

The role of European Pharmacopoeia monographs in setting quality standards for biotherapeutic products

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Place of the Ph. Eur. within the EU regulatory network

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

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Structure of the Ph. Eur.

General notices (essential; applicable to all texts)		
General chapters	Individual monographs	General monographs
➤ analytical methods; ➤ provide methods where there is no monograph; ➤ equipment requirements; ➤ editorial convenience; ➤ mandatory <u>when referred to</u> in a monograph	➤ based on approved specification(s) backed up by batch data ➤ specifications for drug substances or finished products ➤ analytical procedures and acceptance criteria to demonstrate that the substance meets required quality standards	➤ classes of substances or products, dosage forms; ➤ mandatory for all the products within the scope of definition section

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Structure of Ph. Eur.

General notices (essential; applicable to all texts)		
General chapters	Individual monographs	General monographs
 Reference Standards • Chemical Reference Substances (CRSs) • Herbal Reference Substances (HRSs) • Biological Reference Preparations (BRPs) Established specifically for use in monographs or general chapters, as prescribed in the methods given		

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Elaboration procedures: the multi-source approach

- The so called «P1» Procedure
- ✓ Collaboration with more than one manufacturer
- ✓ Classical composition of Groups of Experts (regulatory authorities, OMCLs, industry, academia)
- ✓ The approach traditionally followed for biologicals until 2008

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Feedback received

Elaboration procedure



“Elaborating a monograph based on several products leads the Ph. Eur. to establish a standard of the lowest quality, without taking into consideration the criticality of quality attributes and pre-clinical/clinical evidence”

- **Ph. Eur. monographs are based on specifications approved by licensing authorities**
- **Monographs in a multi-manufacturer situation lead to more robust standards, because they provide a venue for the elaboration of improved consensus procedures between manufacturers that allow the comparison of different products - examples are the insulins and somatropin**

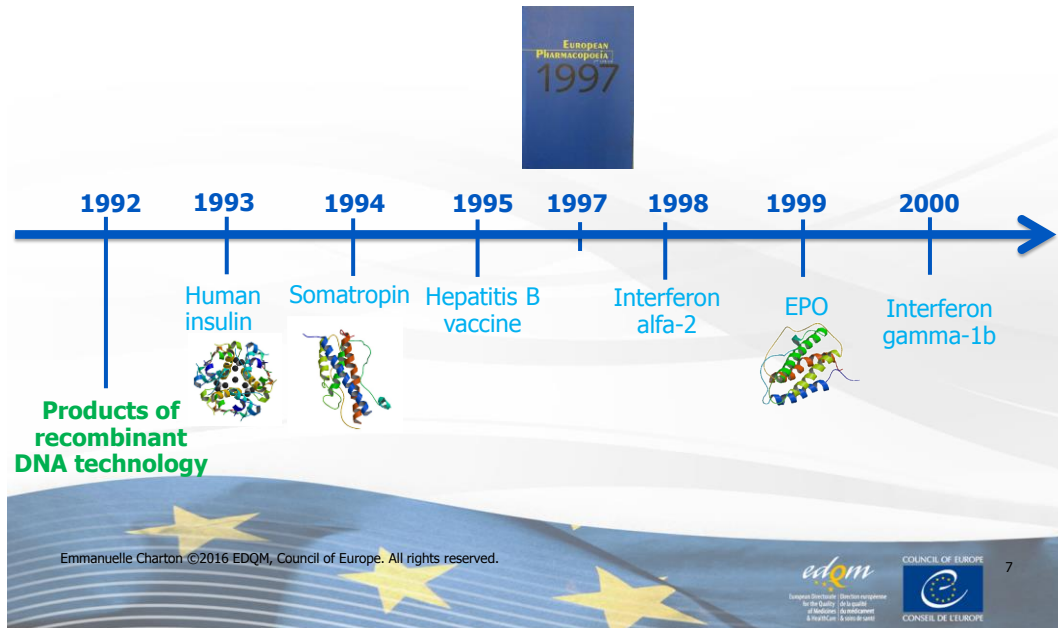
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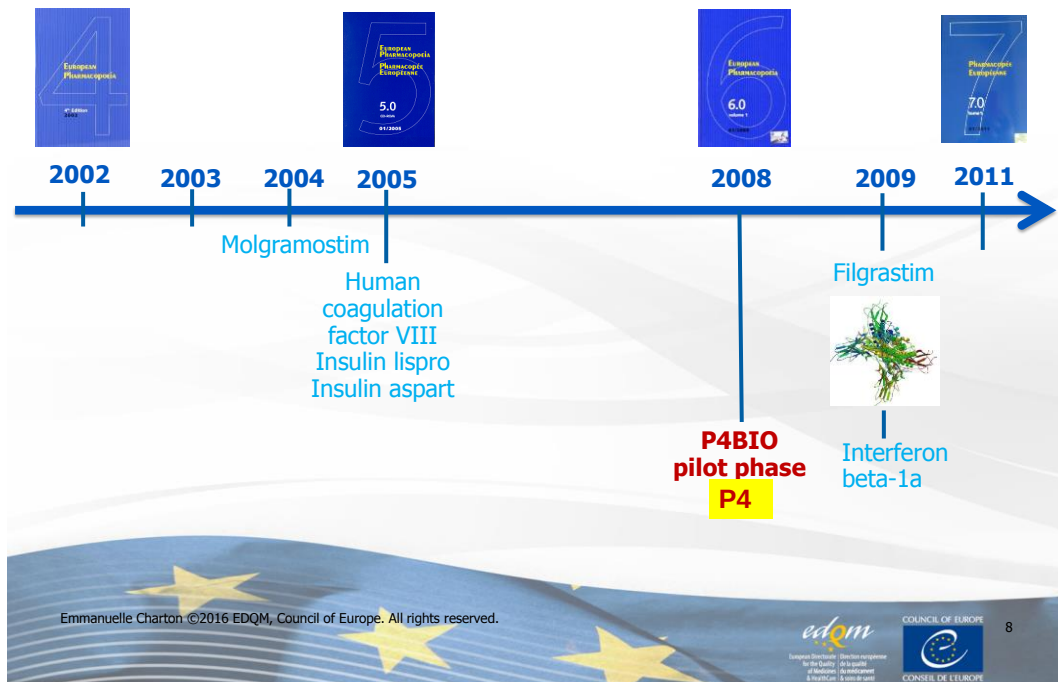
European Pharmacopoeia and Biologicals

rDNA products in the Ph. Eur. (1992-2000)



European Pharmacopoeia and Biologicals

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



Elaboration procedures: the single source approach:

The so called «P4Bio» Procedure (Pilot phase)

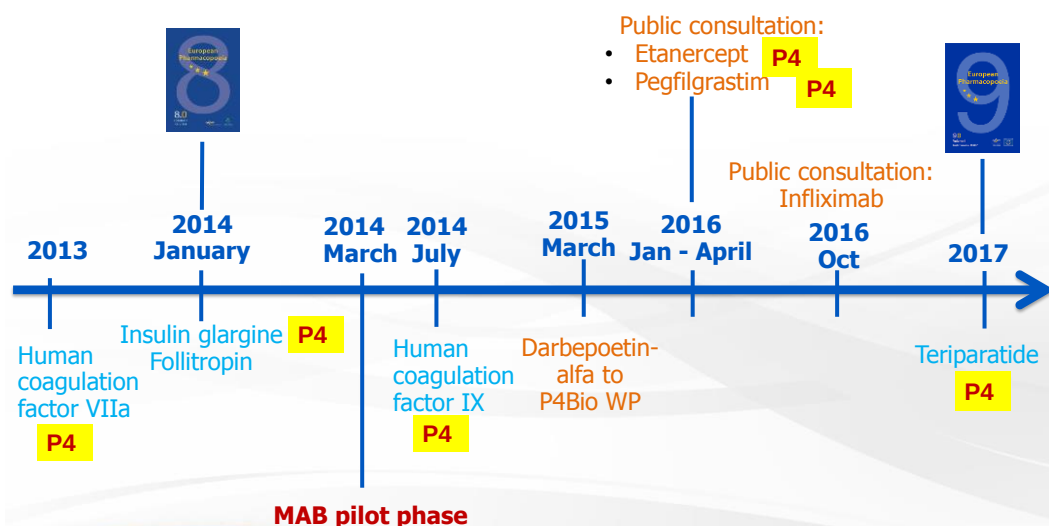
- ✓ Collaboration with innovator while substance under patent protection
- ✓ Monograph in place at patent expiry
- ✓ Specific Group of experts composed only of representatives of national pharmacopoeia secretariats or regulatory authorities

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European Pharmacopoeia and Biologicals rDNA products in the Ph. Eur. (2013-2017)



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Monographs for Biotechnological products: the challenges

Complexity of biologicals



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Monographs and complexity of biologicals



“Due to their inherent complexity and interdependence with their manufacturing processes, the quality and consistency of biologicals can only be defined and ensured through individual and comprehensive process- and product-specific control strategies.”

➤ We fully agree!

- **Biologicals** consist of **complex mixtures** of closely related variants (*i.e.* naturally occurring heterogeneity in glycosylation or other post-translationally modified forms)
- **Manufacturing process is complex**; changes may lead to distinct quality attributes (*e.g.* glycosylation, charge heterogeneity, chemical modification)

**Public standard setting:
complex and challenging exercise**

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Monograph flexibility



How to transfer flexibility into a public standard?

Ph. Eur. biotherapeutic monographs are:

- adapted to **biomolecule complexity**, **potential diversity** in **biosimilar compounds**, and different **manufacturing processes**;
- **flexible**, while being comprehensive and **sufficiently prescriptive**.



PRODUCTION section of the monograph adapted to:

- ✓ reflect **process-dependent heterogeneity** (e.g. glycosylation);
- ✓ include requirements for **consistency of production**.

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Monograph flexibility



Example: Human coagulation factor IX (rDNA) concentrated solution (2522)

Glycan analysis included in the **PRODUCTION** section:

- Glycan profile depends on the **manufacturing process**
- The test prescribes the use of an **in-house reference preparation** (available only to the manufacturer)
- **Generic method of analysis** (Ph. Eur. *Glycan analysis of glycoproteins* (2.2.59); specific **analytical procedure** given as **example**)
- **Acceptance criteria** to be set in **agreement with the competent authority**

Glycan analysis approach:

- ✓ Means of improving **monograph flexibility** under **well-defined conditions**
- ✓ **Compatible** with development of **biosimilars**

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NOT RELEVANT

Complexity of biologicals and legislation

“The EU legislation itself (and even the EDQM certification procedure) excluded biological products from its scope because of the complexity of the molecules”

- *The EU Commission decided that marketing authorisation holders had to have access to complete information about the production of a biological product before they could take full responsibility for the medicinal product*

*“The MAH/applicant for a biological medicinal product could therefore not comply with the requirement to ‘take responsibility for the medicinal product’ without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and should therefore not be allowed for biological active”
CHMP/QWP/227/02.”*

- *This is not comparable to the use of a monograph.*

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Monographs for Biotherapeutic products: the challenges

Complexity of biologicals

Diversity of quality attributes/
analytical methods

Choice of tests

Monograph specifications



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Specifications

➤ How to define the information needed for a public standard?

- **The basis for monograph elaboration** is the **data package** provided by the manufacturer.
- However, the manufacturer's specifications may not be appropriate for a public standard:
 - as part of the **control strategy**, specific **tests are omitted in routine testing** and, therefore, not anymore included in the data package;
 - specific test are performed as **in-process controls**;
 - based on **process capability** of removing a specific impurity to acceptably low levels, routine testing for that impurity may not be required;
- ➔ **specifications** do not cover all quality attributes expected – **not sufficient for a monograph**.

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Analytical methods

➤ Experimental verification

- **Robustness** and **transferability** of the methods included in the data package
- **Method performance**
 - methods are sometimes **out-of-date** or **not robust enough** (e.g. Insulin glargine)
- **Complementary** methods and/or **alternative** (modern) techniques

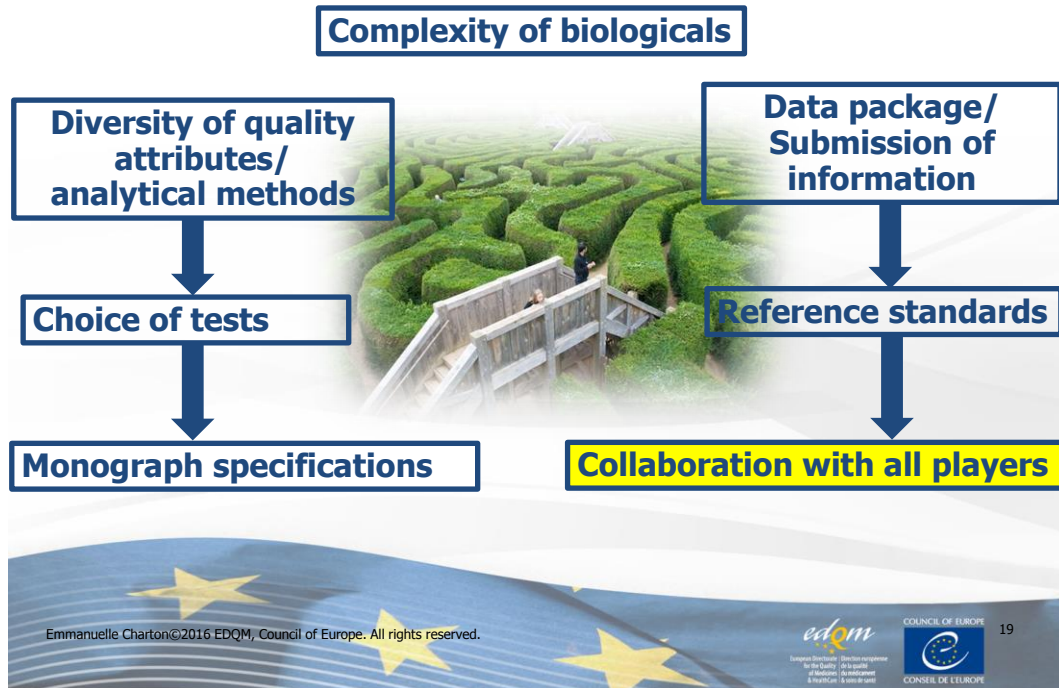
- ✓ Specific instructions added (e.g. additional SST parameters, improved peak resolution)
- ✓ Method improvement (e.g. resolution solution for SST)
- ✓ Reference to existing **pharmacopoeial methods/general chapters** or to **monographs on closely related substances** (e.g. SEC human insulin used for insulin glargine)
- ✓ Refine **technical requirements** for certain tests (e.g. peptide mapping by LC-MS to confirm marker peaks in complex peptide maps)
- Validation needed for implementation of alternative methods (e.g. UHPLC) (**limited resources**)

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Monographs for Biotherapeutic products: the challenges



Collaboration with all players

- **Basis for monograph drafting is the data package** submitted by the manufacturer
- **Close collaboration and exchanges** with the manufacturer - essential in order to find the best path forward for public standard setting

Reference standards

➤ Biological Reference Preparations (BRPs)

- **WHO International Standards** already developed for some of the new generation biologicals and may serve as basis for **setting/calibration of Ph. Eur. BRPs**.
- Simultaneous establishment of WHO International Standard and elaboration of monograph (*e.g.* Etanercept).
- **EDQM/WHO joint efforts** to ensure compatibility of strategies between the two organisations

➤ Chemical Reference standards (CRSs)

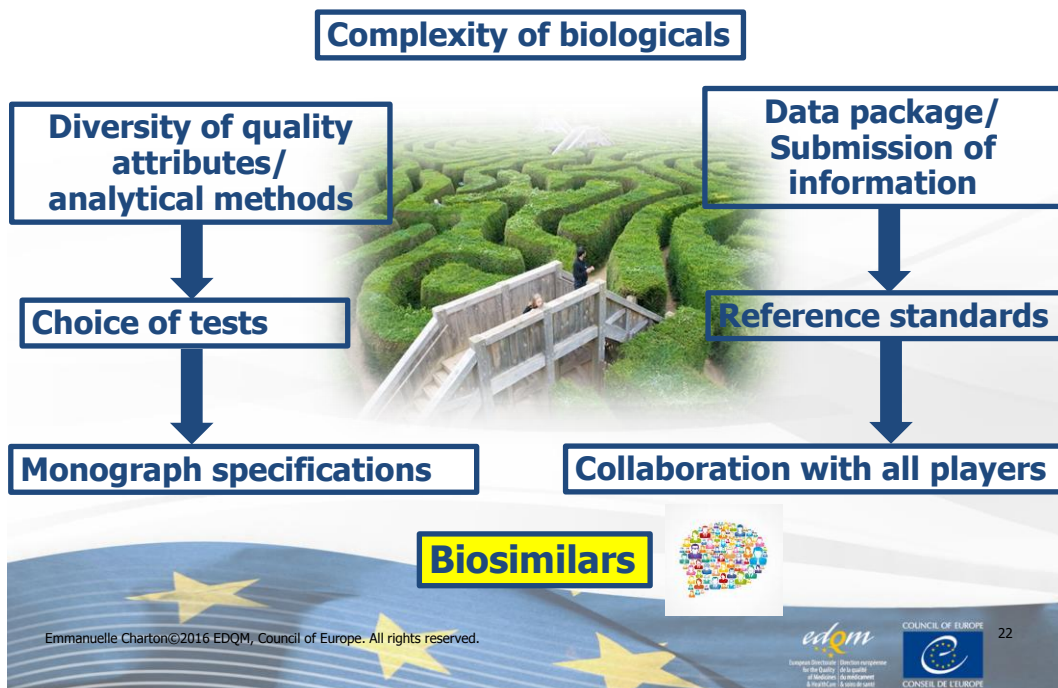
- Candidate reference materials to be provided by manufacturer

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Monographs for Biotherapeutic products: the challenges





Feedback received

Biosimilar legislation



"Some biologicals have been rejected by licensing authorities as being acceptable as biosimilars although they met all the requirements of monographs"

- A comparison of the biosimilar to a publicly available standard, e.g. a pharmacopoeial monograph, is not sufficient for the purposes of comparability (EMA/CHMP/BWP/247713/2012)
- The role of the monograph is to set quality requirements



"Ph. Eur. reference preparations used in individual monographs are inappropriate since they do not reflect the quality of the approved innovator product"

- Ph. Eur. reference standards are intended to be used within the scope of Ph. Eur. monographs (Ph. Eur. Chapter 5.12)
- **Ph. Eur. Reference standards are not intended to be used as reference (comparator) products in the context of applications for biosimilars!**

Should we deny public standards just because they are misused?

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Biosimilars and Ph. Eur.

European
Pharmacopoeia



Biosimilarity/
Comparability



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

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Monographs and registration process

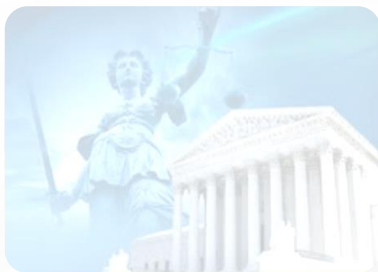


“Individual monographs may exclude products from the market if the requirements of the monographs are not met.”

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

Biosimilars and Ph. Eur. (cont'd)

European
Pharmacopoeia



Biosimilarity/
Comparability



Biosimilars: a class of products that was established to avoid unnecessary pre-clinical and clinical studies. The regulatory pathway to be followed is given in appropriate **guidelines**. **Biosimilars** are developed by companies and evaluated by licensing **authorities**, whether or not a compendial standard exists.



Feedback received

Monographs and registration process



FALSE

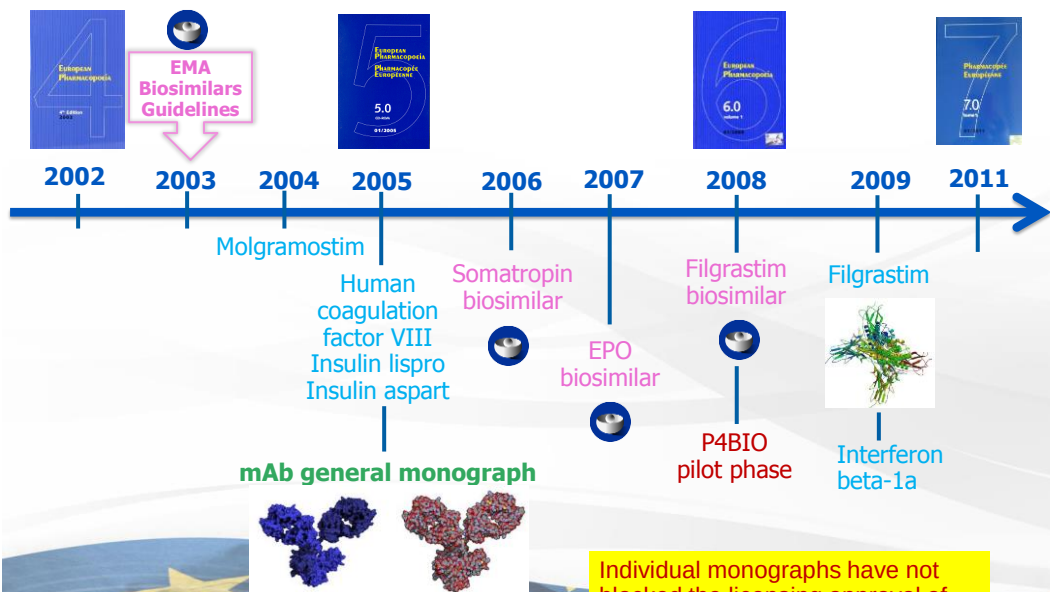
"Individual monographs delay the registration process of biologicals and biosimilar products."

Biological products: The Ph. Eur. is elaborated based on registered products: registration takes place before the monograph is elaborated and therefore the monograph cannot delay product registration

Biosimilars: 18 of the 21 biosimilar products approved in Europe are covered by a monograph: We are not aware that the monographs delayed registration of these biosimilar products

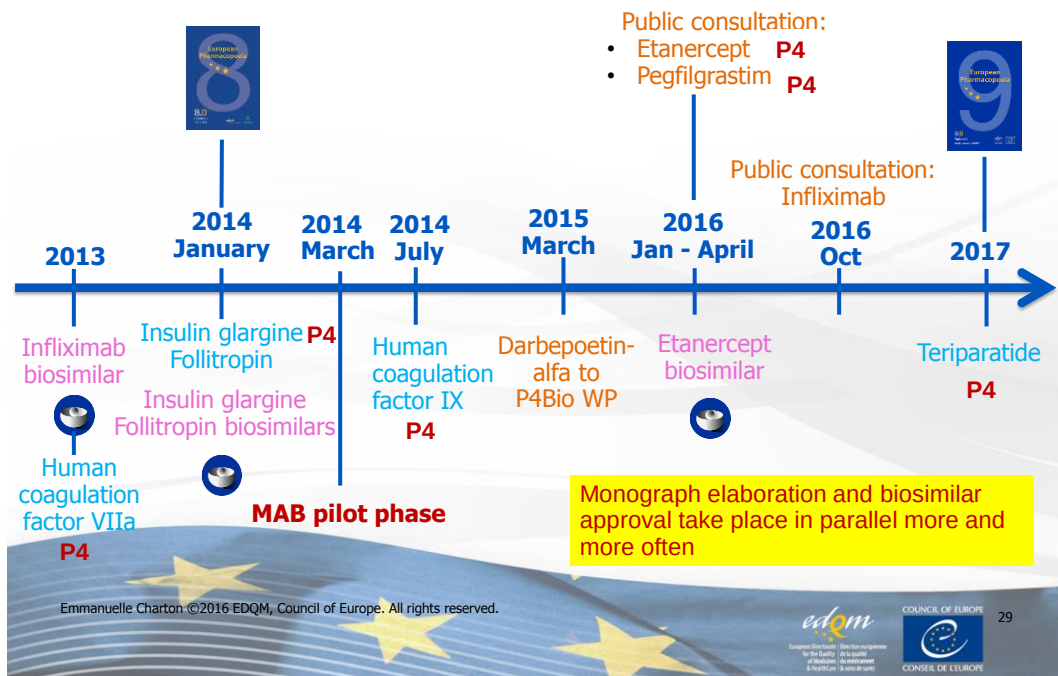
European Pharmacopoeia and Biologicals

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



European Pharmacopoeia and Biologicals

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



Biosimilars and Ph. Eur.

- Ph. Eur. is referred to in EU directives and guidelines
 - Directive 2001/83/EC
 - Guideline on Similar Biological Medicinal Products (CHMP/437/04 Rev 1)
- Biosimilars are **not** referred to in Ph. Eur.
 - The quality of a biotherapeutic product can be defined regardless of the regulatory pathway used for its registration

Biosimilars and Ph. Eur. (cont'd)

European Pharmacopoeia



Biosimilarity/ Comparability



These are complementary instruments that have different purposes but the same goal: to ensure the quality of medicinal products.

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Challenges

- It has proven to be possible to overcome the challenges linked with the complexity of the molecule
- Successful monograph elaboration depends on the willingness of manufacturers to provide the necessary information and candidate materials
- The latter challenge has proven to be more difficult to overcome since the advent of biosimilars, probably due to misunderstandings about the role of Ph. Eur. monographs in European legislation regarding registration of biotherapeutic products

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Challenges

What are the **real** challenges?

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Conclusion

- ✓ Individual monographs play a major role in ensuring a standardised level of quality for medicinal products, thus contributing to patient safety
- ✓ The Ph. Eur. will continue to fulfil its mission as regards setting quality standards for biologicals, the question is **HOW** this role can be played
- ✓ From a quality and standardisation standpoint, biotherapeutic substances should not be viewed differently than any other substances for which monographs exist

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Thank you for your attention!



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The Ph. Eur. Strategy for MABs – Outcome of the Infliximab Pilot Phase

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Outline

- ❑ **Ph. Eur. and mAbs: Background**
- ❑ **MAB Pilot Phase:**
 - **'Bottom-up' approach**
 - **Infliximab case study:** collaborative study, outcome
 - **Elaboration of the monograph for *Infliximab concentrated solution*:** status update
 - **Horizontal approaches:** prospective work
- ❑ **Conclusion and steps forward**

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Monoclonal Antibodies in the Ph. Eur. - background -

MAB Working Party (representatives from licensing authorities, OMCLs and industry)

2002



2005

2008



2011

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

Ph. Eur. Supplement 5.2; 01/2005

Major revision of the mAbs general monograph 2031:

- **visible particles;**
- add terminology used in the draft EMEA "Guideline on production and quality control of monoclonal antibodies and related substances" (3AB4A).

Ph. Eur. Supplement 7.3; 07/2011

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Monoclonal Antibodies in the Ph. Eur. - discussions with stakeholders -

EDQM Workshop on 'The Future of Monographs in the Field of Biologicals' (2011)

2011

- New **biotherapeutics** need to be **adequately covered in the Ph. Eur.**
- **Product-(sub)class** and **product-specific monographs** to be considered.

MAB WP

2013



2014

- Discussions on a **strategy for mAbs quality standards** within the Ph. Eur. framework.

➔ **Need for additional Ph. Eur. standards in the field of mAbs**

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Monoclonal Antibodies in the Ph. Eur. - actions taken-

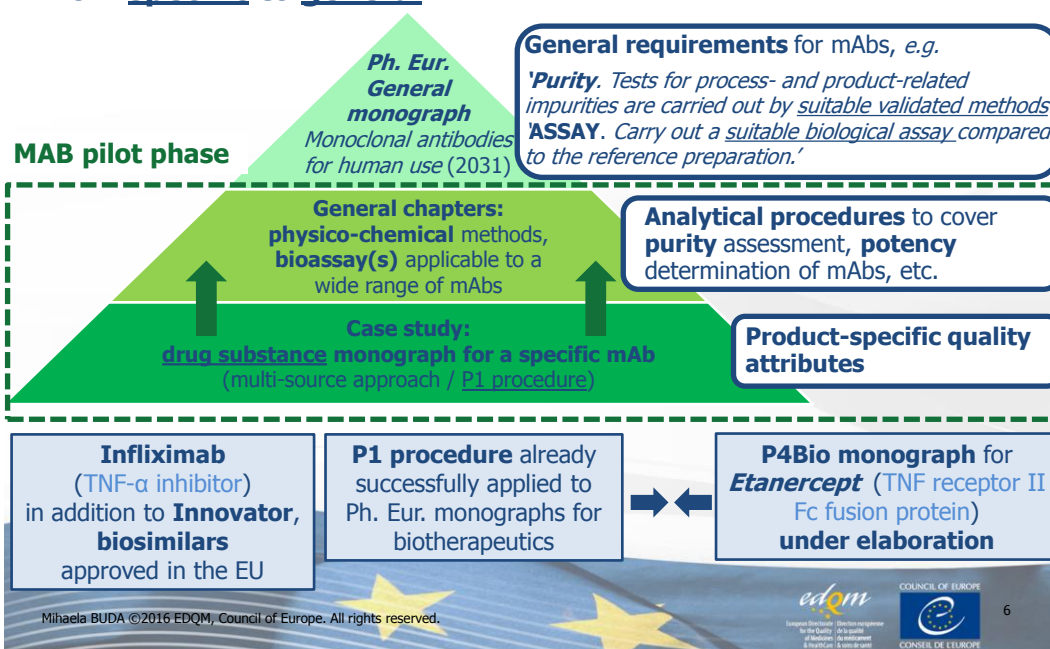
MAB pilot phase:

- Endorsed by the Ph. Eur. Commission in March 2014
- **AIM:** elaboration of **general methods for the analysis of mAbs** and **product-specific monographs** using the **multi-source approach** (P1 procedure).
- **HOW:** use a specific mAb as **concrete example** to address the feasibility of the approach.

Groundwork: **infliximab case study**

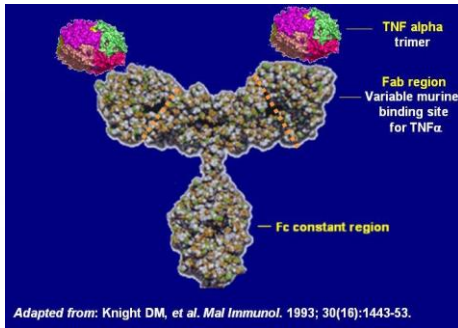
MAB Pilot Phase: a 'Bottom-up' Approach

From specific to general:



Infliximab

- A chimeric human-murine **IgG1 monoclonal antibody against tumour necrosis factor alpha** (TNF- α) used to treat autoimmune diseases
- Produced in mammalian cells by **recombinant DNA technology**



- ❑ Homodimer H_2L_2 (1328 aa)
 - **32 Cys**: 16 S-S bridges
- ❑ **Light chains** (LC): 214 aa $\times$ 2
- ❑ **Heavy chains** (HC): 450 aa $\times$ 2
 - **N-glycosylation** (one site in the -CH2- domain)
 - **Several glycoforms**
- ❑ Main structure **calculated mass**
 - $C_{6428}H_{9912}N_{1694}O_{1987}S_{46}$ (non-glycosylated)

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Infliximab Case Study - design of the study-

Collaborative study undertaken by the MAB WP to explore **feasibility of establishing a monograph** for *Infliximab*:

- Verify **robustness, transferability** and **suitability** of the **test methods** applied to infliximab for use as pharmacopoeial methods.
- Decide on the **choice of tests** and way(s) to express acceptance criteria in the monograph.

Experimental verification of **physico-chemical** and **bioassay test methods** used for infliximab

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

Six batches (from drug substance and drug products approved in EU) and **in-house reference standard** tested

Participating laboratories: **Official Medicines Control Laboratories (4)** and **EDQM Laboratory**

Complementary and/or **alternative** analytical methods investigated

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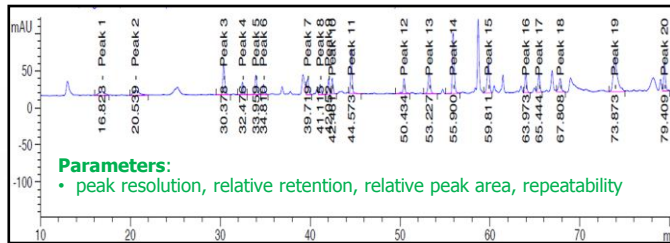


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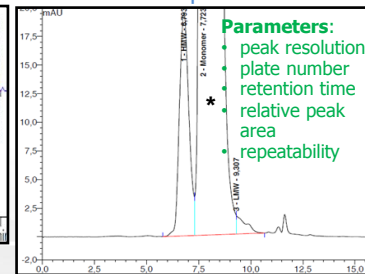
Infliximab Collaborative Study: Results (1)

- physico-chemical testing -

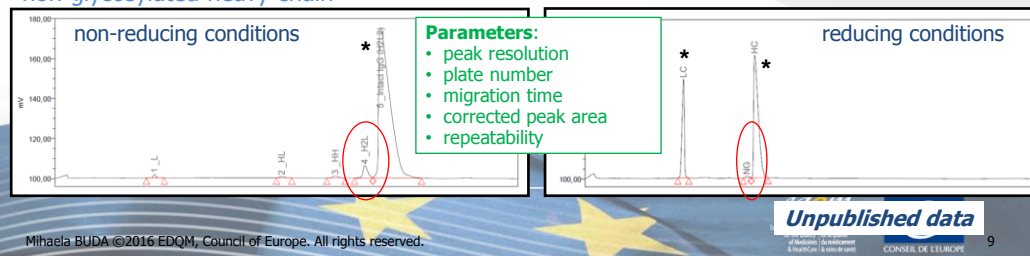
A) Peptide mapping (ID): 20 peptide fragments



B) SEC (size): monomer, HMW and LMW species



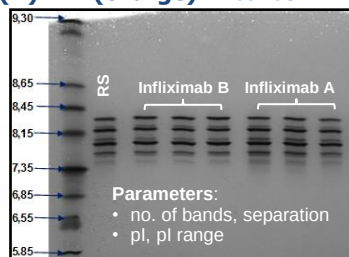
C) Capillary Electrophoresis SDS (size): intact IgG; heavy chain (HC), light chain (LC) and non-glycosylated heavy chain



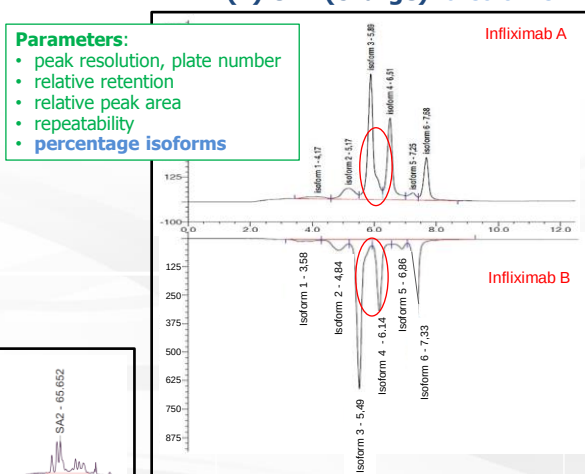
Infliximab Collaborative Study: Results (2)

- physico-chemical testing -

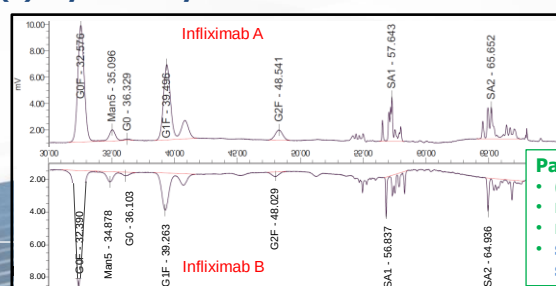
(D) IEF (charge): 7 bands



(E) CEX (charge): 6 isoforms



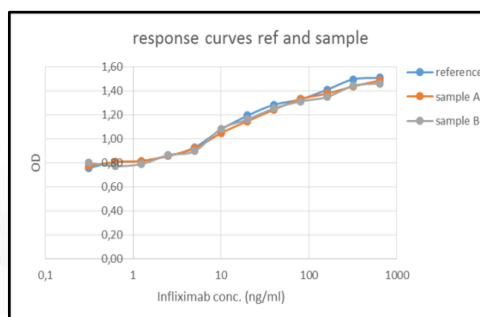
(F) Glycan analysis



Infliximab Collaborative Study: Results

- bioassay -

- ***In vitro* cell-based potency assay**, based on the ability of infliximab to **block TNF-alpha-induced inhibition** of murine fibrosarcoma **WEHI-164 cell proliferation**
- **Cell growth** assessed through a tetrazolium-based **colorimetric assay**



Unpublished data

- Four-parameter logistic curve model (system suitability parameters according to Ph. Eur. General Chapter *Statistical analysis of results of biological assays* (5.3))



Infliximab Collaborative Study

- conclusion -

The collaborative study generated **extensive experimental data in support of the elaboration of a monograph for *Infliximab***:

- ✓ proposed physico-chemical methods and bioassay carried out with **no major problems**; they are **transferable, robust** and **suitable** for a monograph;
- ✓ specific **analytical procedures** and **acceptance criteria** found to be **widely applicable**;
- ✓ **critical parameters** and possible sources of variation **identified**;
- ✓ level of details to be given in the monograph to be defined based on laboratory experiences;
- ✓ **complex analytical procedures** and **mAbs** can be **standardised**.



No obstacles identified so far in the elaboration of a individual monograph for a mAb

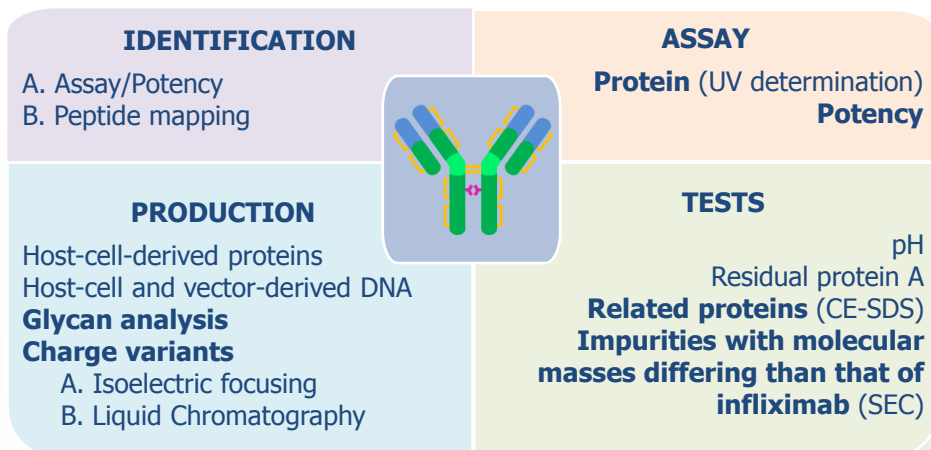
Infliximab Collaborative Study - outcome -

Based on the outcome of an extensive laboratory work/conclusive experimental data generated in the collaborative study, Ph. Eur. MAB WP drafted a monograph proposal for:

Infliximab concentrated solution (2928)

- Special attention given to:
 - choice of **tests** and **acceptance criteria**;
 - **complexity** of analytical procedures;
 - how to best reflect the link between **product quality** and **manufacturing process**;
 - **process-dependent heterogeneity** (*i.e.* glycosylation, charge variants) and **consistency of production**;
- Based on principles outlined in the ***Guide for the elaboration of monographs on synthetic peptides and recombinant DNA proteins.***

Infliximab Concentrated Solution - draft monograph -



Reference standards:

Infliximab Chemical Reference Standard (CRS)
Infliximab Biological Reference Preparation (BRP)
Infliximab in-house reference preparation

Infliximab Concentrated Solution ⁽¹⁾ - tests and acceptance criteria -

TESTS	Analytical procedure	System suitability	Acceptance criteria
Related proteins	CE-SDS (Ph. Eur. 2.2.47) • reducing • non-reducing conditions Detailed analytical procedure <i>Reference solution:</i> infliximab CRS	– RS electropherogram ' qualitatively similar ' with electropherogram in the CRS leaflet.	– electropherogram obtained with test solution consistent with RS electropherograms. Numerical limits: Σpeaks other than HC and LC; Σpeaks other than principal peak.
Impurities with different MW	SEC (Ph. Eur. 2.2.30) Detailed analytical procedure <i>Reference solution:</i> infliximab CRS	– RS chromatogram ' qualitatively similar ' with chromatogram in the CRS leaflet; – peak resolution (molecular mass markers).	– chromatogram obtained with test solution consistent with RS chromatogram. Numerical limit: Σpeaks other than the monomer.

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Infliximab Concentrated Solution ⁽²⁾ - tests and acceptance criteria -

PRODUCTION

Host-cell-derived proteins
 Host-cell and vector-derived DNA
Glycan analysis
Charge variants
 A. Isoelectric focusing
 B. Liquid Chromatography

- ☐ Due to **complexity** and the **link between DS quality and manufacturing process**, tests that measure **process dependent heterogeneity** are mainly seen as a **demonstration of production consistency**.
- ☐ These **tests cannot be included in the TESTS section** of the monograph as a direct transfer of the lot-release specifications set.

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Infliximab Concentrated Solution ⁽³⁾ - tests and acceptance criteria -

PROD.	Analytical procedure	System suitability	Acceptance criteria
Glycan analysis	Ph. Eur. 2.2.59: - Release of glycans - Labelling of released glycans (if needed) - LC analysis (suitable technique) Detailed analytical procedure given as example Reference solution (a): infiximab CRS Reference solution (b): in-house RS	Reference solution (a): - RS chromatogram 'qualitatively similar' with chromatogram in the CRS leaflet; 7 peaks visible.	Comparative procedure (reference solution (b)) - test solution chromatogram consistent with in-house RS chromatogram; - no additional peaks. Limits: % fucosylated, fucosylated and sialylated species: as authorised by the competent authority.



Infliximab Concentrated Solution ⁽⁴⁾ - tests and acceptance criteria -

PROD.	Analytical procedure	System suitability	Acceptance criteria
Charge variants	IEF (Ph. Eur. 2.2.54) Detailed analytical procedure Reference solution (a): infiximab CRS Reference solution (b): in-house RS Reference solution (c): pI calibration solution	Reference solution (a): 7 bands visible, within specific pI range. Reference solution (c): - all expected bands visible, within specific pI range.	Comparative procedure (reference solution (b)) - test solution electropherogram consistent with in-house RS electropherogram; - for each band, difference in pI (test vs in-house RS) within defined limits; - no additional bands.
	CEX (Ph. Eur. 2.2.29) Detailed analytical procedure Reference solution (a): infiximab CRS Reference solution (b): in-house RS	Reference solution (a): - RS chromatogram 'qualitatively similar' with chromatogram in the CRS leaflet; - peak resolution.	Comparative procedure (reference solution (b)) test solution chromatogram consistent with in-house RS chromatogram. Limits: % isoforms: as authorised by the competent authority.

Infliximab Concentrated Solution

- PRODUCTION section-

Glycan analysis and **tests for charged variants** tests are included in the **PRODUCTION** section (*Ph. Eur. General Notices*), as they cannot be performed by an independent analyst:

- the glycan profile and charge heterogeneity depend on the manufacturing process;
- the tests prescribe the use of an **in-house reference preparation** and this material is available only to the manufacturer;
- the user needs **acceptance criteria in form of numerical limits**, which are **not prescribed** in the monograph;
- given the variability of the glycan profile and the heterogeneity of the charged variants associated with process changes, acceptance criteria in form of "one-fit-all" numerical limits may not be suitable and have to be **set** by the manufacturer in **agreement with the competent authority**.

Infliximab Case Study

- Summary:** Proposed monograph for ***Infliximab concentrated solution (2928)*** is the result of a **collaborative effort** of Ph. Eur. Experts and of a large number of laboratories, and of a careful assessment of the process dependent product heterogeneity

Feedback from users on the new monograph fundamentals

- Steps taken:** Ph. Eur. Commission reviewed the MAB pilot phase – in view of the extent of conclusive experimental data agreed to publish this draft monograph in **Pharmeuropa** to collect comments from users.

4	XXXX:2928
5	
6	INFILXIMAB CONCENTRATED SOLUTION
7	
8	Infliximabum solutio concentrata
9	
10	description: benzoyl-L-histidine-L-alanine ester (heavy chain); L-lysine (light chain)
11	229HC1-809HC1, 1479HC1-209HC1, 2239HC1-2149HC1, 2299HC1-2299HC1,
12	2329HC1-2329HC1, 2339HC1-2339HC1, 2349HC1-2349HC1, 2359HC1-2359HC1,
13	2369HC1-2369HC1
14	Aglycosylation site:
15	Asn 300
16	$C_{1422}H_{1012}N_{108}O_{182}S_{46}$ (non-glycosylated) M_r approx. 144 190
17	DEFINITION
18	Infliximab is a monoclonal antibody consisting of 1328 amino acid residues, with a
19	molecular weight of 144 190 Da, which binds with high affinity to both soluble and
20	transmembrane forms of TNF α .
21	Infliximab is a chimeric human-murine IgG1 monoclonal antibody representing a
22	glycosylated immunoglobulin with one N-linked glycosylation site (Asn 300) in the CH2
23	domain of each heavy chain. The detected oligosaccharides are mostly G0F (absence
24	of terminal galactose) and G1F (one terminal galactose) structures. Each heavy chain
25	consists of 450 amino acids with 11 cysteine residues, and each light chain consists of
26	214 amino acids with 5 cysteine residues. All cysteines in heavy and light chains are
27	involved in either intra- or inter-disulfide bonding.

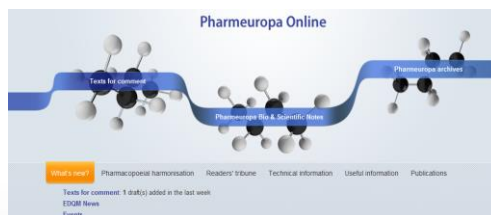
Pharmeuropa 28.4 (pharmeuropa.edqm.eu): 1st October 2016;
deadline for comments – 31st December 2016

All stakeholders encouraged to provide comments

How to comment

➤ Recommendations given in the **Guide for the work of the European Pharmacopoeia:**

- comments should be submitted either via the National Pharmacopoeia Authority or via the Ph. Eur. Secretariat (via the EDQM Helpdesk if outside Europe)



- The **addresses of the national pharmacopoeia authorities** and of the EDQM are published on the **Pharmeuropa** website under the tab **Useful information**.
- Comments are to be submitted before the specified deadline (**Pharmeuropa 28.4 / 31st December 2016**).
- Please refer to the "**How to comment**" notice available at the top of each published text.
- Further details: http://pharmeuropa.edqm.eu/home/menupage/English/Useful%20Information/ImportantNotice_E.pdf

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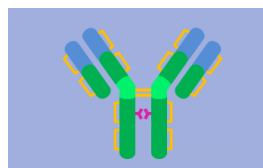


21

MAB Pilot Phase: What's Next?

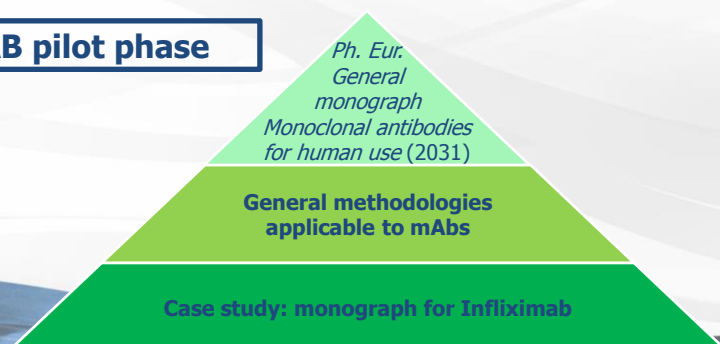
Draft monograph for Infliximab

- **Outcome of Pharmeuropa** public enquiry: review of comments, discussion in the Ph. Eur. MAB WP and **Ph. Eur. Commission**



Decision on the adoption of the final text for publication in the Ph. Eur.

Progress the MAB pilot phase



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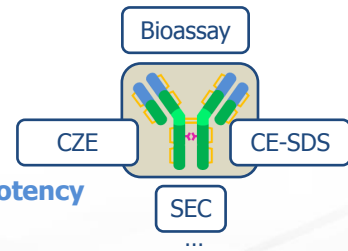
22

MAB Pilot Phase: Prospective Work

Horizontal approaches

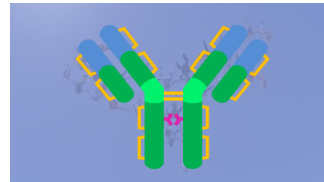
➤ **Current reflections and preliminary work undertaken by the Ph. Eur. MAB WP for:**

- Elaboration of a **general chapter to cover potency determination** for anti-TNF-alpha mAbs.
- Elaboration of a **general chapter to cover physico-chemical methodologies** applied to various mAbs:
 - examples include capillary electrophoresis (CE-SDS), capillary zone electrophoresis (CZE), size-exclusion chromatography (SEC)



All stakeholders are encouraged to participate in the work of the Ph. Eur. Group of Experts

**THANK YOU VERY MUCH
FOR YOUR ATTENTION!**



Setting Pharmacopoeial Standards for Biotherapeutic Products – An Assessor's Perspective

Dr. Brigitte Brake /BfArM Germany

EDQM Workshop:
Setting Pharmacopoeial Standards for
Biotherapeutic Products,
27./28. Sept. 2016, Tallin, Estonia

Disclaimer

The views and opinions expressed in the following
presentation are solely those of the individual presenter
and do not reflect the views or opinions of BWP or any
Regulatory Authority

Monographs

1. Public standards
2. Legally binding
3. Established based on the specification of an approved active substance

What is a biological substance

Dir. 2001/83/EC

- A biological medicinal product is a product, the **active substance of which is a biological substance**. A biological substance is a substance that is produced by or extracted from a biological source and that needs for its characterisation and ***the determination of its quality a combination of physico-chemical-biological testing, together with the production process and its control.***

The process is the product

The entire manufacturing process determines the quality of a biotech medicinal product,

- Raw-/starting materials (e.g. cell banks, media, reagents)
- Fermentation
- Purification
- Formulation/Filling/....

The entire manufacturing process and its controls should be described in detail (reflecting process knowledge)

Minor process changes may affect quality, safety and efficacy
(ICH Q5E)

Biotech products and heterogeneity

No single batch of a given product is identical

Concept of Heterogeneity in ICH Q6B: An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them.

The desired product can be a mixture of anticipated post-translationally modified forms (e.g., glycoforms).

Routine control of Biotherapeutic Products (BTP)

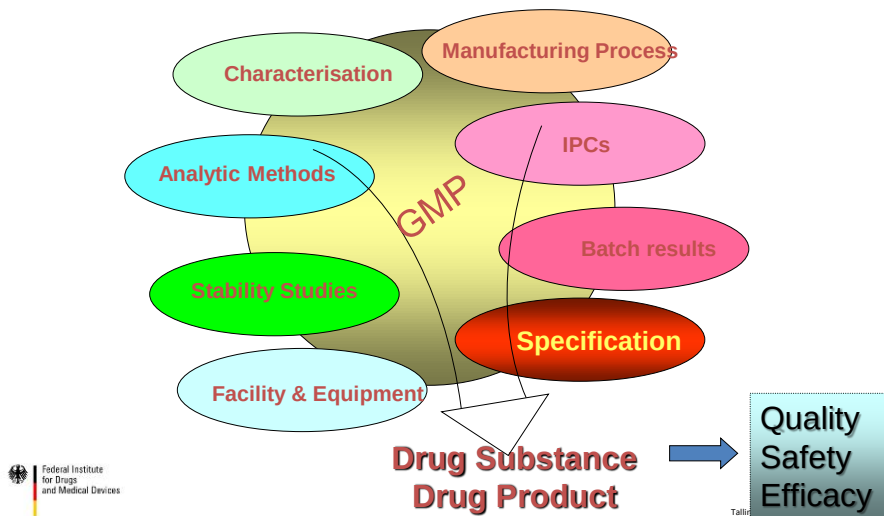
→ Process = Product

Due to the inherent complexity and interdependence with the manufacturing processes, the quality and consistency of BTPs can only be ensured through individual process and product-specific control strategies. End-product testing alone does not ensure quality, safety, and efficacy.

→ Compendial tests and acceptance criteria are not sufficient to ensure product quality

→ Specifications are part of an overall control strategy

Specification as part of a total control strategy



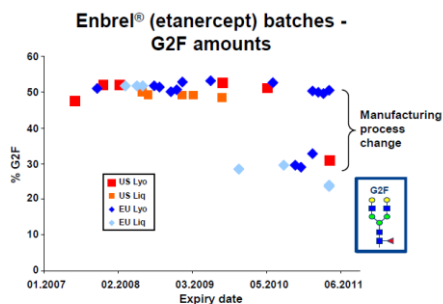
Specifications

Justification of specification according to ICH Q6B

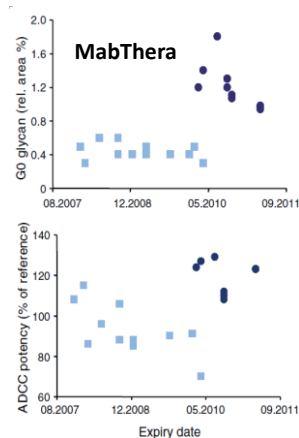
- linked to preclinical and clinical studies
 - linked to a manufacturing process
 - should account for the stability of drug substance and drug product
 - linked to analytical procedures
-
- Quality attributes / specification limits can be changed during the lifecycle of a product (many examples)
 - Certain analytical test may be removed based on enhanced process-/ product understanding or replaced by RTTR and or surrogate tests

➡ Monographs: Sufficient flexibility and dynamic should be built in.

Changes in the manufacturing process of biotech products are normal



Source
www.fda.gov/.../committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm510494.pdf



Schiestl M. et al, Nat Biotech, April 2011

Heterogeneity of batches and changes of the manufacturing process

- Changes of the manufacturing process are normal and can affect the quality profile
- Comparability pre- and post- change needs to be demonstrated (Q/S/E) (Comparability Exercise)
- Changes are assessed / approved in a Variation procedure

Drug Substance Critical Quality Attributes (ICH Q11)

- A **CQA** is a physical, chemical, biological, or microbiological property or characteristic that should be within an **appropriate limit, range, or distribution to ensure the desired product quality.**
- Drug substance CQAs **typically include** those properties or characteristics that affect **identity, purity, biological activity and stability** ... plus others
- *Do all manufacturers classify the same quality attributes as CQAs?*
- *Do monographs for BTP only include CQAs?*
- *How to reflect progress and refinement in product knowledge?*

Applicability of monographs for BTP to follow-on-products(me too / biosimilars)

- Covers common aspects of different products
- Biosimilarity cannot be established based on a monograph.

“A biosimilar is a biological medicinal product that contains [a version of the active substance](#) of an already authorised original biological medicinal product (reference medicinal product).

[Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established”](#)

A biosimilar is manufactured and controlled according to its own development, taking into account state-of-the-art information on manufacturing processes and consequences on product characteristics.

Analytical tools commonly used in protein characterisation

- [Amino acid sequence and modifications](#)
 - MS, LC-MS, peptide mapping, N- and C-terminal sequencing, AA content
- [Disulphide bridging, protein folding and higher-order structures](#)
 - Peptide mapping, Ellman's assay, CD, FTIR, HDX-MS, NMR, DSC, X-ray crystallography
- [Glycosylation and glycation](#)
 - LC-MS, Anion exchange, enzymatic digestion, peptide mapping, CE, MS, BAC Maldi TOF, ESI MS
- [Size heterogeneity](#)
 - SEC, AUC, AF4, MALDI-TOF, CE-SDS, SEC-MALLS
- [Heterogeneity of charge and hydrophobicity](#)
 - cIEF, IEX, RP-HPLC, CZE
- [Functional characterisation and bioassays](#)
 - Target and/or receptor binding; SPR, ELISA, cell-based assays
 - Bioassays; Signal transduction, ADCC, CDC, other cell-based assays

Analytical methods for BTP

- Monograph methods are validated, require verification
- Advantage for both, applicants and assessors
- Robustness and transferability is needed.

The robustness for an analytical *“a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage”*.

- If alternative methods are used the applicant needs to demonstrate that the method is at least equivalent/non inferior. (E.g. better resolution, methods less time consuming, etc.)

ICH Q6B *“New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate”*.

Specification – List of tests based on ICH Q6B

The following tests and acceptance criteria are normally covered and applicable to all drug substances :

- Appearance and description
- Identity (more than 1 test)
- Quantity
- Purity (Combination of tests)
- Impurities (process/product related)
- Potency
- Variants
- pH-, bioburden, endotoxin etc.

normally covered by monographs

Identity

ICH Q6B

The identity test(s) should be **highly specific** for the drug substance and should be based on unique aspects of its molecular structure and/or other specific properties. **More than one test** (physicochemical, biological and/or immunochemical) may be necessary to establish identity. The identity test(s) can be qualitative in nature.

Examples (physico-chemical, biological and/or immunochemical):

Peptide mapping (sample pre-treatment, reduction and alkylation, protease digestion, analysis using an LC system able to cope with specific columns and/or harsh mobile phase).

Electrophoresis (capillary or gel electrophoresis); for gel electrophoresis, commercially available (pre-cast) gradient gels not yet described in the Ph. Eur. or new types of gels may be used.

Charge heterogeneity (ion-exchange chromatography), isoforms (isoelectric focusing).

Assay/Potency determination: cell-based assays (cell proliferation, cytotoxicity assays), ELISA, coagulation tests etc.



Tallin, 27. September 2016, | Page 17

Potency

- ICH Q6B: A **relevant, validated potency assay** should be part of the specifications for a biotechnological or biological drug substance and/or drug product.In some cases, the measurement of specific activity may provide additional useful information.
- Demonstrates a biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). Usually, prior to initiation of phase I clinical studies, the biological activity should be determined using an appropriate, reliable and qualified method.
- The biological activity is assessed by comparing the dose-response curve of the preparation to be examined to that of a reference preparation calibrated in International Units. The International Unit is the activity contained in a stated amount of the International Reference Preparation.



Tallin, 27. September 2016, | Page 18

Potency

Bioassays based on different formats

- *in vitro* cell-based potency
- complex analytical method
- high level of variability
- can be difficult to
- robustness and

Acc. 80-120% relative to
solution

ence limits
(5) 80-125% of
ed potency

- Potency of products from different origin
- Bench mark for biological activity

Problems, e.g.:

- non-commercially available
- availability of cells line
- consumables (e.g microtitre plates).

Carbohydrate moiety

Examples: Erythropoietin, Etanercept

- Glyco structures are heterogeneous and variable from batch to batch
- Structure function relationship not always defined, can play a critical role in protein structure/conformation and its MoA / effector function
- Glycan analysis should be to monitor the consistency of oligo-saccharides structure and distribution including the degree of sialylation and the presence/absence of unwanted glycan structures

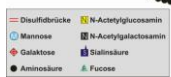
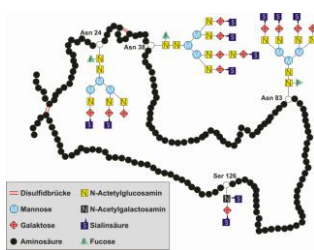
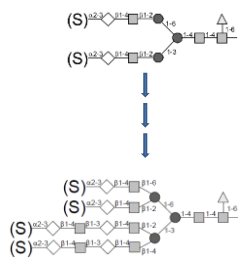
➡ Analytical tests for isoforms such as IEF or CZE are not sufficient (e.g. Epo)

➡ Etanercept Draft Monograph: N-Glycans - no acceptance criteria! As authorised! Production section

Erythropoietin

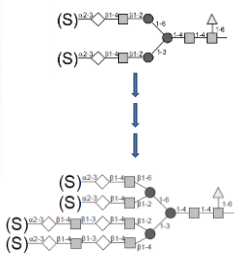
Reference Product

bi- to tetraantennary,
complex N-Glycans



Biosimilar

bi- to tetraantennary,
complex N-Glycans

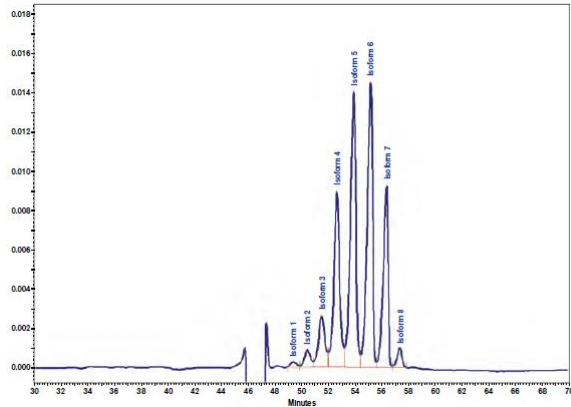


Phosphorylated high-mannose structures



EPO Glycan structures

Electropherogram with Epo BRP batch 3



Isoform	Content (per cent)
1	0 - 15
2	0 - 15
3	1 - 20
3	10 - 25
5	15 - 40
6	10 - 35
7	5 - 25
8	0 - 15

Source:
<https://scix.com/Documents/tech%20notes/IB-17030.pdf>

Considerations - what should be in or out

Monographs for BTP should include limits for potency

Monographs for BTP should not include limits for parameters that are highly depended on the manufacturing process, e.g.:

- glycan structures
- process related impurities (e.g. HCP, DNA)
- product related substances and impurities (??)
- pH
- bioburden,
- endotoxin

Monographs specific for BTP

- Monographs can facilitate early phases of development (CT /IMP) and acceptance of proposed limits for certain quality attributes
- For MAA requirements based on process and product knowledge and the resulting control strategy might sometimes lead to conflicting situations
- Several monographs are from the late 1990s (e.g. Insulin, Somatropin, Erythropoietin) and do not take into account current thinking and do not sufficiently reflect variability of BTP
- Current draft monographs reflect specificities of BTP to a greater extent

Monographs for BTP

- Considering the **structural complexity and variability of BTP**, sufficient flexibility should be built in
- Do not replace complete and state-of-the-art characterisation
- Should not just copy „the“ specification
- Should include up-to-date state-of-the-art methods
- Should not include limits for parameters that are highly dependent on the manufacturing process
- A mechanism should be in place to timely trigger regular updates/ revisions reflecting current knowledge

Thank you very much for
your attention!



Common standards for biotech products: an OMCL perspective

Jaana Vesterinen, PhD, Fimea
Tallinn, Estonia, 27-28. Sept 2016

Disclaimer

The views in the following presentation do not represent the official view of the Finnish Medicines Agency, but they are the views and opinions of the presenter.

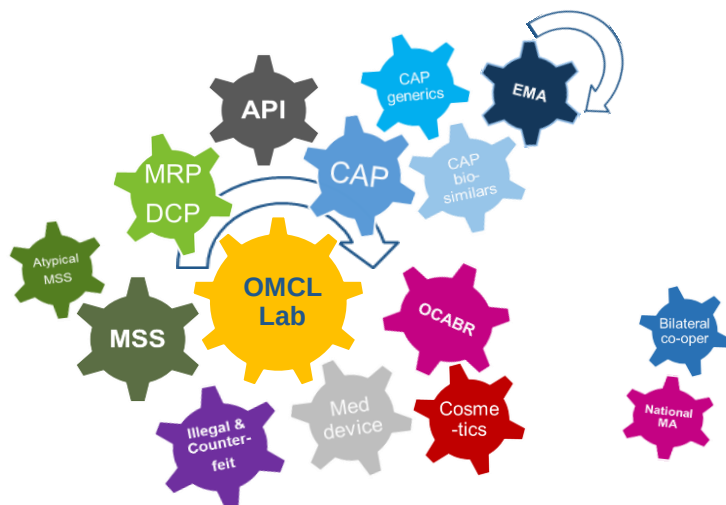
Official Medicines Control Laboratory = OMCL

- An **Official Medicines Control Laboratory (OMCL)** is a public institution, performing laboratory testing of medicinal products for a Competent Authority
- Testing includes medicinal products for both animals and humans
- **OMCL Network** is co-ordinated by EDQM and it has 57 full, 9 associated and 3 limited members
- *Unbiased testing by independent OMCL laboratories is an important part of regulatory control of medicines to achieve safety and good quality*
 - *a credit for MAH*
 - *needed in emergency cases (pharmacovigilance / falsification)*
- Within EU, the mandate is given by directives (2011/83/EC and 2011/82/EC) and related national legislation

The testing activities of OMCL

- Batch release and *post marketing surveillance (PMS)* of medicinal products and APIs are the main activities of OMCLs
- Testing can also occur prior to approval of marketing authorisation approval (*preauthorisation testing*)
- Testing may also include medicinal devices, cosmetics, food supplements, illegal drugs, etc.
- The centrally approved products are tested in the CAP-program, planned by EMA, co-ordinated by EDQM and tested in national OMCLs.
- The other products (licenced via MRP/DCP or national process) to be tested are chosen by risk based evaluation or safety triggers
- Samples to be tested are taken from the market or by inspectors

Many types of medicinal products to be tested ...



Lääkealan turvallisuus- ja kehittämiskeskus | 2016-09-27 | EDQM / Setting pharmacopoeial standards for biotherapeutic products

| 5 |

Which methods to apply? MAH's methods, Ph.Eur. methods, in-house methods

- Most of the biotech products to be tested are approved via the centralised procedure, and their testing (CAP testing) is planned by EMA, coordinated by EDQM and performed by national OMCL-laboratories
 - MAH methods / Ph. Eur. methods
- Testing of products accepted via MRP/DCP or national licensing
 - MAH methods / Ph. Eur. methods / OMCL in-house methods
- Most MAH methods are used once or few times only. Method transfer from MAH is based on SOPs.

Lääkealan turvallisuus- ja kehittämiskeskus | 2016-09-27 | FIMEA / Setting pharmacopoeial standards for biotherapeutic products

| 6 |

Challenges for OMCL

- **Method transfer**

The success of the method transfer depends on

- Robustness of the method
- Quality and level of details of the method description
- Level of system suitability requirements

Method transfer is easier for LC methods, challenging for biological assays

- **Potency testing, an important quality aspect of biologicals**

- complex assays (cell based / ELISA)
- Not many public reference standards available
- Most methods depend on proprietary reagents/cells/standards

- **Availability of standards**

Method transfer is labor intense work which needs standards and well described, validated/verified methods

Ph. Eur. methods vs. MAH methods

Benefits

- Methods in monographs are written in a defined format, easy to follow
- MAH methods contain more details
- Monographs' system suitability criteria are simple when used together with well-defined public standards BRP/CRS/IS
- Monograph methods verified by multiple laboratories (OMCL/others) → improved robustness and likely success in method transfer

Drawbacks

- MAH's documentation may include a lot of unrelated data (eg. for handling in-process samples)
- Some monographs have too few details
- MAH's system suitability requirements may not be suitable for OMCL purposes

OMCL view of an ideal monograph

- Flexible but contain enough details enabling testing without further instructions
 - Monograph lists **alternative methods**
(LC → UPLC and SDS-PAGE → CE)
 - Monograph contains **detailed methods as examples**
 - Monograph contains **methods which can be carried out with publicly available reagents and standards**
- Monograph has clear system suitability criteria to verify successful method transfer by reference standards (CRS/BRP/IS)
- Monograph contains the methods suitable for evaluating the essential quality aspects of the product
- *Limits?*

fimea Example 1. Digestion, DS monograph vs. general text

07/2010:2206
corrected 7.6

FILGRASTIM CONCENTRATED SOLUTION

E. Peptide mapping (2.2.55).

SELECTIVE CLEAVAGE OF THE PEPTIDE BONDS

Test solution. Introduce a volume of the preparation to be examined corresponding to 25 µg of protein into a polypropylene tube. Add 25 µL of a 0.1 mg/mL solution of glutamyl endopeptidase for peptide mapping R. Dilute to 100 µL with 0.02 M sodium phosphate buffer solution pH 8.0 R, stopper the tube and incubate at about 37 °C for 17 h. Cool to 2-8 °C until analysis.

Reference solution. Prepare at the same time and in the same manner as for the test solution but using filgrastim CRS instead of the preparation to be examined.

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (2.2.29).

Column:

- size: $l = 0.10$ m, $\varnothing = 2.1$ mm;
- stationary phase: octadecylsilyl silica gel for chromatography R (5 µm) with a pore size of 20 nm;
- temperature: 60 °C.

Mobile phase:

- mobile phase A: dilute 0.5 mL of trifluoroacetic acid R in 950 mL of water R, add 50 mL of acetonitrile for chromatography R and mix;
- mobile phase B: dilute 0.5 mL of trifluoroacetic acid R

01/2010:20255

2.2.55. PEPTIDE MAPPING⁽⁷⁾

Peptide mapping is an identity test for proteins, especially those obtained by rDNA technology. It involves the chemical or enzymatic treatment of a protein resulting in the formation of peptide fragments followed by separation and identification of these fragments in a reproducible manner. It is a powerful

...

Establishment of optimal digestion conditions. Factors that affect the completeness and effectiveness of digestion of proteins are those that could affect any chemical or enzymatic reactions.

pH of the reaction milieu. The pH of the digestion mixture is empirically determined to ensure the optimisation of the performance of the given cleavage agent. For example, when

This chapter provides detailed assistance in the application of peptide mapping and its validation to characterise the desired protein, to evaluate the stability of the expression construct of cells used for recombinant DNA products and to evaluate the consistency of the overall process, to assess product stability as well as to ensure the identity of the protein, or to detect the presence of protein variant.

fimea Example 2. Filgrastim DS monograph, pepmap LC

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (2.2.29).

Column:

- size: $l = 0.10$ m, $\varnothing = 2.1$ mm;
- stationary phase: octadecylsilyl silica gel for chromatography R (5 μ m) with a pore size of 20 nm;
- temperature: 60 °C.

Mobile phase:

- mobile phase A: dilute 0.5 mL of trifluoroacetic acid R in 950 mL of water R, add 50 mL of acetonitrile for chromatography R and mix;
- mobile phase B: dilute 0.5 mL of trifluoroacetic acid R in 50 mL of water R, add 950 mL of acetonitrile for chromatography R and mix;

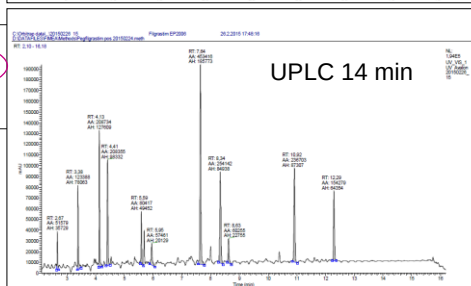
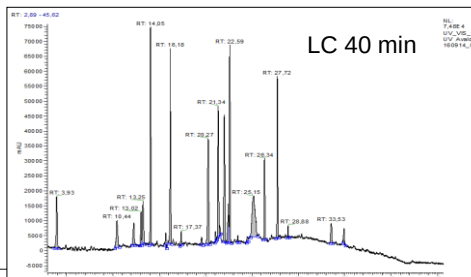
Time (min)	Mobile phase A (per cent V/V)	Mobile phase B (per cent V/V)
0 - 8	97 → 94	3 → 6
8 - 25	94 → 66	6 → 34
25 - 40	66 → 10	34 → 90
40 - 45	10	90

Flow rate: 0.2 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 10 μ L.

System suitability: the chromatogram obtained with the reference solution is similar to the chromatogram of filgrastim digest supplied with filgrastim CRS.

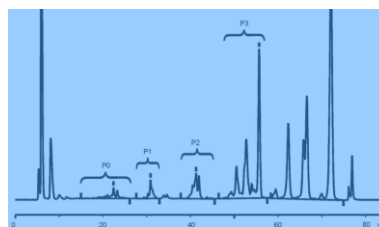


fimea Example 3. Factor IX (rDNA) monograph, glycans

No. 2522: Assay system suitability standard

System suitability:

- the chromatogram obtained with *reference solution (a)* is qualitatively similar to the chromatogram supplied with *human coagulation factor IX (rDNA) CRS*; 5 groups of oligosaccharide peaks corresponding to P0 neutral, P1 mono-, P2 di-, P3 tri- and P4 tetrasialylated...
- no significant peaks are observed in regions P0 to P4 in the chromatogram obtained with the blank solution.



Results:

- the profile of the chromatogram of the test solution corresponds to the chromatogram obtained with the reference solution (a);
- the relative retentions of the peaks in groups P0 to P4 obtained with the test solution are similar to the reference solution (b);
- the tetrasialylated peak area in the test solution is *within the limits* authorized by the *competent authority*.

Use of assay system suitability standard creates flexibility

- CRS for method performance check-up
- In-house reference for calculating and approving results

fimea Example 4. Etanercept monograph draft, potency

6 **Potency.** The potency of the preparation to be examined is determined by
 7 comparison of the dilutions of the test preparation with the dilutions of *etanercept*
 8 *BRP*. Carry out the assay using a suitable cell-based assay based on the inhibitory
 9 action of etanercept on the biological activity of TNF- α and a suitable readout for
 10 assessing the inhibitory effect.

11 *The following method has been found suitable.*

12 Carry out an apoptosis-based assay based on the ability of etanercept to induce
 13 apoptosis in histiocytic lymphoma cell-line U937 (ATCC No. CRL-1593.2) via
 14 caspase activation. U937 cells are incubated with varying dilutions of test and
 15 reference preparations of etanercept, in the presence of TNF- α . They are then
 16 incubated with Caspase-Glo 3/7 reagent, which results in caspase cleavage of a
 17 luminogenic substrate, release of a luciferase substrate and generation of a
 18 luminescent signal. Luminescence is proportional to the amount of caspase activity
 19 present.

20 *The following indications are given as an example.*

fimea

Future wish list

- More monographs using method-specific assay suitability standards together with active substance specific reference standards
Eg. FIX monograph 2522
- Establishment of general monographs (for methods) with more details
Eg. CE for monoclonal antibody drugs
- Establishment of DS monographs general enough to enable simultaneous testing of different products with the same active substance (**horizontal testing of biosimilars**)
Eg. Filgrastim DS monograph 2206
- *Establishment of verified, scientifically sound bioassays* without manufacturer specific reagents not available publicly
Eg. TNF- α neutralisation assays?

Why do we need public standards?

- *Public reference standards (CRS/BRP/IS) are thoroughly tested and reliable, they form a cornerstone for calibration of manufacturers' primary standards to avoid drifting*
 - Public standards (CRS/BRP/IS) *facilitate development of in-house methods* in OMCLs
 - Public standards lay the *basis for OMCL testing in emergency cases* (pharmacovigilance / falsification)
 - Heparin
 - Herceptin
- *Development of the Ph Eur monographs and reference standards is invaluable and urgently needed to provide tools to ensure the quality, efficacy and safety of new biotech products, including the monoclonals*

→ *Development of the public documents and reference standards is invaluable and urgently needed to provide tools to ensure the quality, efficacy and safety of new biotech products, including the monoclonals*

The public standard enhances the use of regulatory resources for public purposes and the benefit of patients

Discussion on how to develop the standards needs all stakeholders!

THANK YOU!!

Erin Wang, Neil Schwarzwald, Consultant, Compendial Affairs, Global Quality Laboratory
Matthew Borer, Ph.D., Sr. Research Advisor, Corporate Reference Standard Organization,
Eli Lilly and Company



Acknowledgements

- ◆ Joe Albanese, Associate Director–Product Lifecycle Management, Janssen Research and Development, LLC
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- ◆ Mark Wiggins, Director, Compendial Affairs, Merck & Co., Inc. (MSD)
- ◆ John J Dougherty, Sr. Research Advisor, Global Regulatory CMC Biotech/Insulins, Eli Lilly and Company
- ◆ Michael De Felippis, Sr. Research Fellow, Bioproduct Research/Development, Eli Lilly and Company

Overview

- ◆ Value of Pharmacopoeia Standards
- ◆ Manufacturers' Perspective
- ◆ Path Forward
 - General Principles
 - General Notices / General Monographs
 - General Chapters
- ◆ Reference Standard for Biotherapeutic Products
 - Importance of Reference Standard
 - Industry Challenges
- ◆ Summary and Considerations

Value of Pharmacopoeia Standards

- ◆ Pharmacopoeias define public quality standards for pharmaceutical products, active ingredients, and components
 - Bring consistency to medicines
 - Contain general requirements which apply to manufacturing, storage, labeling, and other aspects
 - Minimum quality standard to be met by all manufacturers
 - Provide common methodologies through General Chapters
 - Flexible to adapt to new technologies
 - Supports regulatory standards
- ◆ Enforced by regulatory agencies
 - Simplify and maintain registrations
 - Flexible to adapt to new manufacturing
- ◆ Market surveillance by health authorities

Manufacturers' Perspective

Manufacturers have expressed support for non-specific public standards (general chapters, general monographs) for biopharmaceutical products, but have concerns over monographs for specific molecules in products.

- ◆ The complex high-molecular-weight, three-dimensional structures of biopharmaceuticals, their heterogeneity, and their dependence on production in living cells makes them different from classical chemical drugs.
- ◆ Current analytical methods cannot fully characterize these complex molecules sufficiently to confirm structural equivalence with reference molecules.
- ◆ ...there are currently no analytical techniques to establish biopharmaceutical equivalence.

*Biosimilar Therapeutics – What do we need to consider?

Huub Schellekens, Utrecht University, Netherlands, NDT Plus. 2009 Jan; 2 (Suppl. 1): i27 – i36

Manufacturers' Perspective

Small Molecules



 CMC - standard information



 Clinical bioequivalence

Biotherapeutics



 CMC - standard information

 CMC - comparability

 Nonclinical data

 Clinical bioequivalence

 Clinical efficacy

 Clinical safety

- ◆ Molecular structure of a small molecule must be identical to the reference product whereas for the Biotherapeutics, molecular differences are expected and manufacturing process being unique for each “similar” Biotherapeutics produced.
 - Monograph for Biotherapeutics adds regulatory complexity
 - Denying an application and access to the therapy
 - Enforcement of the monograph information during an inspection

Path Forward

A few general principles:

- ◆ Develop public standards within the capabilities of current science.
- ◆ Ensure flexibility for manufacturers and regulatory authorities.
- ◆ Emphasize reference to limits approved by competent authority rather than including specific limits.
- ◆ Harmonize across pharmacopoeias and regions.
- ◆ Provide a framework for future development.

General Notices / General Monograph

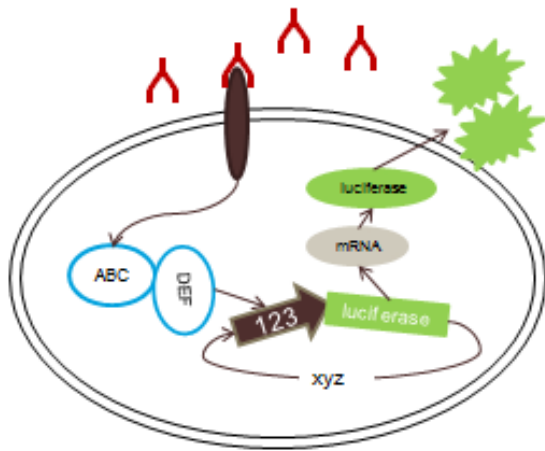
- ◆ Possible clarification in General Notices or General Monograph:
 - Standards for biosimilarity or interchangeability of biotechnology products are set by regulatory agencies based on additional clinical, non-clinical and quality data.
 - Determination of acceptability is made by regulatory authorities based on additional data not addressed in compendial monographs.

General Chapters

- ◆ Develop meaningful harmonized general chapters for biotherapeutics resulting from industry development and scientific evolution
 - Stakeholders have opportunity to review planned activities from pharmacopoeias before significant work is performed
 - Discipline is needed within pharmacopoeia; focus on role of pharmacopoeia in setting public standards rather than writing textbooks or SOPs
 - Consideration of biotherapeutics when general chapters on analytical techniques are drafted that apply to both small molecule and biotherapeutics (e.g. ion-exchange chromatography chapter)

Reference Standard for Biotherapeutic Products - Importance

- The basis for patient dose
 - *There is no way to correlate biological activity to physicochemical test results so the reference standard serves this purpose*
 - *Proper management of the reference is essential to prevent drift in dose from pivotal clinical studies (especially difficult in the face of variable assays for potency)*
- The basis for product identity
 - *Not only the identity of the main entity but also the fingerprint of variants and impurities*
 - *Plays a key role in monitoring the manufacturing process for consistency*



Reference Standard for Biotherapeutic Products - Industry Challenges

- Regulatory authorities require manufacturers to use a reference standard that is highly representative of their manufacturing process. If not, the reference standard is not suitable for potency testing and must be replaced.
 - *How can a compendial standard be useful to more than one manufacturer?*
- It is not possible to correlate potency to physicochemical tests. Instead, a two-tier reference standard system is required of manufacturers to maintain potency consistent with pivotal clinical studies.
 - *How can a compendial standard be assigned a potency without comparison to the original manufacturer's in-house standard?*
 - *Harmonization, WHO, NIBSC etc.*
- All approaches that are scientifically sound for monitoring the stability of potency require routine execution of the potency test (e.g., cell-based assay) in an expert lab that is also releasing product.
 - *How can compendial agencies monitor potency of their reference standards?*

Summary and Considerations

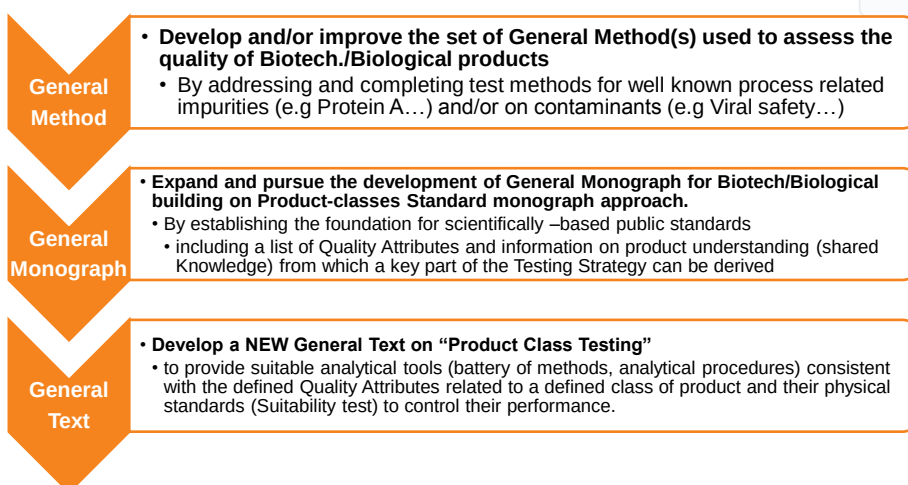
- ◆ COLLABORATION: Manufacturers, Regulators and Compendia should work together to find opportunities to advance pharmacopoeia standard for biotherapeutics as well as Pharmacopoeial Processes to benefit patients without restricting new manufacturing development.
- ◆ HARMONIZATION: To promote public health by providing safe and effective biotherapeutics with consistent quality to extend and improve the lives of patients around the world.
- ◆ FUTURE: Scientific Advancements vs Public Standard
 - Better understanding
 - Relationship between structure and potency for biotherapeutics
 - Biotherapeutic manufacturing and how process parameters affect potency
 - Improved physicochemical methods that are sensitive to properties that affect potency

WORKSHOP: SETTING PHARMACOPOEIAL STANDARDS FOR BIOTHERAPEUTIC PRODUCTS

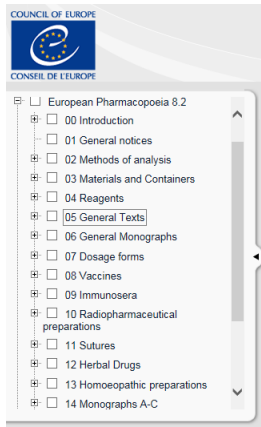
Industry's Perspective (2)



Industry Expectations/Perspectives



Ph. Eur. content is extensively and successfully used for biotherapeutic products



- Methods of Analysis
 - Osmolality, pH, Color, Sterility, Bioburden, Endotoxin,...
- Materials and Containers
 - Glass Container, Stopper, Silicon Oil,...
- Reagents
 - Aminoacids, Gases,...
- General Tests
 - Pharmaceutical Preparations,...
- General Monographs
 - MAb - Products
- Dosage forms
 - Parenteral Preparations,...
- Monographs
 - Excipients, Water for Injection (Wfi),...

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Example 1: Implementation of Mycoplasma standard for Real-Time PCR



- 1st WHO International Standard for mycoplasma DNA for Nucleic Acid Amplification Techniques-based assays designed for generic mycoplasma detection
- Replacement of cell culture based method by state of the art Real-Time PCR for CHO cell-based products
- Successful validation and comparability between RT-PCR using the 1st WHO International Standard.

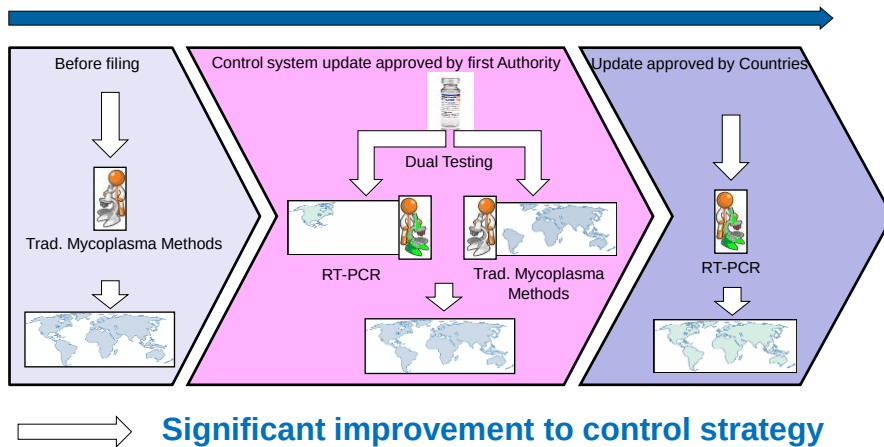
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Example 1:

Implementation of Mycoplasma standard for Real-Time PCR

Dual Testing – Replacement Methods Have Long Global Approval Time

4 years from first to final Health Authority approval

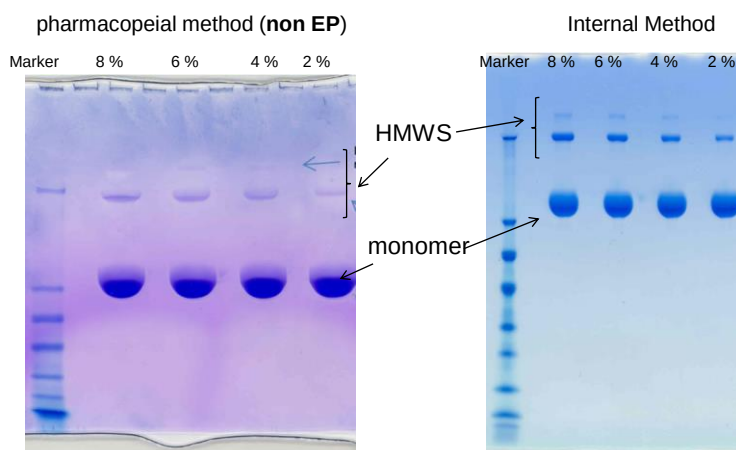


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Example 2:

Introduction of different procedures in monograph

	Pharmacopeial Method	Internal Method
Gradient Gels	4% - 12%	8 % - 16 %
Conditions	Non-Reducing	Reducing
Sample Load	≥ 10 µg	2 µg



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Example 3: Product specific vs Class specific monograph

CLASS SPECIFIC	PRODUCT SPECIFIC
LMM HEPARINS	LMM HEPARINS
- IDENTIFICATION A. NMR spectrometry B. Ratio anti-Fxa/anti-FIIa C. Average relative mass by SEC D. Reaction of sodium or calcium	- IDENTIFICATION - LMMH 1: Test A, C and D - LMMH 2: Test A, C and D + Anion exchange chromatography (including identification of 26 specific derivatives)

How specific should a product specific monograph be?

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Case Study: The safety of a BTP/SBP relates to much more than finished product testing



- Epoietin alfa products rarely (<1:1000) induce anti drug antibodies (ADA) that neutralize endogenous erythropoietin, resulting in severe anemia called pure red cell aplasia (PRCA).
- HX575 is an epoietin alfa (Erypo/Eprex®) biosimilar approved by EMA for **intravenous use** treating anemia in renal disease*.
- When HX575 was compared to Eprex® in **subcutaneous use** (where PRCA risk is higher) a substantial safety problem emerged¹.
 - 2 of 174 renal disease patients on HX 575 (none on Eprex®) developed ADA that neutralized erythropoietin.
 - One developed PRCA, the other died shortly after ADA developed
 - Immunogenicity attributed to interactions with tungsten in syringe².

¹ Haag-Weber M et al., Clin Nephrol. 2012; 77:1, 8-17

² Seidl A et al., Pharm Res. 2011; DOI: 10.1007/S11095-011-0621-4

* Subcutaneous route is approved for HX575 in cancer and major elective orthopedic surgery indications

Despite high analytic similarity and clinical similarity in intravenous use study, subcutaneous use study revealed clinically important difference in immunogenicity.

Case Study: Only a total control strategy can ensure BTP/SBP safety and efficacy



•**Purpose** Following two cases of neutralizing antibodies to epoetin alfa in an investigational clinical study, **a small number of individual syringes of two drug product batches were found to contain unusually high levels of aggregation** at the end of the clinical trial.

•**Results** **Soluble tungsten was found in the syringes**, most likely derived from the pins used to manufacture the syringes. Spiking of epoetin alfa with sodium polytungstate or an extract of tungsten pins used to manufacture the syringes induced the formation of aggregates.

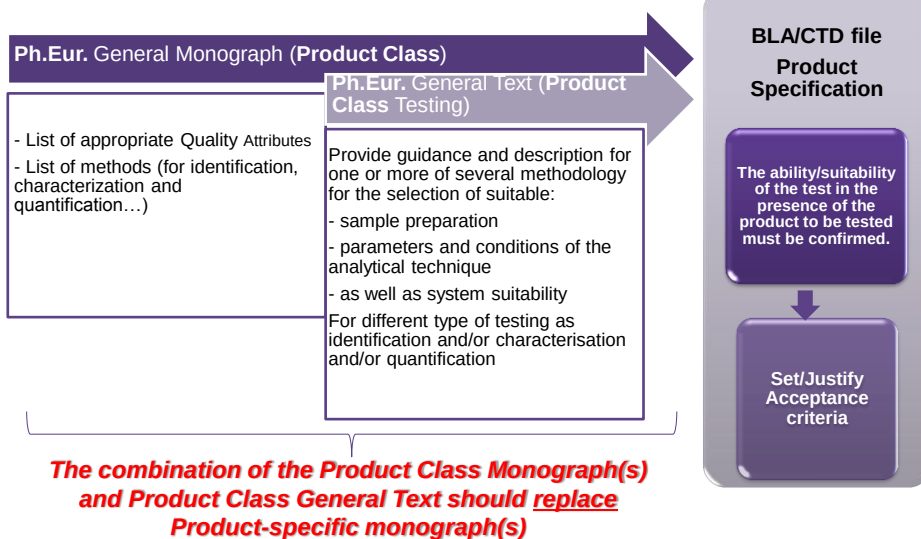
•**Conclusions** **We propose tungsten-mediated unfolding and aggregation of epoetin alfa in pre-filled syringes as a potential root cause** for increased immunogenicity.

Pharm Res (2012) 29:1454–1467
DOI 10.1007/s11095-011-0623-4
RESEARCH PAPER

Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity

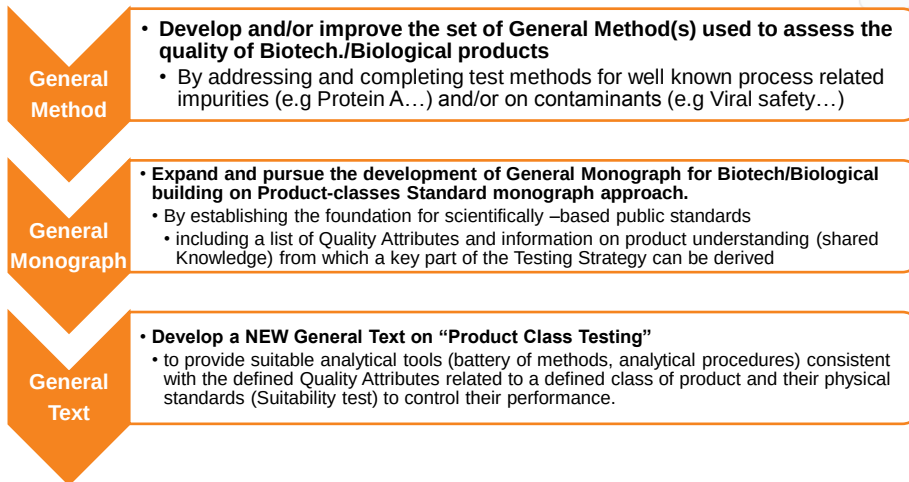
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Industry Expectations/Perspectives



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Industry Expectations/Perspectives



Doing now what patients need next

The United States Pharmacopeia (USP) Strategy on Biotherapeutic Products Standards

Jaap Venema, Ph.D.
Chief Science Officer and Chair, Council
of Experts

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U.S. Pharmacopeia – Who We Are

- ▶ Scientific, independent, volunteer-driven, nonprofit organization
 - Established in 1820: Headquartered in Rockville, MD
 - Laboratory facilities in India, China, Brazil, and Ghana
- ▶ Sets public quality standards for prescription and over-the-counter medicines, excipients, dietary supplements, food ingredients, and healthcare quality and safety (including compounding)
- ▶ Recognition of USP Standards in Federal Food Drug and Cosmetic Act (FDCA)
- ▶ Standards recognized in ~40 countries and used in over 140 countries



Global Expertise | Trusted Standards | Improved Health

COPYRIGHT 2016. ALL RIGHTS RESERVED.



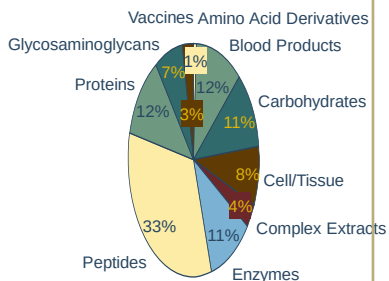
USP's long-term investment in biologics has led to the development of a broad set of standards

Documentary Standards (General Chapters)

53 written chapters that provide industry with guidance and best practice on procedures and testing related to biologics, some of which are enforceable by law

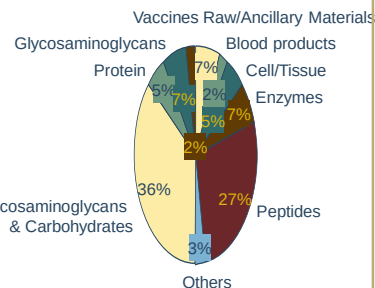
Documentary standards (monographs)

112 documentary standards split across 8 categories:



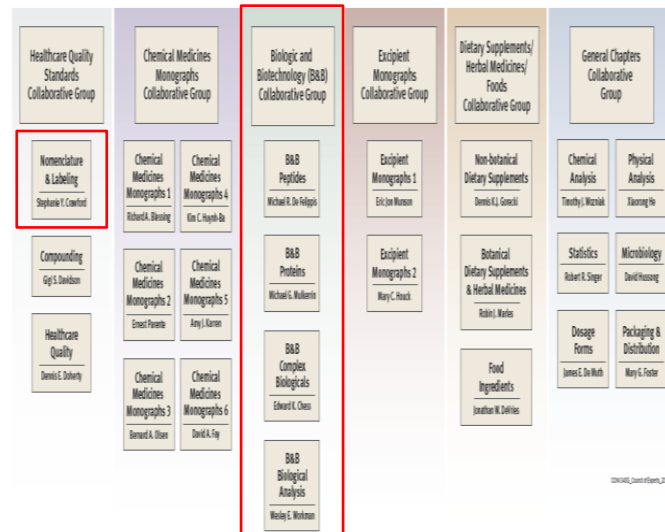
Physical (Reference) Standards

130 physical standards (in catalog or readily available) standards split across 10 categories:



USP Biologics – Council of Experts & Expert Committees

2015–2020 Council of Experts Expert Committees and Collaborative Groups





USP Biologics Strategy

2015–2020 Strategies

- Continue to develop and improve USP's portfolio of quality standards for biological medicines:
 - Continue to modernize standards for legacy products
 - Continue to eliminate animal-based bioassays
 - Grow portfolio of ancillary and raw materials standards
 - Grow portfolio of procedural and system suitability tools for the analysis of all biologics
 - Development new standards for biologics based on broad understanding of public health, regulatory, and technology impact

Strategies

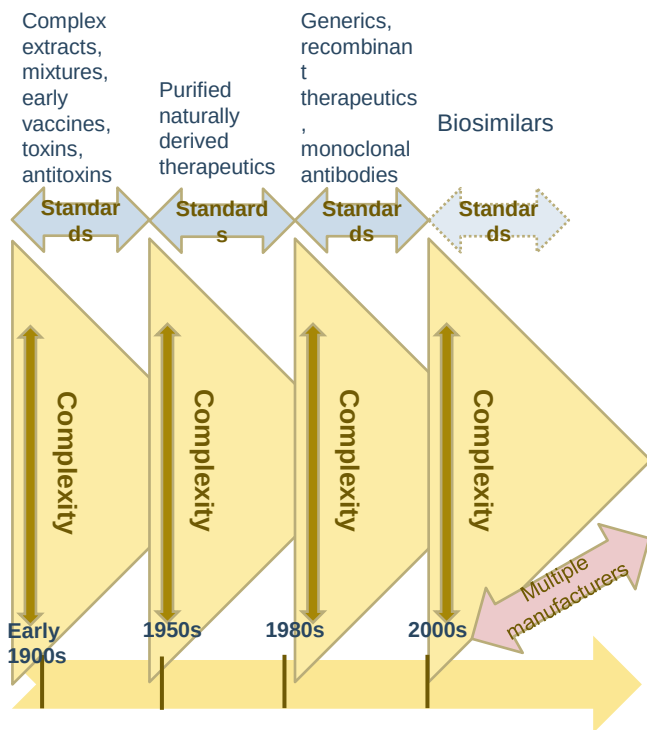


Biological Medicines: Key Challenges

- Broad Scope of Products
 - Blood and Blood Products
 - Cell, Gene, Tissue Therapies
 - Therapeutic Proteins, Recombinant and Naturally-derived
 - Vaccines
- Multi-components (e.g. raw materials) manufacturing:
 - Potential supply chain issues (e.g. animal derived materials)
 - Testing of quality of components before manufacturing begins
- Complex manufacturing processes with impact on:
 - Quality attributes of finished products
 - Challenging regulatory approval pathways
- Control of the quality, safety and efficacy of biologics is difficult, but feasible due to technological advances
 - Orthogonal methods needed to address a single quality aspect
 - Higher order structures, often addressed by a biological assay



Role of Standards in the Biologics Evolution



The Many Benefits of Public International Standards for Biological Medicinal Products

- ▶ Promotes transparency
- ▶ Promotes international regulatory convergence
- ▶ Increases quality of and confidence in standards by utilizing and leveraging international scientific expertise
- ▶ Supports access to high quality products worldwide by enabling multiple manufacturers
- ▶ Provides continuity of biological activity through changes in marketplace (e.g. helps identify drift within or between products)
- ▶ Enables and assures assay suitability
- ▶ Protects against counterfeits and sub-standard products (e.g., utilized in laboratories)
- ▶ Helps address public health concerns/crisis

➤ Public standards provide tools to industry, regulators, and other stakeholders that can be utilized throughout a product lifecycle - development, approval, compliance, market surveillance - to help ensure patient access to quality biological medicinal products



Case Study 1: Filgrastim

Filgrastim

RECOMBINANT GRANULOCYTE COLONY-STIMULATING FACTOR (r-metHuG-CSF)
UNPHEXOMERIZED POLYPEPTIDE
OPHTHALMIC SOLUTION
CATIONIC LIPID FORMULATION
CATIONIC LIPID FORMULATION

$C_{845}H_{1339}N_{223}O_{243}S_9$
[121181-53-1]

18,799 daltons

DEFINITION

Filgrastim is a recombinant form of human granulocyte colony-stimulating factor (r-metHuG-CSF). It is a single chain, 175 amino acid nonglycosylated polypeptide produced by *Escherichia coli* bacteria transfected with a gene encoding a methionyl human granulocyte colony-stimulating factor. When prepared as a drug substance, it contains NLT 0.9 mg/mL of Filgrastim. Formulation contains one or more suitable buffering and/or stabilizing agents. The presence of host cell DNA and protein in Filgrastim is process-specific. The capability of the process to clear host-derived DNA and protein requires validation and is determined by validated methods. It has a biological potency of NLT 80% and NMT 125% relative to standard on a mass-to-mass basis.

IDENTIFICATION

- **A.** It meets the requirements in the Assay.
- **B.** The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained as directed in the test for Organic Impurities, Related Compounds.
- **C. PEPTIDE MAPPING**
(See Biotechnology-Derived Articles—Peptide Mapping (1055).)

In addition to the originator, 2 recent products are licensed in the US:

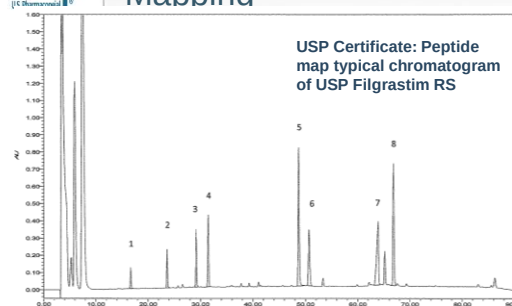
tbo-filgrastim (PHS 351a, Teva)
filgrastim-sndz (PHS 351k, Sandoz)

USP tested 3 batches from filgrastim-sndz; these meet the USP Filgrastim drug substance monograph criteria for:

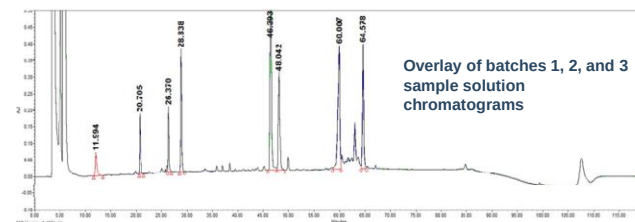
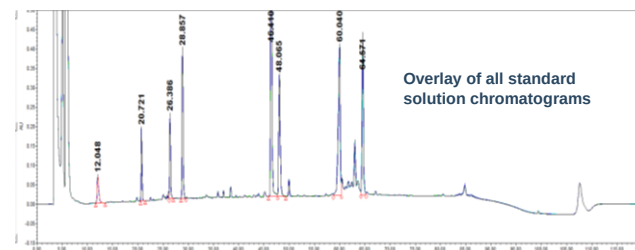
- Identification (data on next slide)
- Assay
- Impurities
- Other requirements



Filgrastim: Identification C – Peptide Mapping



System suitability: Eight major peaks should be present in each chromatogram as illustrated in the reference chromatogram provided with USP Filgrastim RS.



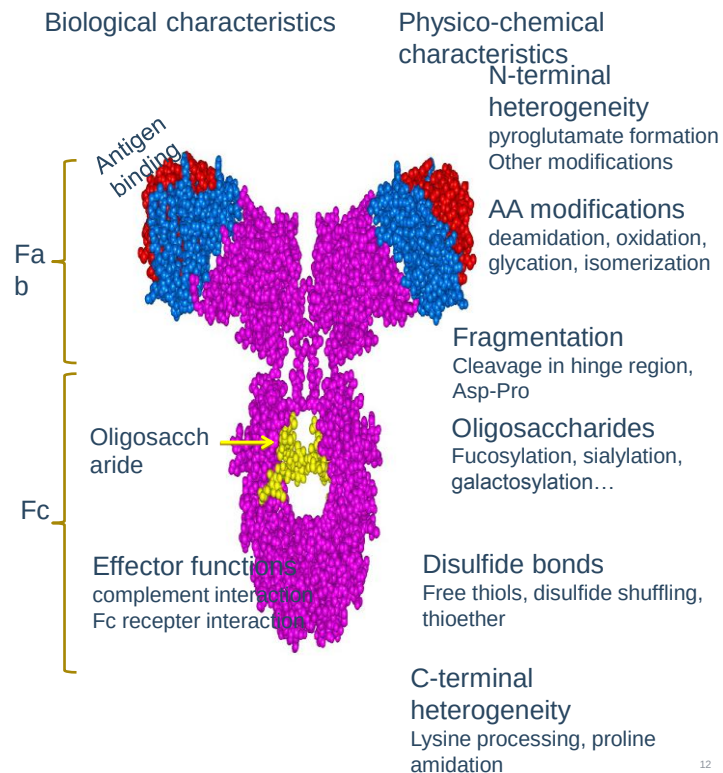
Unpublished Data

Case Study 2: Approach to Quality Attributes Across Product Classes

Impurities	Physicochemical Tests	Potency Assays and Content Measurement
• <509> Residual DNA Measurement • <1132> Measurement of Residual Host Cell Proteins	• <212> Oligosaccharide Analysis • <210> Monosaccharide Analysis • <121.1> Insulin Physicochemical Analysis • <129> Analytical Procedures for Recombinant Therapeutic Monoclonal Antibodies • <209> Low Molecular Weight Heparin Molecular Weight Determinations	• <507> Protein Determination Procedures • <123> Glucagon Bioidentity Tests • <124> Epoetin Bioassays • <126> Somatropin Bioidentity Tests • <208> Anti-Factor IIa and Xa Assays for Unfractionated and Low Molecular Weight Heparins

11

Which Quality Attributes to Consider?



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Quality Control Assays for MABs

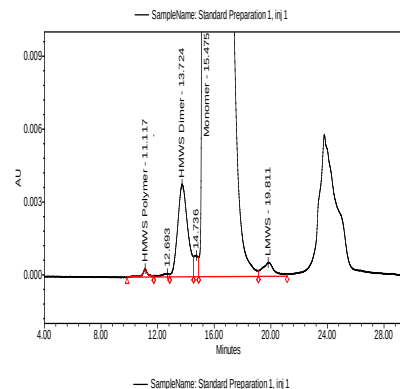
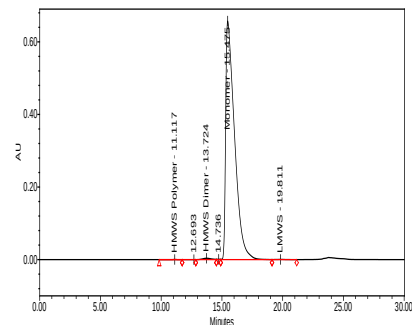
- ▶ Included in <129> chapter
 - Size exclusion chromatography
 - Purity: CE-SDS
 - Oligosaccharide assays (for *N*-linked oligosaccharides and sialic acid)
- ▶ Included in other USP chapters
 - Content: <507> *Total Protein Measurement*, new in PF in 2015
 - Identity: <1055> *Biotechnology-Derived Articles—Peptide Mapping*
 - Process Related Impurity assays
 - <1132> *Residual Host Cell Protein Measurement in Biopharmaceuticals*
 - <509> *Residual DNA Testing*, new in PF in 2016
 - <130> *Protein A Quality Attributes*
 - <791> *pH*
 - <631> *Color and Achromicity*
 - <71> *Sterility Tests*

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Example: Monoclonal IgG System Suitability

SEC-HPLC Chromatograms

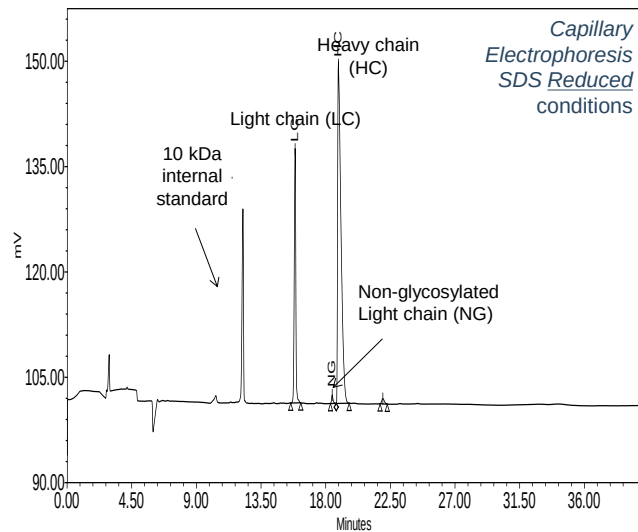


- ▶ RS chromatograms must be consistent with the typical chromatogram provided in the USP certificate

- ▶ The area percent for the high molecular weight species (HMWS), the main peak, and the low molecular weight species (LMWS) must meet the criteria.

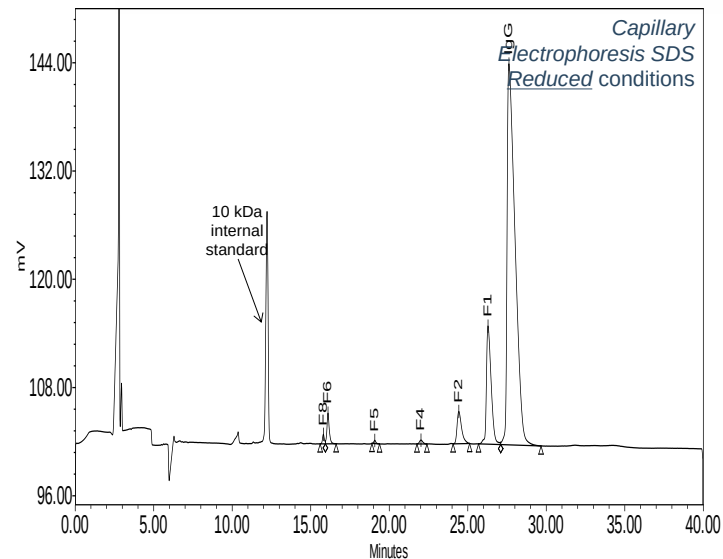
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Example: Electropherogram for Monoclonal IgG System Suitability



- Sensitive method for the quantitation of non glycosylated vs. other forms (half antibodies, and other fragments) , analysis of LC, HC.
- Main peak of the heavy chain (HC) must be clearly identified, the resolution criteria between nonglycosylated HC and intact HC must be met

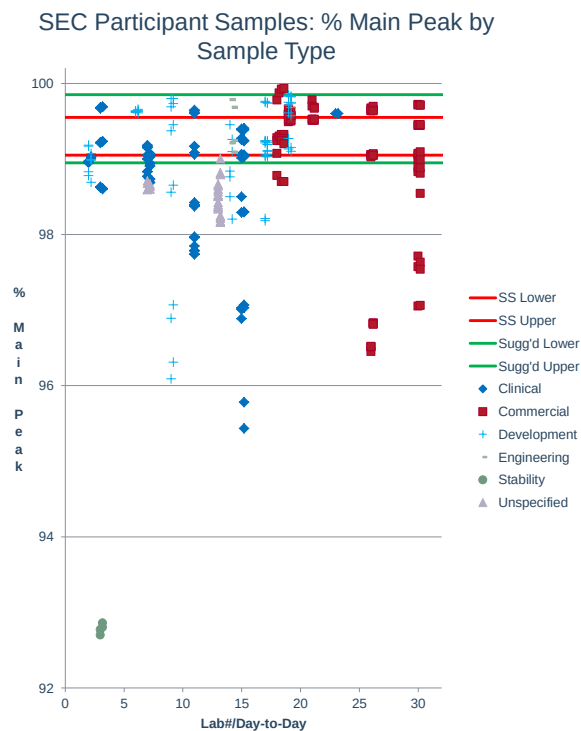
Example: Electropherogram for Monoclonal IgG System Suitability



- The IgG main peak must be clearly identified
- The resolution criteria between IgG main peak and Fragment 1 must be met
- The area percent of main IgG peak must be met.



Assay fitness for purpose across product and sample types



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Product-Specific Quality Attributes of MABs

- ▶ Several quality attributes of MABs can be highly product specific
- ▶ Such attributes should be addressed at the monograph level
- ▶ For example:
 - Charge heterogeneity, analyzed by IEX chromatography or cIEF
 - Hydrophobic interaction chromatography
 - Ligand binding, e.g. by ELISA
 - Cell-based potency assay

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Role of Standards in the Biologics – Summary

- ▶ Modern public standards form an integral part of the multi-tiered safety net that assures access to high quality medicines.
- ▶ They are intended to support and complement regulatory assessment and apply throughout the product lifecycle.
- ▶ USP monographs can be supported by more than one reference standard, these can be used to control product variants during the lifecycle of a therapeutic products.
- ▶ USP standards for biologics are continually revised to address key quality attributes of these products.



Thank You