D -
Etanercept*	●	◗	◗	◗
Infliximab*	◗	●	◗	◗
Certolizumab pegol	◗	◗	●	◗
Adalimumab**	◗	◗	◗	●
Golimumab**	○	◗	○	○

● signifies that procedure has been validated
◗ signifies that suitability has been demonstrated during verification experiments
○ signifies that suitability has not been evaluated
* Ph. Eur. monograph
** Draft monograph under elaboration

TNF-alpha Bioassay Horizontal Standard

Cell-based assay for potency determination of TNF-alpha antagonists (2.7.26)*

- **NEW type of general chapter** with experimentally verified cell-based assays
- TNF-alpha neutralisation assays (procedures A, B, C and D):
  - ➔ different cell lines/readouts
  - ➔ validated for specific TNF-alpha antagonists
  - ➔ suitability (specificity and precision) demonstrated for each TNF-alpha antagonist, during verification experiments
  - ➔ assay applied to substances outside the scope of the initial validation or not covered in an individual monograph for a TNF-alpha antagonist requires validation
- Diversifies the choice of bioassays and facilitates migration to different assays
- Use of other assays that are acceptable to the competent authority not excluded

- Cell preparation
- TNF-alpha working solutions preparation
- Test solution preparation
- Reference solution preparation (product-specific: BRP or IHRS)
- Assay execution
- Dose-response curve construction
- Calculation of reportable result

*Ph. Eur. Supplement 11.1

Analytical procedure control strategy

- ✓ system suitability test: quality of RS and control curves, proper functioning of the system (max to min ratio between controls)
- ✓ sample suitability assessment: compare performance of the sample to the performance of the RS (similarity/parallelism)
- ✓ **procedure-independent performance controls and one-size-fits all criteria**

Sources of variability identified and potential mitigation strategies described:

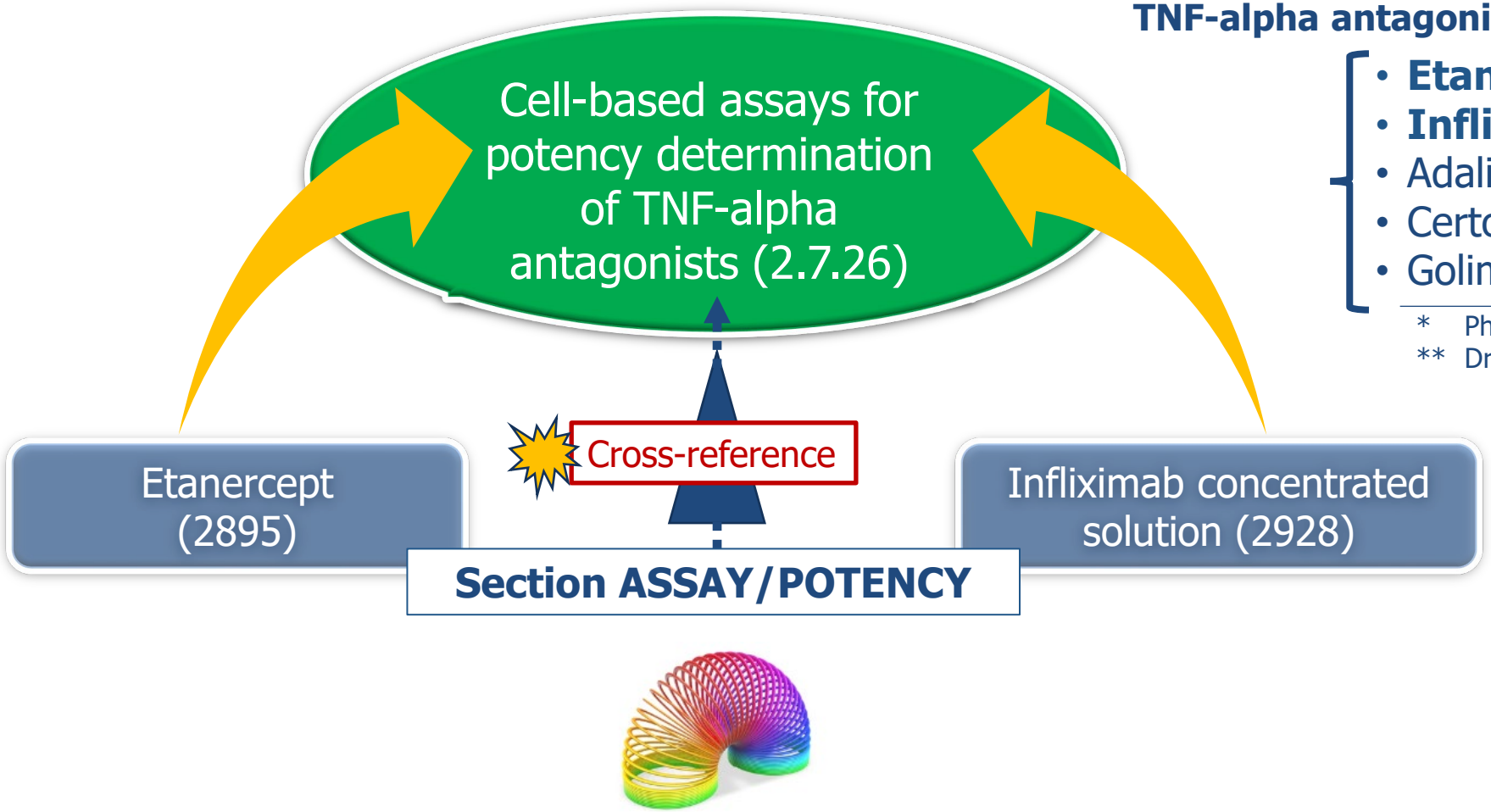
- ✓ adjustment of assay conditions to satisfy the system suitability criteria without fundamentally modifying the procedures

Link between Chapter and Individual Monographs

Cell-based assays for potency determination of TNF-alpha antagonists (2.7.26) – scope:

- **Etanercept***
- **Infliximab***
- Adalimumab**
- Certolizumab pegol
- Golimumab**

* Ph. Eur. monograph
** Draft monograph under elaboration



Link between Chapter and Individual Monographs

Potency. The potency of etanercept is determined by comparison of dilutions of the test preparation with the dilutions of *etanercept BRP* using a suitable cell-based assay based on the inhibitory action of etanercept on the biological activity of TNF-α and a suitable readout for assessing this inhibitory effect.

The following procedure is given as an example.

U937 apoptosis assay (*2.7.26, Procedure A*). Carry out the assay as described with the following modifications.

Test solution. Dilute the preparation to be examined with assay medium to obtain a concentration of about 21 ng/mL. Use this solution to prepare 10 additional test sample dilutions (a dilution step of 1.4 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

Reference solution. Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 42 IU/mL. Use this solution to prepare 10 additional reference sample dilutions on a dilution plate to generate the standard curve (a dilution step of 1.4 has been found suitable). Analyse 2 independent dilutions per plate.

Result: the estimated potency is not less than 80 per cent and not more than 140 per cent relative to the reference solution. The confidence limits ($P = 0.95$) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

In addition, the following procedures have been found suitable:

WEHI-164 cytotoxicity assay (*2.7.26, Procedure B*). Carry out the assay as described with the following modifications.

Test solution. Dilute the preparation to be examined with assay medium to obtain a concentration of about 96 ng/mL. Analyse 2 independent dilutions per plate.

Reference solution. Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 192 IU/mL. Analyse 2 independent dilutions per plate.

Plate preparation. Add 300 µL of the test or reference solutions (column 2, rows A-H). Further prepare a series of 1.5-fold dilutions (columns 3-12, rows A-H), by removing 200 µL from column 2 and transferring to the adjacent well in column 3, repeating for subsequent wells.

NF-κB-inducible reporter gene assay (*2.7.26, Procedure C*). Carry out the assay as described with the following modifications.

Test solution. Dilute the preparation to be examined with assay medium to obtain a concentration of about 1000 ng/mL. Use this solution to prepare 11 test sample dilutions in the range 1.0-200.0 ng/mL (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

Reference solution. Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 400 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

L929 cytotoxicity assay (*2.7.26, Procedure D*). Carry out the assay as described with the following modifications.

Test solution. Dilute the preparation to be examined with assay medium to obtain a concentration of 45 ng/mL. Use this solution to prepare 11 test sample dilutions, starting from 10 ng/mL (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

Reference solution. Reconstitute the contents of 1 vial of *etanercept BRP* with sterilised *water for injections R* to obtain a concentration of 10 000 IU/mL. Further dilute with assay medium to obtain a concentration of 20 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

Etanercept (2895)

Potency. The potency of infliximab is determined by comparison of dilutions of the test preparation with dilutions of *infliximab BRP* using a suitable cell-based assay based on the inhibitory action of infliximab on the biological activity of TNF-α with a suitable readout for assessing this inhibitory effect.

The following procedure is given as an example.

WEHI-164 cytotoxicity assay (*2.7.26, Procedure B*). Carry out the assay as described with the following modifications.

Reference solution. Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 6.4 IU/mL. Analyse 2 independent dilutions per plate.

Result: the estimated potency is not less than 80 per cent and not more than 120 per cent relative to the reference solution. The confidence limits ($P = 0.95$) are not less than 80 per cent and not more than 125 per cent of the estimated potency.

In addition, the following procedures have been found suitable:

U937 apoptosis assay (*2.7.26, Procedure A*). Carry out the assay as described with the following modifications.

Reference solution. Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 12.5 IU/mL. Use this solution to prepare 10 additional reference sample dilutions on a dilution plate to generate the standard curve (a dilution step of 2 has been found suitable). Analyse 2 independent dilutions per plate.

NF-κB-inducible reporter gene assay (*2.7.26, Procedure C*). Carry out the assay as described with the following modifications.

Reference solution. Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 8 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

L929 cytotoxicity assay (*2.7.26, Procedure D*). Carry out the assay as described with the following modifications.

Reference solution. Reconstitute the contents of 1 vial of *infliximab BRP* with sterilised *water for injections R* to obtain a concentration of 500 IU/mL. Further dilute with assay medium to obtain a concentration of 1.0 IU/mL. Use this solution to prepare 10 additional reference sample dilutions (a dilution step of 1.7 has been found suitable) on a dilution plate. Analyse 2 independent dilutions per plate.

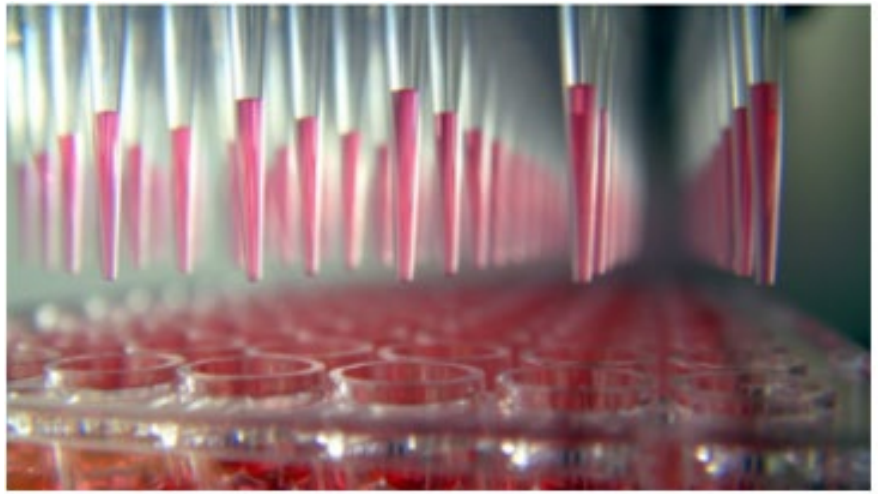
Infliximab concentrated solution (2928)

Suitable TNF-alpha neutralisation assay – calibration with:	
Etanercept BRP	Infliximab BRP
The following procedure is given as an example	
U937 apoptosis assay (*2.7.26, Procedure A*)	WEHI-164 cytotoxicity assay (*2.7.26, Procedure B*)
In addition, the following procedures have been found suitable	
2.7.26, Procedures B, C, D	2.7.26, Procedures A, C and D

"suitable", "example procedure" defined in Ph. Eur. General Notices

TNF-alpha Bioassay Package

- **General chapter 2.7.26**:
  - provides analytical tools and practical guidance to further build on and support testing.
  - helps establish an accepted and shared analytical language that will help standardise the potency determination of TNF-alpha antagonists, both currently available and in the pipeline.
- **Link created with monographs on TNF-alpha antagonists (Etanercept, Infliximab):**
  - diversifies the choice of suitable bioassays for potency determination
  - reinforces and maintains the flexibility already built into the monographs and the use of Ph. Eur. reference standards.



Ph. Eur. Supplement 11.1

Horizontal Standard Development Beyond Product Class

- *2.5.44 Capillary isoelectric focusing for recombinant therapeutic monoclonal antibodies:*
  - cIEF and imaged cIEF procedures for analysis of charge heterogeneity of mAbs, to monitor identity, quality, production consistency
  - based on data generated in multi-laboratory verification study
  - guidance on the aspects to consider for product-specific application (development and validation)

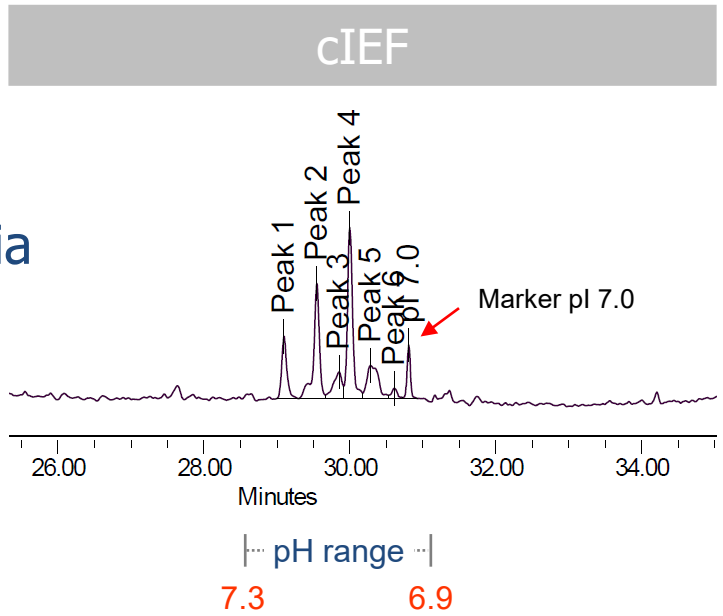
- *2.5.43 Size exclusion chromatography for recombinant therapeutic monoclonal antibodies:*
  - widely used methodology for determination of size variants (monomer, HMWS); quantitation of LMWS can be highly variable depending on the mAb analysed
  - SE-HPLC and SE-UPLC procedures, widely applicable to mAbs, given as examples
  - suitability of selected SEC procedures demonstrated by collaborative study

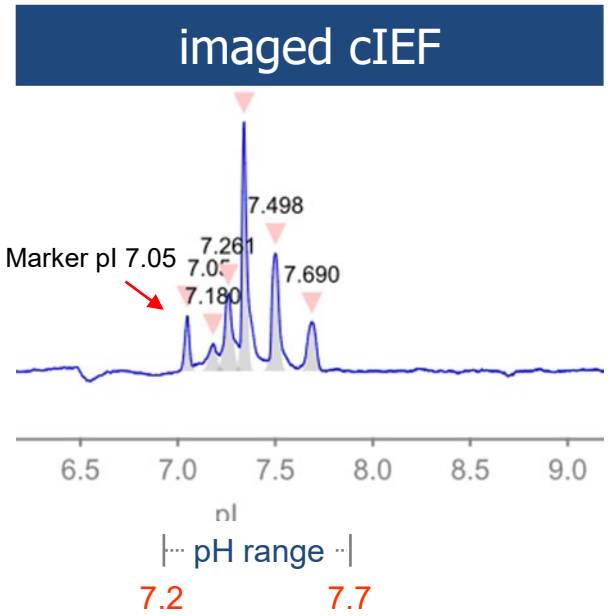
"Performance-based standards"

➡ well-defined analytical procedures and **tools to control analytical procedure performance** (including reference materials)
➡ facilitate evaluation of key quality attributes of mAbs (charge heterogeneity, size variants)

Performance-based Standards: Key Aspects

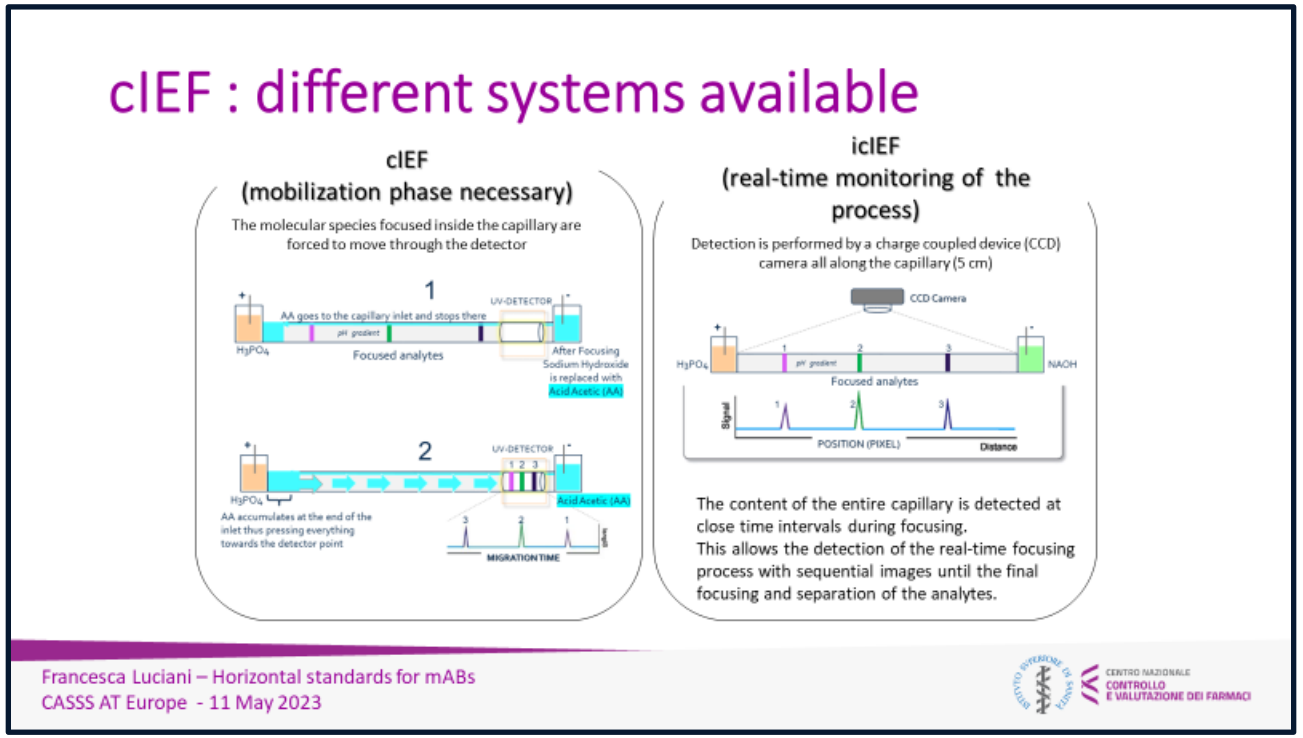
- Based on validated analytical procedures (mAb-specific), extended to a wide range of mAbs
- Evaluation of selected analytical procedures through **collaborative studies involving multiple laboratories**, with the aim to:
  - verify their applicability as suitable generic/multi-product procedures for mAb analysis
- Knowledge/data gathered on:
  - analytical procedure performance characteristics and associated criteria
  - system suitability, system performance, assay acceptance criteria
  - requirements for peak resolution and guidance on peak integration approaches
  - identification of appropriate controls and reference materials





Capillary IEF for MAbs: Draft General Chapter 2.5.44

- Provides a detailed description of two procedures base on traditional- and whole-column imaging cIEF systems
- The two sets of test conditions may be used as is or can be considered as starting conditions for the development of a cIEF or imaged cIEF procedure for a specific mAb.
- The **extent of analytical procedure optimisation** of the should be determined based on suitability for an individual mAb (case-by-case):
  - measured pI values are affected by the testing environment
  - shape of the pH gradient changes with the ampholytes used in the analysis → careful consideration should be given to selection of ampholytes
  - optimisation (e.g. mixing ampholytes) may be needed to reach the desired resolution



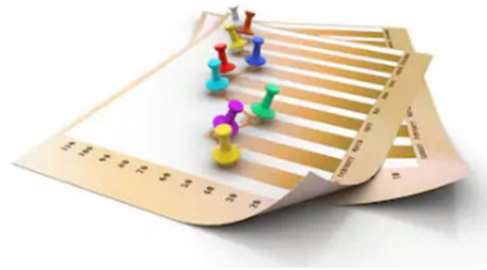
Validation needed for each mAb, to demonstrate suitability of the analytical procedure for the intended purpose

Draft General Chapter 2.5.44: Outline

- **Introduction and scope** (including reference to general chapter *Capillary electrophoresis (2.2.47)*)
- **Principle** [traditional- and whole-column imaging cIEF]
- **Procedure** (materials/test and reference solutions; operating conditions):
  - Procedure A (two-step cIEF)
  - Procedure B (imaged cIEF)

Common sections

- **System performance** - *monoclonal antibody for system performance CRS*
- **System suitability** - pI markers
- **Assay acceptance criteria** - in-house reference preparation
- **Data analysis**
  - Identification of peaks
- **Results**:
  - Identification test
  - Quantitative test



- **General recommendations**
  - **Points to consider in analytical procedure development** – recommended steps:
    - testing of the default conditions
    - selection of carrier ampholytes and pI markers
    - increasing resolution
    - enzymatic treatment
  - **Validation**:
    - Qualitative analysis (identification)
    - Quantitative analysis (purity, stability and production consistency)

Draft General Chapter 2.5.44: Current Status

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PHARMEUROPA TEXTS FOR COMMENT

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HOME EN MIHAELA BUDA

2.5.44. CAPILLARY ISOELECTRIC FOCUSING FOR RECOMBINANT THERAPEUTIC MONOCLONAL ANTIBODIES 7

INTRODUCTION AND SCOPE 8

This general chapter covers general capillary isoelectric focusing (cIEF) and imaged capillary isoelectric focusing (icIEF) procedures (*2.2.47*) that can be employed for qualitative and quantitative determination of charged variants (isoforms). Charge heterogeneity is an important quality attribute that can impact the safety, efficacy and stability of therapeutic monoclonal antibodies (mAbs). It results from post-translational modifications (e.g. glycation, sialylation and phosphorylation), degradation (e.g. deamidation, oxidation, fragmentation and pyroglutamate formation, amino acid deletions [e.g. C-terminal lysine clipping] and C-terminal amidation) and, more rarely, amino acid misincorporations. Charge heterogeneity arises during the upstream manufacturing process or during storage; it may be highly sensitive to process changes and thus has to be considered when addressing process consistency and comparability. 9

Unless otherwise specified in the individual monograph, cIEF and icIEF may be used to monitor the stability, quality and production consistency of mAbs, as well as to confirm their identity by discriminating between closely related molecules. Additional analytical procedures may be required for confirmation of identity, as appropriate. 10

The following analytical procedures are described for two-step cIEF (Procedure A) and icIEF (Procedure B), respectively. These procedures may be suitable as is or can be used as starting conditions for the development of analytical procedures for specific articles. They should be validated for the article to be examined, unless the specific procedure is described in an individual monograph. Validation should confirm that the analytical procedure is suitable for the intended use and purpose. Continued performance should be confirmed, for example using control samples or reference materials, to ensure that the analytical procedure continues to perform as expected. Further guidance is given in the section *General recommendations*. 11

Pharmeuropa 35.4

- Public deadline: 2023-12-31
- NPA deadline: 2024-02-29

PA/PH/Exp. MAB/T (21) 21 ANP

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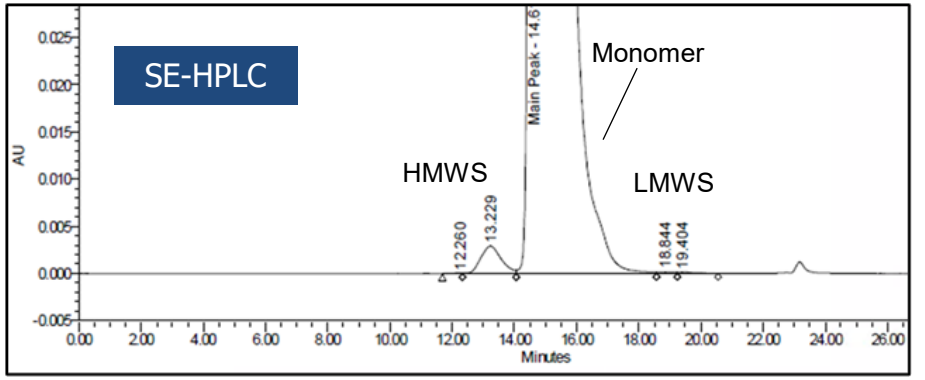
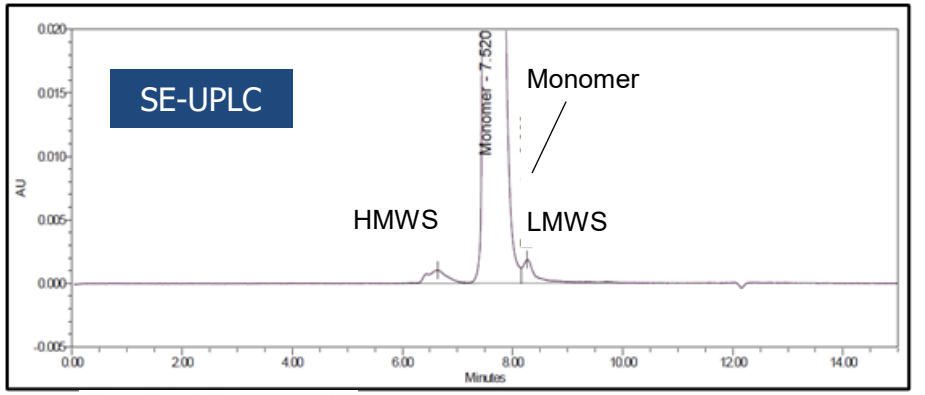
Development of Multi-Product SEC Procedures

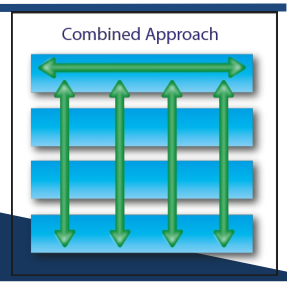
- **Draft general chapter** on *Size exclusion chromatography for recombinant therapeutic monoclonal antibodies (2.5.43)* – under elaboration:
  - describes ***platform analytical procedures*** for determination of high molecular weight species (SE-HPLC and SE-UPLC)
  - includes **SST requirements** (*monoclonal antibody for system suitability CRS*)
  - addresses aspects related to the **peak integration** mode and LMWS quantification, i.e. stating when fragments should be integrated and excluded, and when not
  - based on data gathered in the collaborative study, provides general considerations on the **performance of SEC procedures** (performance characteristics and associated criteria)
  - provides recommendations on **product-specific application** of the described SEC procedures, including **validation tests** required for a specific mAb





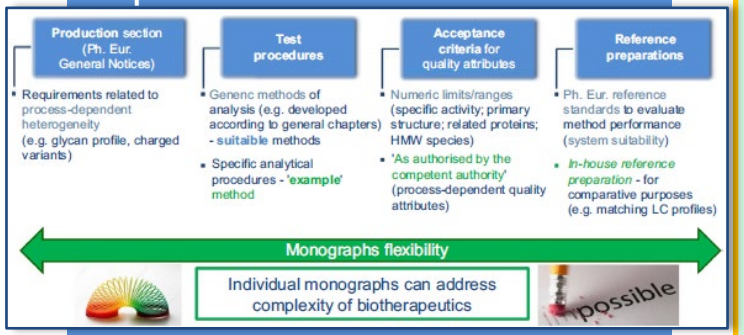
Ph. Eur. Standards for mAbs: Summary

Ph. Eur. Standards for Therapeutic Monoclonal Antibodies: Development Approaches



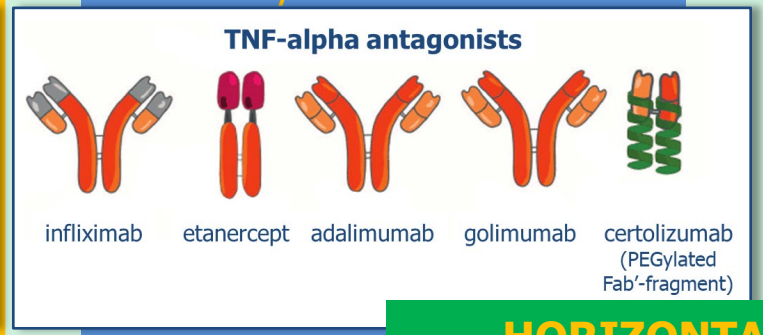
MONOGRAPHS*

- built-in *flexibility*
- *examples* of suitable procedures



PRODUCT CLASS - BASED STANDARDS

- product classes/sub-classes quality attributes
- *TNF-alpha neutralisation*



PERFORMANCE-BASED STANDARDS

- *platform* methodologies
- performance characteristics
- reference standards

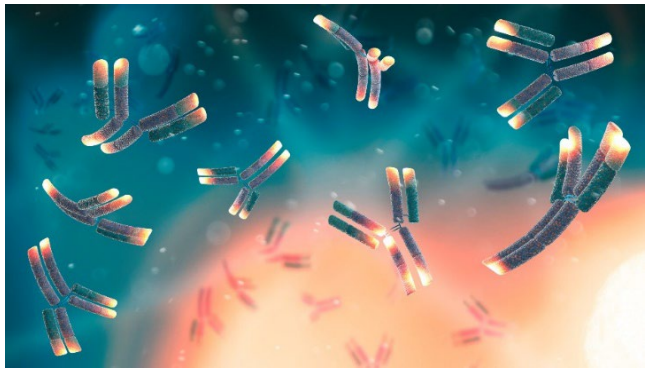
HORIZONTAL STANDARDS

PRODUCT KNOWLEDGE, CASE STUDIES, COLLABORATIVE TESTING

* Buda M., Kolaj-Robin O., Charton E. *Biotherapeutic Products in the European Pharmacopoeia: Have all Challenges Been Tackled?* Generics and Biosimilars Initiative Journal. 2022;11(1)
Buda M. *Development of Ph. Eur. standards for therapeutic monoclonal antibodies: infliximab case study.* Generics and Biosimilars Initiative Journal. 2022;11(3)

Horizontal Standard Development: Concluding Remarks

- Explore flexible concepts of standardisation in an increasingly evolving multi-product market
- Reflect key quality attributes and associated testing strategies
- Provide common expectations and general methodologies applicable to wide range/classes of mAbs
- Contribute to standardisation of therapeutic monoclonal antibodies through rationalisation of methodologies and common functionalities
- Help guide analytical procedure development, enabling flexibility for the adoption of newer analytical technologies throughout the product lifecycle and the use of alternative methods.



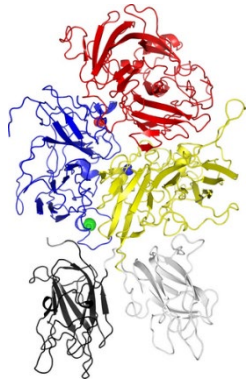
What (else) is in the Pipeline?

Human Coagulation Factor VIII (rDNA) Monographs

Human coagulation factor VIII (rDNA) (1643)

Covers both **active substance** and **medicinal product**

Applies to **full-length** and **B-domain-deleted** rFVIII



Human coagulation factor VIII (rDNA), **concentrated solution** (3105)

Human coagulation factor VIII (rDNA), *B-domain deleted*, **concentrated solution** (3107)

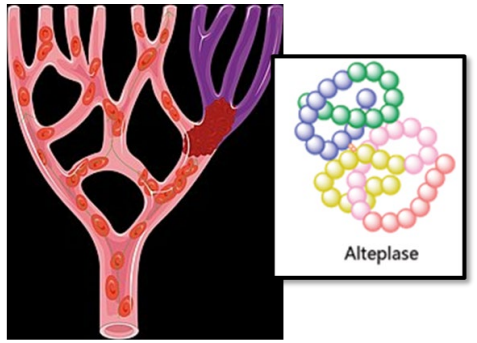
Human coagulation factor VIII (rDNA), **powder for injection (3106)**

Human coagulation factor VIII (rDNA), *B-domain deleted*, **powder for injection** (3108)

Alteplase Monographs

Alteplase for injection (1170)

Covers both **active substance** and **medicinal product**



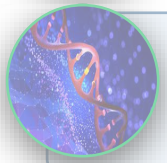
Blood flow obstructed by coagulated blood that could potentially be reversed with alteplase.

Revision and monograph re-development

Alteplase **concentrated solution** (3197)

Alteplase **injection** (1170)

Gene Therapy Medicinal Products - New Approach



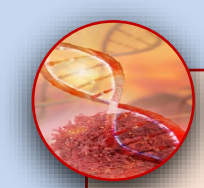
General chapter
Gene transfer medicinal products for human use (5.14)

Pharmeuropa 34.3

General monograph
Gene therapy medicinal products for human use (3186)

General chapter
Raw materials of biological origin for the production of cell-based and gene therapy medicinal products (5.2.12)

Pharmeuropa 35.2



General chapter
Additional information on gene therapy medicinal products for human use (5.34)

Pharmeuropa 34.3

Cell Therapy Products WP: Latest Developments

Text	Status	Scope	Publication Ph. Eur.
2.6.39 Microbiological examination of human tissues	New	Recommendations on the selection of analytical methods for the assessment of the microbiological quality of human tissues	11th Edition (July 2022)
2.7.28 Colony-forming cell assay for human haematopoeitic progenitor cells	Revised	Inclusion of automated technologies Improvement of standardisation Description of validation	Supplement 11.3 (July 2023)
2.7.29 Nucleated cell count and viability	Revised		Supplement 11.3 (July 2023)
2.6.27 Microbiological examination of cell-based preparations	Revised	Harmonisation of the incubation time with *2.6.1. Sterility*	Supplement 11.5 (Jan. 2024)

Cell Therapy Products: Draft Texts in Preparation

Need for a general text covering quality of cell-based preparations

Cell-based preparations (5.32)

General requirements

- Production
  - → Source cells
  - → Preparation and processing of cells
  - → Substances used in production
  - → In-process controls
- Final lot
  - → Identification
  - → Tests
  - → Assays

Specific sections

- Mesenchymal stem cells
- Haematopoietic stem cells
- Limbal stem cells
- Chondrocytes

Flow cytometry (2.7.24)

- Principles of the method
- Technical considerations
- Sample preparation
- Data acquisition and analysis
- Examples of application
- System qualification
- Assay validation

Pharmeuropa 35.4

Public deadline: 2023-12-31
NPA deadline: 2024-02-29

General update of the chapter to reflect techniques currently in use

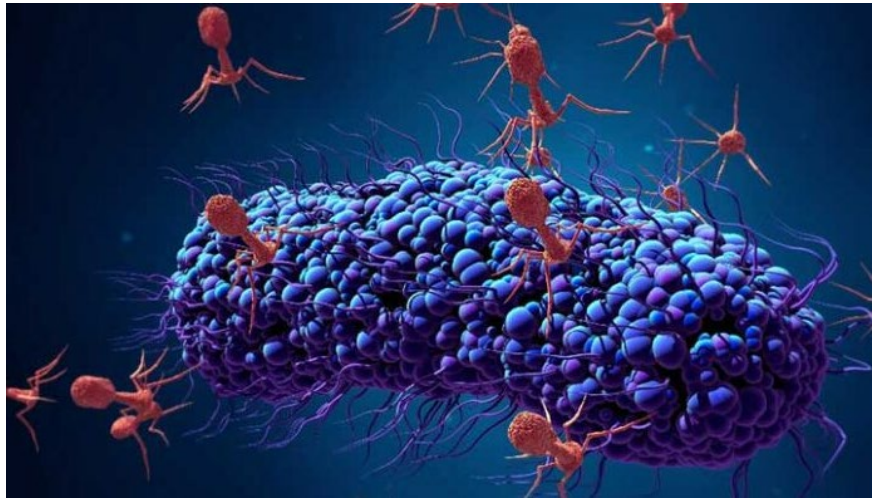
Chapter aimed to be general enough to encompass both:

- products that are already on the market
- new products to come

New General Chapter on Bacteriophages

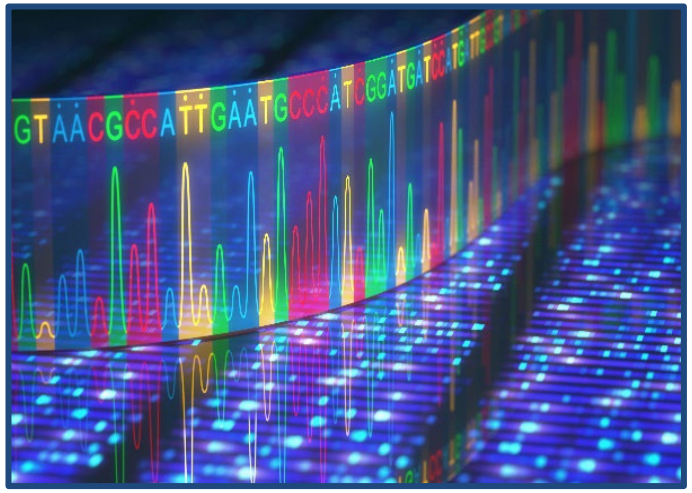
Phage therapy active substances and medicinal products for human and veterinary use (chapter 5.31)

- Phage therapy: alternative to antibiotic treatment
- Text under elaboration by BACT Working Party
- Publication in Pharmeuropa 35.2 (Apr-Jun 2023)



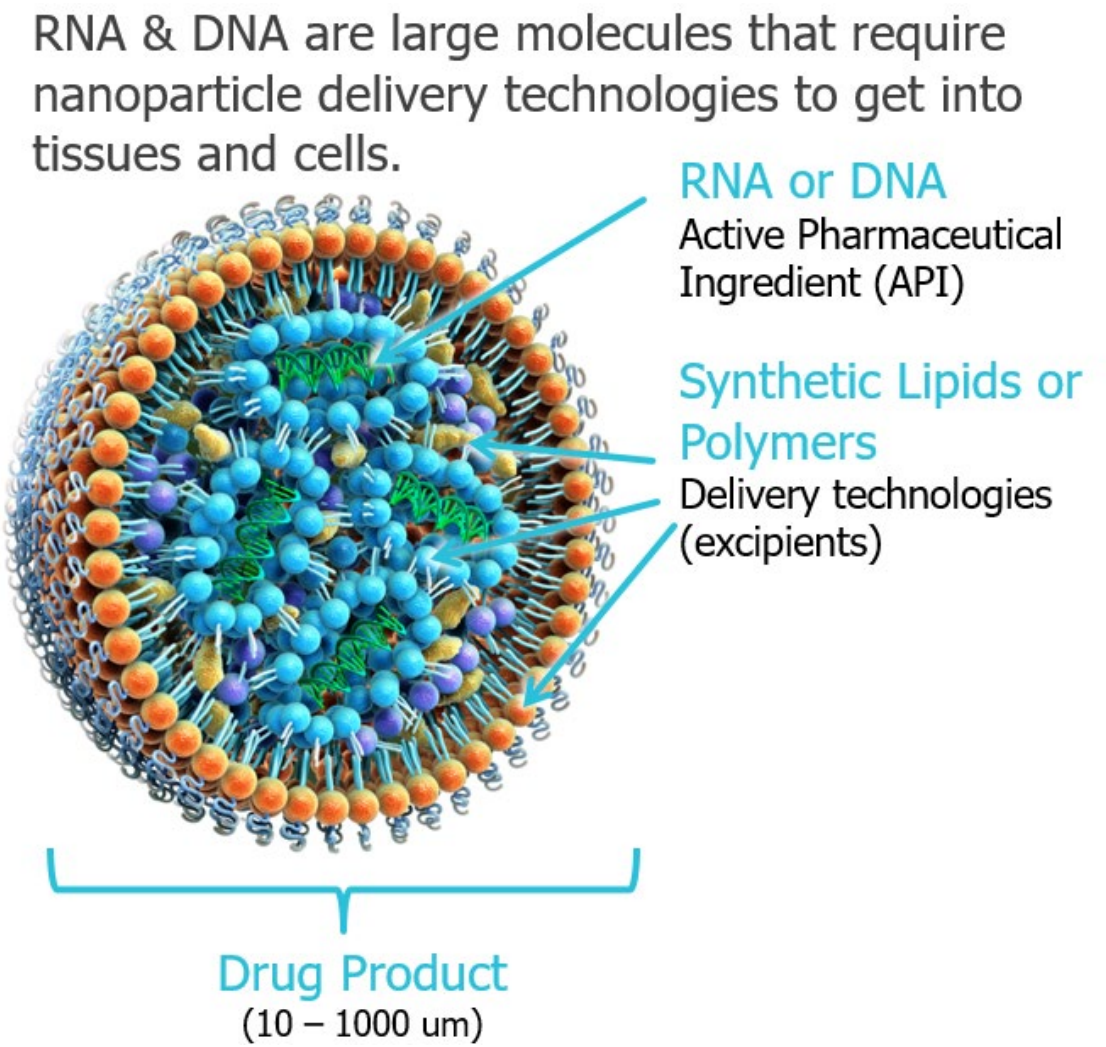
New General Chapter on HTS

High Throughput Sequencing for the detection of extraneous agents in biological products (2.6.41)



- Non-binding general chapter
- Proposed content: description of the technology, **guidelines for method validation**
- Publication in Pharmeuropa (tentative): 2024

Quality of mRNA Vaccines and Their Components



Ph. Eur. Commission kicked off elaboration of three general texts on mRNA vaccines and components, assigned to the mRNAVAC WP [175th session, March 2023]

- ***mRNA Vaccines for human use (5.36)*** - the mRNA packaged in lipid nanoparticles, i.e. mRNA-LNP medicinal product
- ***mRNA Substances for the production of mRNA vaccines for human use (5.39)*** - the mRNA active substances in the manufacture of mRNA vaccines
- ***DNA Template for the preparation of mRNA transcript (5.40)*** - the starting material for the preparation of the mRNA component

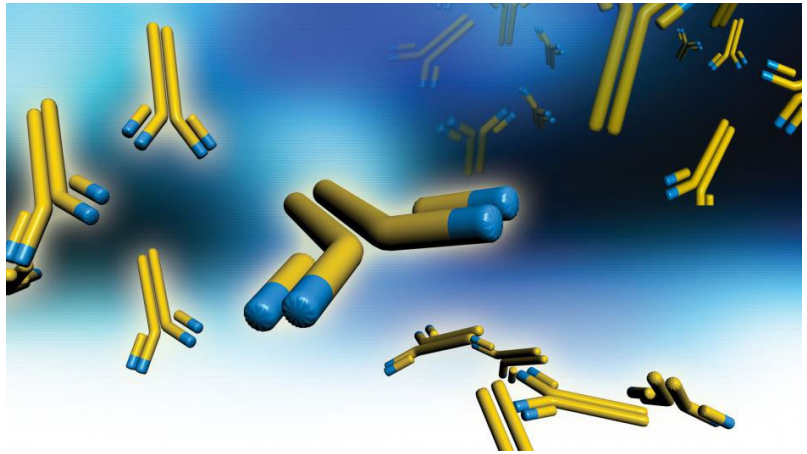
➔ Publication in Pharmeuropa (tentative): April 2024

Acknowledgements

All Experts of the MAB Working Party

⁂

Jaana Vesterinen (Chair MAB WP)
Francesca Luciani



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