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.

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

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

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

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**

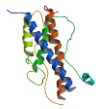
European Pharmacopoeia and Biologicals

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

1992 — Products of recombinant DNA technology

1993 — Human insulin

1994 — Somatropin

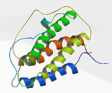


1995 — Hepatitis B vaccine

1997

1998 — Interferon alfa-2

1999 — EPO



2000 — Interferon gamma-1b

European Pharmacopoeia and Biologicals

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

2002

2003 — Molgramostim

2004

2005 — Human coagulation factor VIII; Insulin lispro; Insulin aspart

2008 — P4BIO pilot phase P4

2009 — Filgrastim

2011 — Interferon beta-1a

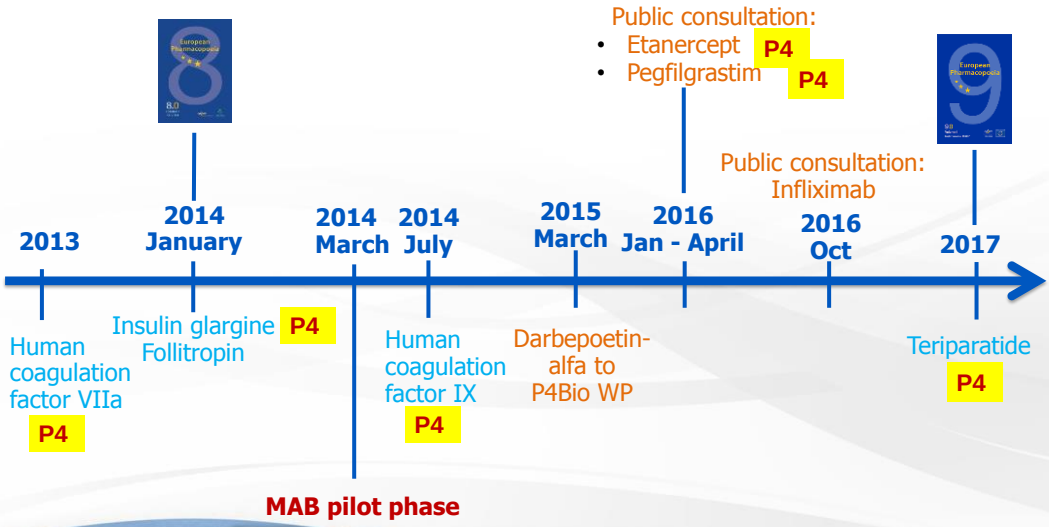
Elaboration procedures: the single source approach:

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

European Pharmacopoeia and Biologicals

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



Monographs for Biotherapeutic products: the challenges

Complexity of biologicals

Feedback received

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

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;**

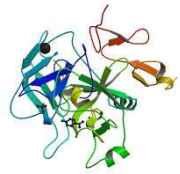
→ **flexible**, while being comprehensive and **sufficiently prescriptive.**

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

✓ reflect **process-dependent heterogeneity** (*e.g.* glycosylation);

✓ include requirements for **consistency of production.**

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**

Feedback received

Complexity of biologicals and legislation

NOT RELEVANT

"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*.**

Monographs for Biotherapeutic products: the challenges

Complexity of biologicals

Diversity of quality attributes/ analytical methods

Choice of tests

Monograph specifications

.....

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.**

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)

Monographs for Biotherapeutic products: the challenges

Complexity of biologicals

Diversity of quality attributes/ analytical methods

Choice of tests

Monograph specifications

Data package/ Submission of information

Reference standards

Collaboration with all players

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

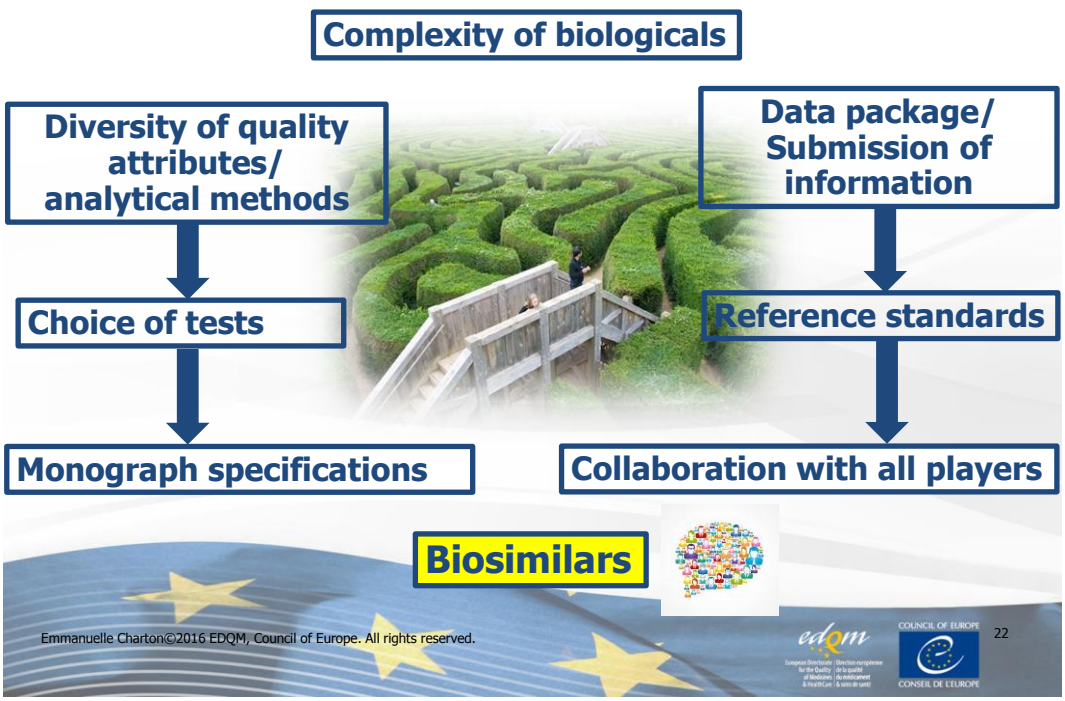
➢ Biological Reference Preparations (BRPs)

- **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

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?

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**.

Feedback received

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

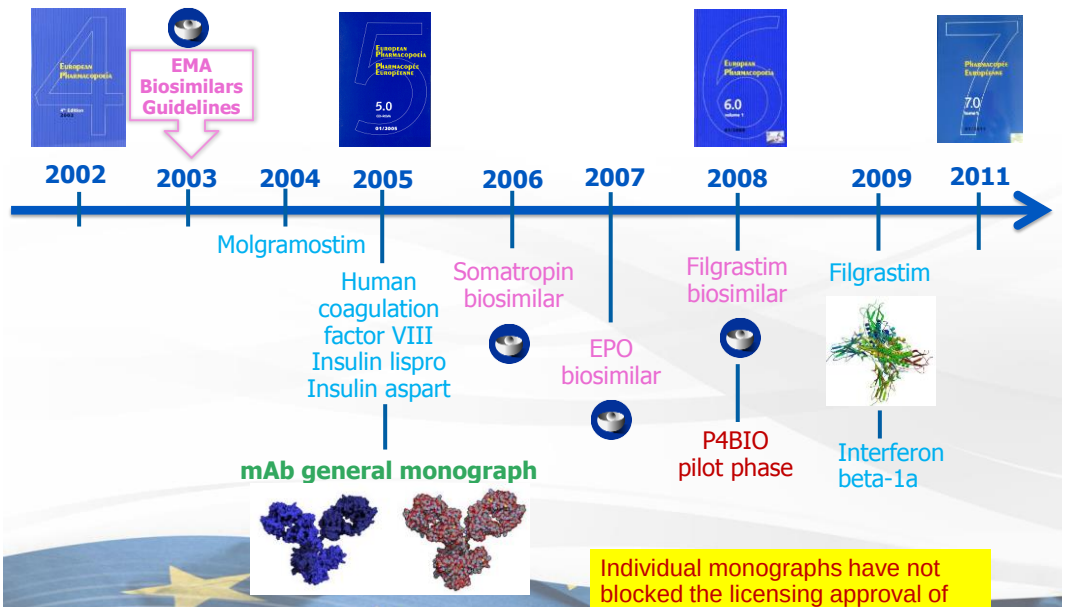
"Individual monographs delay the registration process of biologicals and biosimilar products."

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

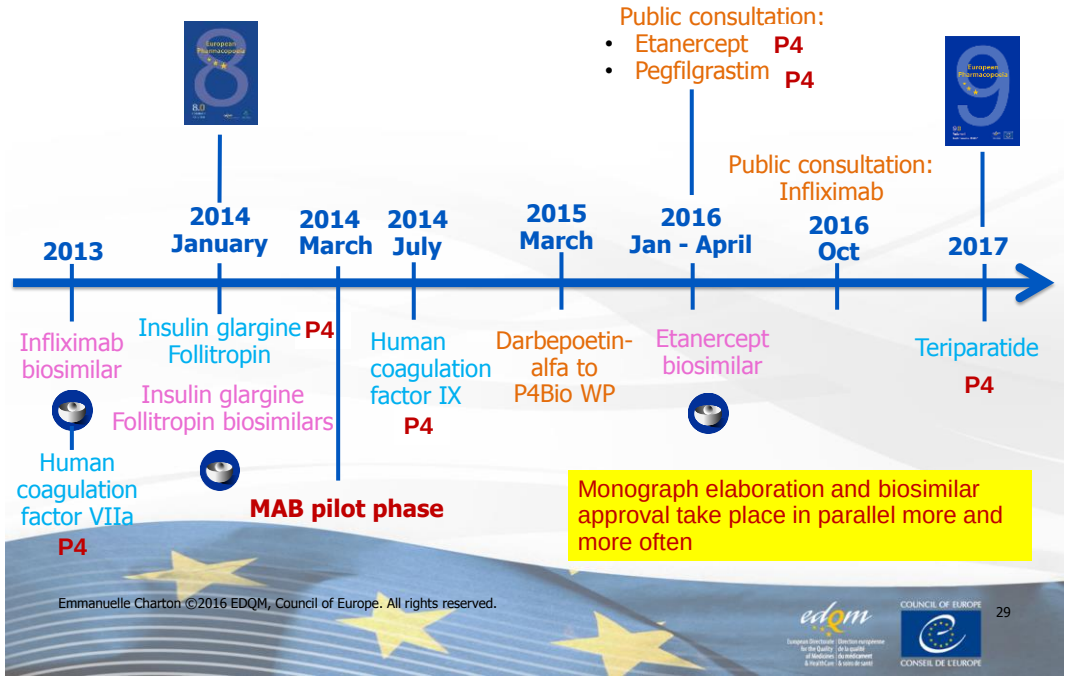
rDNA products in the Ph. Eur. (2002-2011)



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

European Pharmacopoeia and Biologicals

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



Biosimilars and Ph. Eur.

- 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.

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

Challenges

What are the real challenges?

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

Thank you for your attention!

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**

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:

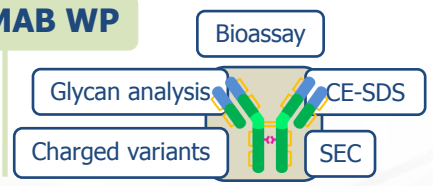
- **visible particles;**
- add terminology used in the draft EMEA "*Guideline on production and quality control of monoclonal antibodies and related substances*" (3AB4A).

Ph. Eur. Supplement 7.3; 07/2011

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

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

MAB WP



2011 — 2013 — 2014

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

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

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

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

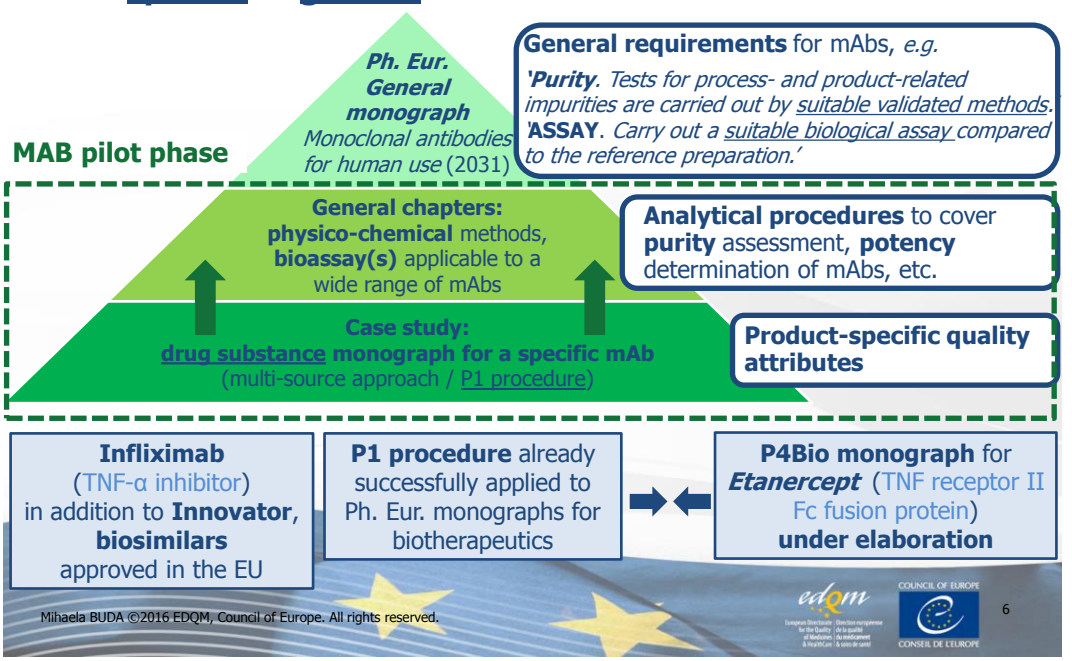
MAB pilot phase:

- 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

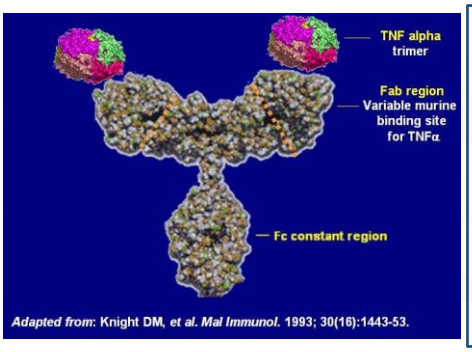
MAB Pilot Phase: a 'Bottom-up' Approach

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 × 2
- ❑ **Heavy chains** (HC): 450 aa × 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)

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)

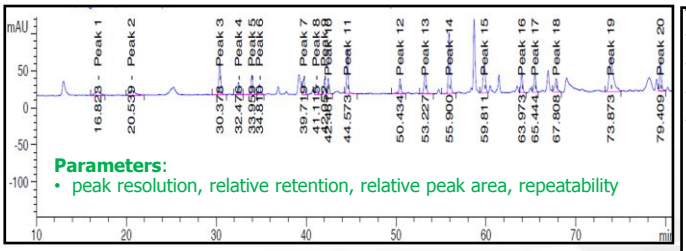
Six batches (from drug substance and drug products approved in EU) and **in-house reference standard** tested

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

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

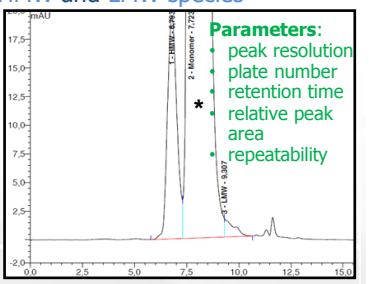
Infliximab Collaborative Study: Results (1)
- physico-chemical testing -

A) Peptide mapping (ID): 20 peptide fragments



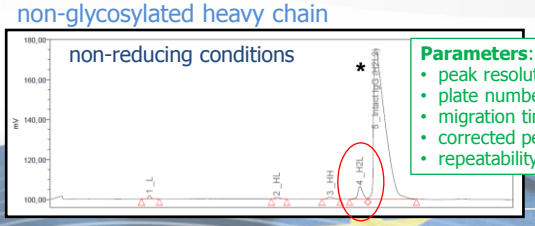
Parameters:
- peak resolution, relative retention, relative peak area, repeatability

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

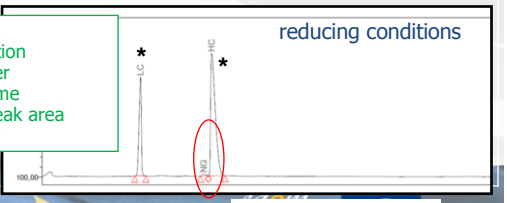


Parameters:
- peak resolution
- plate number
- retention time
- relative peak area
- repeatability

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



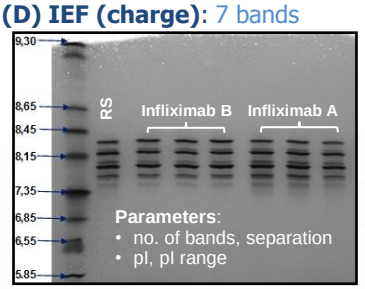
Parameters:
- peak resolution
- plate number
- migration time
- corrected peak area
- repeatability



Unpublished data

Infliximab Collaborative Study: Results (2)
- physico-chemical testing -

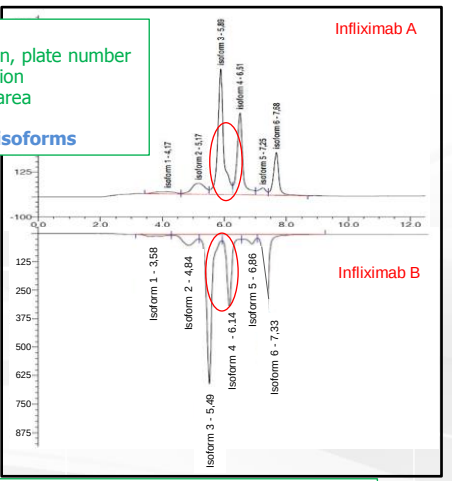
(D) IEF (charge): 7 bands



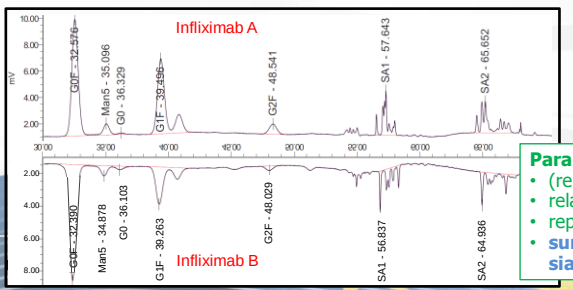
Parameters:
- no. of bands, separation
- pI, pI range

(E) CEX (charge): 6 isoforms

Parameters:
- peak resolution, plate number
- relative retention
- relative peak area
- repeatability
- **percentage isoforms**



(F) Glycan analysis

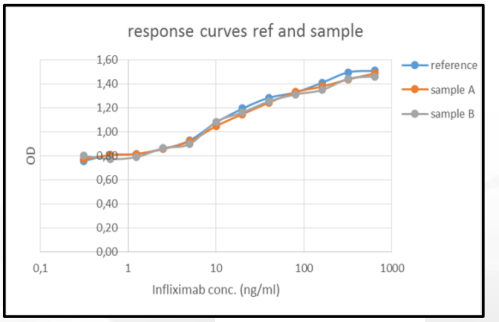


Parameters:
- (relative) retention
- relative peak area
- repeatability
- **sum** of **fucosylated**, of **afucosylated** and of **sialylated species**

Unpublished data

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 **suitabl**e 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***.

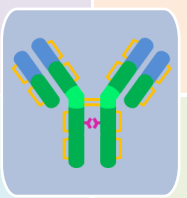
Infliximab Concentrated Solution
- draft monograph -

IDENTIFICATION

A. Assay/Potency
B. Peptide mapping

ASSAY

Protein (UV determination)
Potency



PRODUCTION

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

TESTS

pH
Residual protein A
Related proteins (CE-SDS)
Impurities with molecular masses differing than that of infliximab (SEC)

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*** *Reference solution*: infliximab CRS	– RS electropherogram '***qualitatively similar***' with electropherogram in the CRS leaflet.	– electropherogram obtained with test solution consistent with RS electropherograms. **Numerical limits**: ∑peaks other than HC and LC; ∑peaks other than principal peak.
Impurities with different MW	**SEC** (Ph. Eur. 2.2.30) ***Detailed analytical procedure*** *Reference solution*: 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**: ∑peaks other than the monomer.

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.

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)*: infliximab 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)*: infliximab 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)*: infliximab 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:

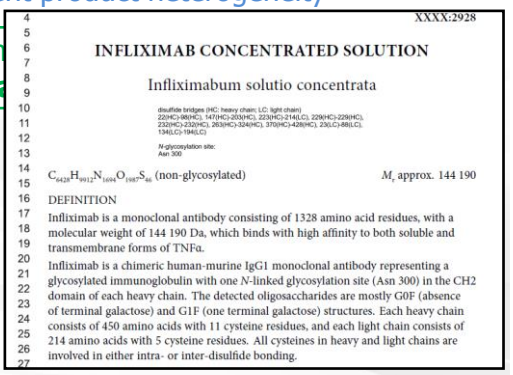
- the glycan profile and charge heterogeneity depend on the manufacturing process;
- the tests prescribe the use of an in-house reference preparation and this material is available only to the manufacturer;
- the user needs acceptance criteria in form of numerical limits, which are not prescribed in 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 n
fundamenta

- **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.



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INFLIXIMAB CONCENTRATED SOLUTION

Infliximabum solutio concentrata

disulfide bridges (HC: heavy chain; LC: light chain)
22(HC)-96(HC), 147(HC)-203(HC), 223(HC)-214(LC), 229(HC)-229(HC), 232(HC)-232(HC), 263(HC)-324(HC), 370(HC)-428(HC), 23(LC)-88(LC), 134(LC)-194(LC)

N-glycosylation site:
Asn 300

$C_{6426}H_{9912}N_{1694}O_{1987}S_{46}$ (non-glycosylated) M_r approx. 144 190

DEFINITION

Infliximab is a monoclonal antibody consisting of 1328 amino acid residues, with a molecular weight of 144 190 Da, which binds with high affinity to both soluble and transmembrane forms of TNFα.

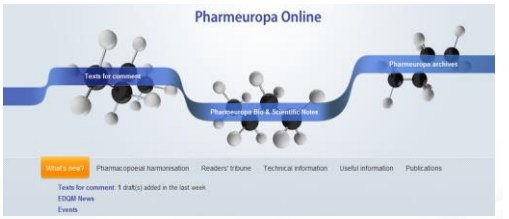
Infliximab is a chimeric human-murine IgG1 monoclonal antibody representing a glycosylated immunoglobulin with one *N*-linked glycosylation site (Asn 300) in the CH2 domain of each heavy chain. The detected oligosaccharides are mostly G0F (absence of terminal galactose) and G1F (one terminal galactose) structures. Each heavy chain consists of 450 amino acids with 11 cysteine residues, and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteines in heavy and light chains are 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)

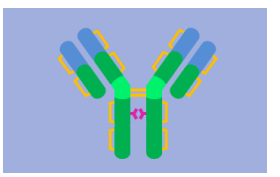


- The **addresses of the national pharmacopoeia authorities** and of the EDQM are published on the **Pharmeuropa** website under the tab **Useful information.**
- Comments are to be submitted before the specified deadline (**Pharmeuropa 28.4 / 31st December 2016**).
- Please refer to the "**How to comment**"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

MAB Pilot Phase: What's Next?

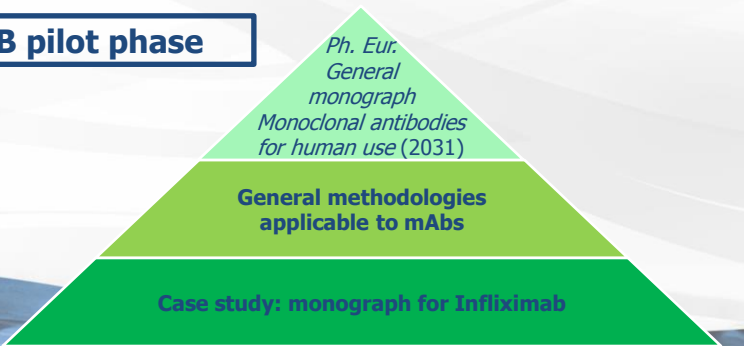
Draft monograph for Infliximab

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



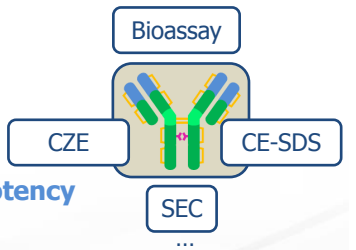
Decision on the adoption of the final text for publication in the Ph. Eur.

Progress the MAB pilot phase



MAB Pilot Phase: Prospective Work

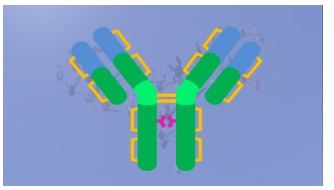
Horizontal approaches



- **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!

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 ist 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)

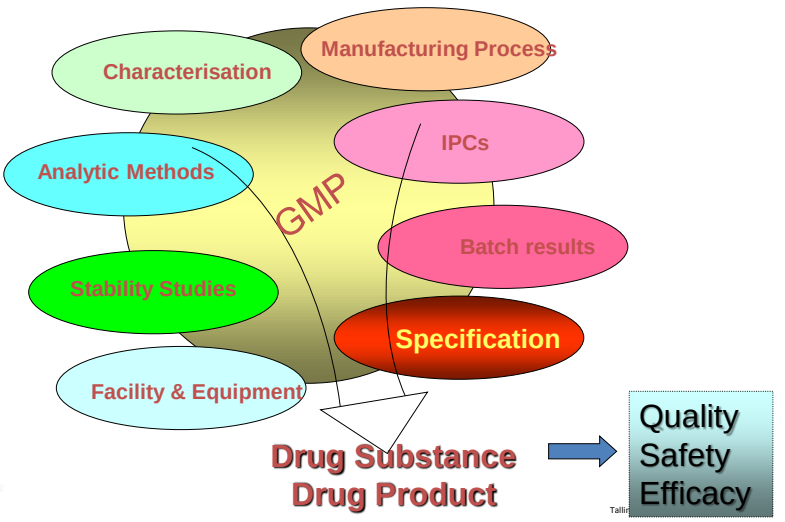
- Process = Product

  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

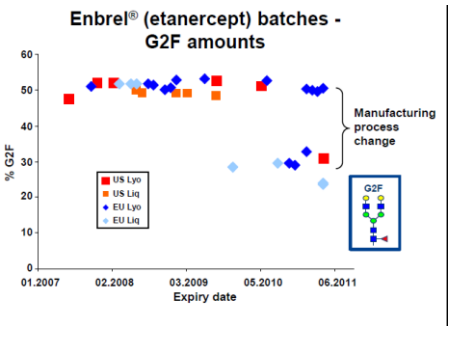
Justification of specification according to ICH Q6B

- 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

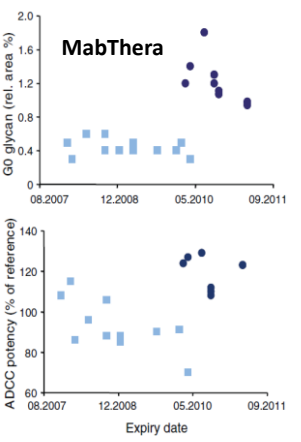
- Quality attributes / specification limits can be changed during the lifecycle of a product (many examples)
- Certain analytical test may be removed based on enhanced process-/ product understanding or replaced by RTRT and or surrogate tests

➡ 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 profil
- Comparability pre- and post- change needs to be demonstrated (Q/S/E) (Comparability Excercise)
- 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 inlcude 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 demonstrated that the method is at least equivalent/non inferior. (E.g. better resolution, methods is 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 c…red applicable to all drug substances :

- Appearance and description
- Identity (more than 1 test)
- Quantity
- Purity (Combination of …
- Impurities (process/prod…t 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.

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.

Potency

Bioassays based on different formats

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

Acc. 80-120% relative to
solution

dence limits
5) 80-125% of
ed potency

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

Problems, e.g.:

- non-commercially a
- availability of cells lin
- 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

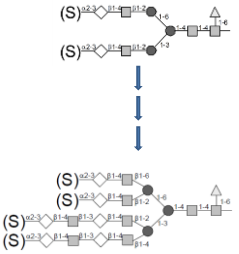
→ Analytical tests for isoforms such as IEF or CZE are not sufficient (e.g. Epo)

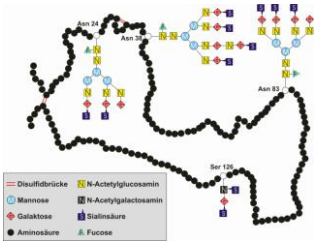
→ Etanercept Draft Monograph: N-Glycans - no acceptance criteria! As authorised! Production section

Erythropoietin

Reference Product

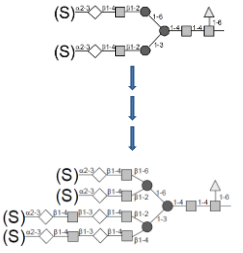
bi- to tetraantennary, complex N-Glycans



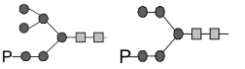


Biosimilar

bi- to tetraantennary, complex N-Glycans

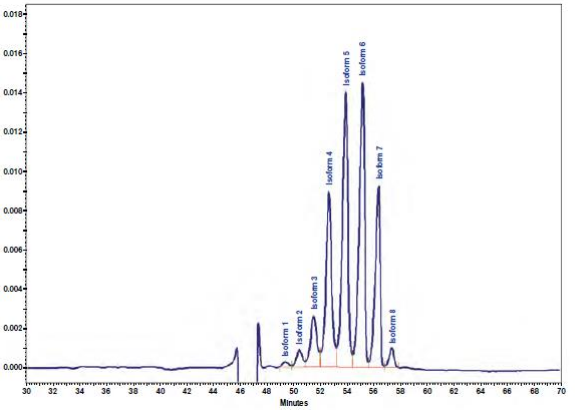


Phosphorylated high-mannose structures



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://sciex.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.

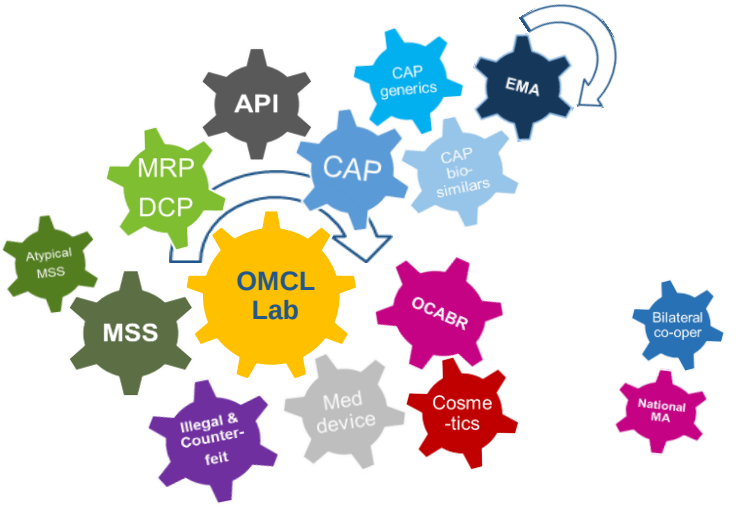
Official Medicines Control Laboratory = OMCL

- 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 …



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.

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 reqirements

  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 furher 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?*

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, Ø = 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.

Example 2. Filgrastim DS monograph, pepmap LC

CHROMATOGRAPHIC SEPARATION. Liquid chromatography (*2.2.29*).

Column:

- *size*: *l* = 0.10 m, Ø = 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* in 50 mL of *water R*, add 950 mL of *acetonitrile for chromatography R* and mix;

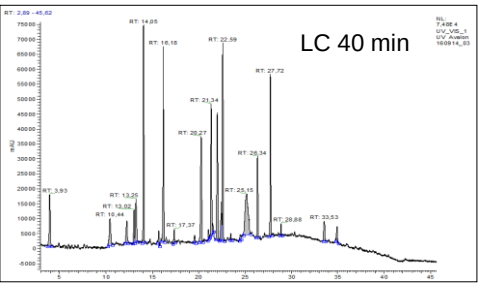
Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	97 → 94	3 → 6
8 - 25	94 → 66	6 → 34
25 - 40	66 → 10	34 → 90
40 - 45	10	90

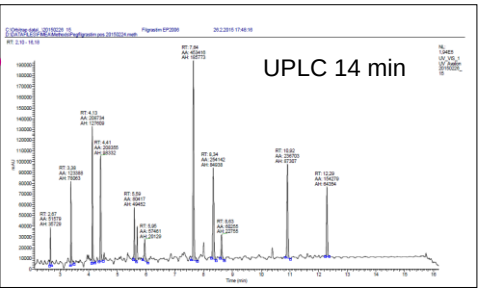
Flow rate: 0.2 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 10 µL.

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





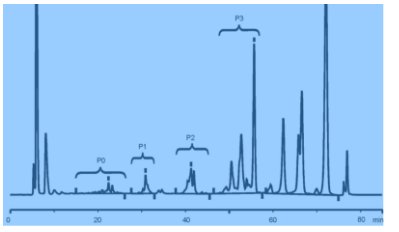
Example 3. Factor IX (rDNA) monograph, glycans

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.



…atogram for the test for glycan … factor IX (rDNA)

Results:

– the profile of the chromatog… the test solution correspon… chromatogram obtained w…

– the relative retentions … peaks in groups P0 to P… obtained with the test sol… reference solution (b);

– the tetrasialylated peak are… solution is *within the limits autho… competent authority*.

Use of assay system suitability standard creates flexibility

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

Example 4. Etanercept monograph draft, potency

Potency. The potency of the preparation to be examined is determined by comparison of the dilutions of the test preparation with the dilutions of *etanercept BRP*. Carry out the assay 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 the inhibitory effect.

The following method has been found suitable.

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

The following indications are given as an example.

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 (horisontal 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 aviod 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!

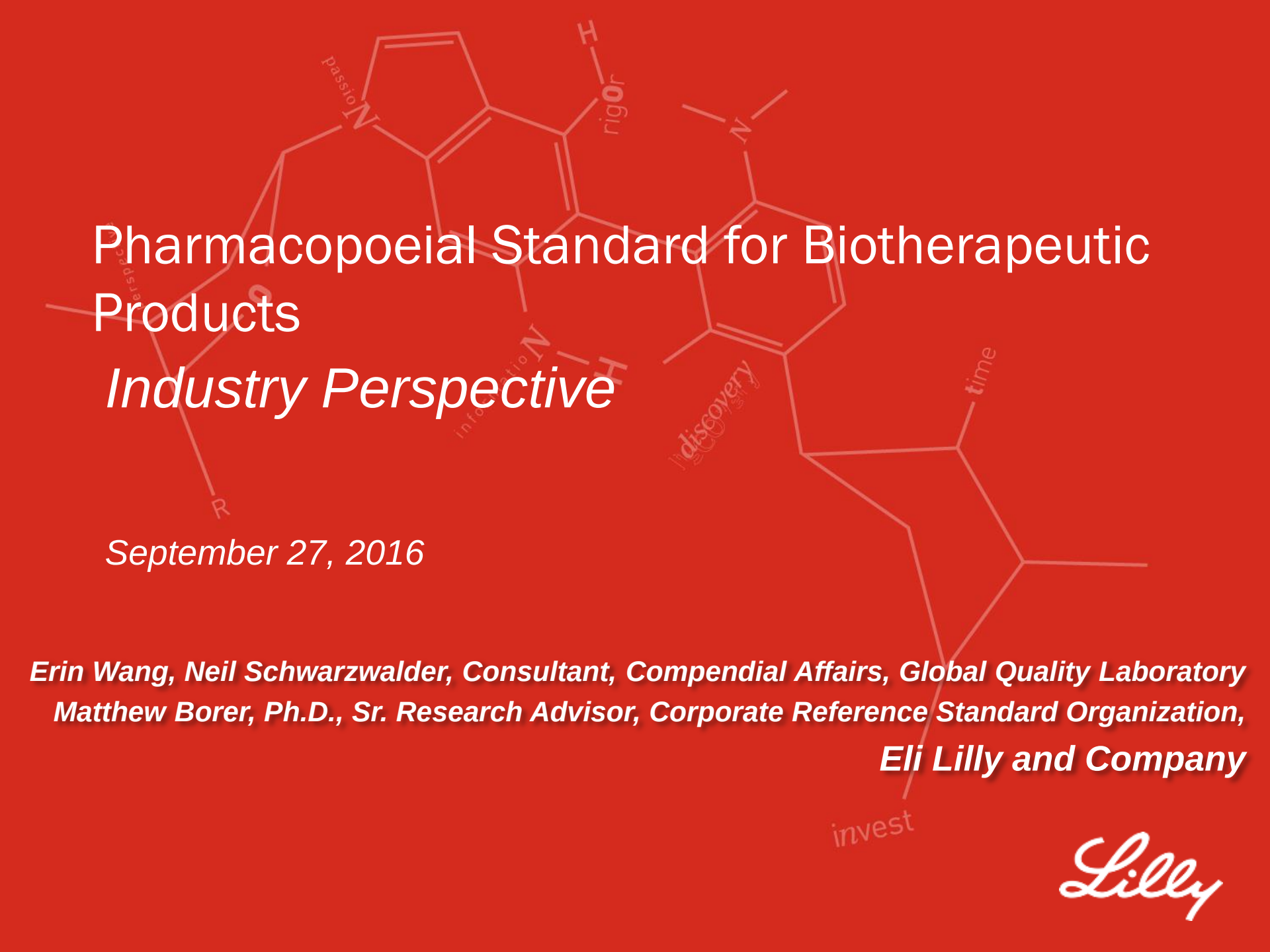
THANK YOU!!

Pharmacopoeial Standard for Biotherapeutic Products

Industry Perspective

September 27, 2016

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



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- Philip Travis, Manager/Team Leader, Global Quality Intelligence and Compendial Affairs, Pfizer, Inc.
- 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

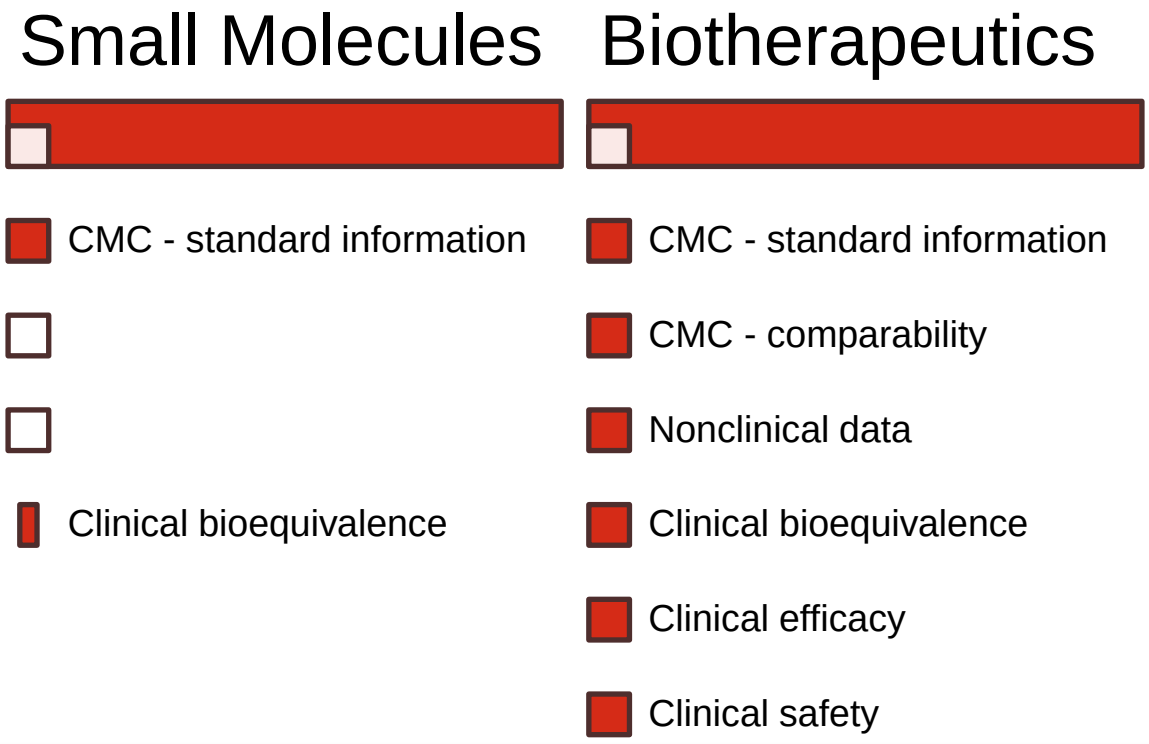
Manufacturers' Perspective

Manufacturers have expressed support for non-specific public standards (general chapters, general monographs) for biotherapeutic 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



- 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

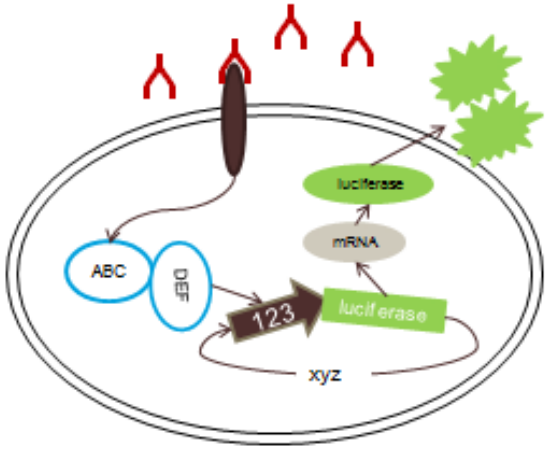
- Possible clarification in General Notices or General Monograph:
  - Standards for biosimilarity or interchangeability of biotechnology products are set by regulatory agencies based on additional clinical, non-clinical and quality data.
  - Determination of acceptability is made by regulatory authorities 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

General Method

- **Develop and/or improve the set of General Method(s) used to assess the quality of Biotech./Biological products**
  - By addressing and completing test methods for well known process related impurities (e.g Protein A…) and/or on contaminants (e.g Viral safety…)

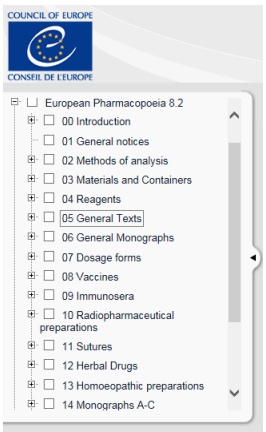
General Monograph

- **Expand and pursue the development of General Monograph for Biotech/Biological building on Product-classes Standard monograph approach.**
  - By establishing the foundation for scientifically –based public standards
    - including a list of Quality Attributes and information on product understanding (shared Knowledge) from which a key part of the Testing Strategy can be derived

General Text

- **Develop a NEW General Text on "Product Class Testing"**
  - to provide suitable analytical tools (battery of methods, analytical procedures) consistent with the defined Quality Attributes related to a defined class of product and their physical standards (Suitability test) to control their performance.

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),...

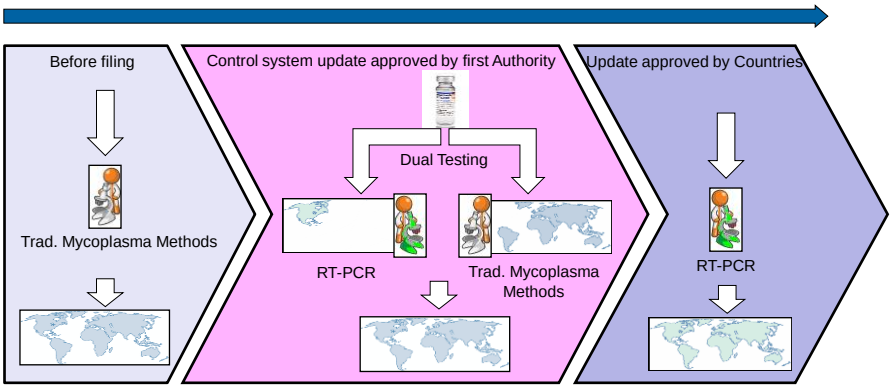
Example 1: Implementation of Mycoplasma standard for Real-Time PCR

- 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.

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

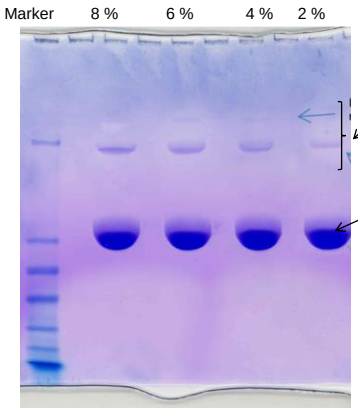


Significant improvement to control strategy

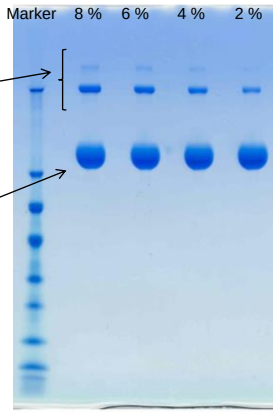
Example 2:
Introduction of different procedures in monograph

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

pharmacopeial method (**non EP**)



Internal Method



Example 2:
SDS-PAGE Internal vs pharmacopeial

Roche

Attribute	Spike	Pharmacopeial method [area-%]	Internal method [area-%]
Monomer	8 %	95	75
Monomer	6 %	96	78
Monomer	4 %	97	83
Monomer	2 %	99	89
HMW species	8 %	5	21
HMW species	6 %	4	17
HMW species	4 %	3	12
HMW species	2 %	1	9

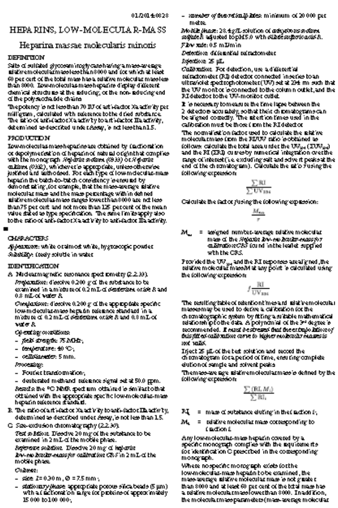
- Internal method more sensitive
- All batches pass acceptance corresponding methods
- Methods and acceptance criteria do not match

⇨ **Compliance risk**

⇨ **Change to pharmacopeial method? Dual testing?**
Testing according to each pharmacopeia?

Roche

Example 3:
Product specific vs Class specific monograph


01/2014:0828

HEPARINS, LOW-MOLECULAR-MASS

Heparina massae molecularis minoris

DEFINITION

PRODUCTION

CHARACTERS

IDENTIFICATION

- HEPARINS, LOW-MOLECULAR MASS
- IDENTIFICATION
  - A. NMR spectrometry
  - B. Ratio anti-Fxa/anti-FIIa
  - C. Average relative mass by SEC
  - D. Reaction of sodium or calcium

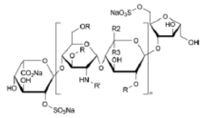
Identification

- Test A, C and D

01/2008:1195

DALTEPARIN SODIUM

Dalteparinum natricum



n = 3 to 20 , R = H or SO_3Na , R' = SO_3Na or $CO\text{-}CH_3$
R2 = H and R3 = CO_2Na or R2 = CO_2Na and R3 = H

DEFINITION

Dalteparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by nitrous acid depolymerisation of heparin from porcine intestinal mucosa. The majority of the components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 6-O-sulfo-2,5-anhydro-D-mannitol structure at the reducing end of their chain.

Dalteparin sodium complies with the monograph Low-molecular-mass heparins (0828) with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 5600 and 6400, with a characteristic value of about 6000.

The degree of sulfatation is 2.0 to 2.5 per disaccharide unit.

The potency is not less than 110 IU and not more than 210 IU of anti-factor Xa activity per milligram, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 35 IU/mg and not more than 100 IU/mg, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 1.9 and 3.2.

PRODUCTION

Dalteparin sodium is produced by a validated manufacturing and purification procedure under conditions designed to minimise the presence of N-NO groups.

The manufacturing procedure must have been shown to reduce any contamination by N-NO groups to approved limits using an appropriate, validated quantification method.

IDENTIFICATION

Carry out identification test A as described in the monograph *Low-molecular-mass heparins (0828)* using *dalteparin sodium CRS*.

Carry out identification test C as described in the monograph *Low-molecular-mass heparins (0828)*. The following requirements apply.

The mass-average relative molecular mass ranges between 5600 and 6400. The mass percentage of chains lower than 3000 is not more than 13.0 per cent. The mass percentage of chains higher than 8000 ranges between 15.0 per cent and 25.0 per cent.

TESTS

Appearance of solution. Dissolve 1 g in 10 mL of *water R*. The solution is clear (2.2.1) and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour (2.2.2, *Method II*).

Nitrite. Not more than 5 ppm. Examine by liquid chromatography (2.2.29). *Rinse all volumetric flasks at least three times with water R before the preparation of the solutions.*

Test solution. Dissolve 80.0 mg of the substance to be examined in *water R* and dilute to 10.0 mL with the same solvent. Allow to stand for at least 30 min.

Reference solution (a). Dissolve 60.0 mg of *sodium nitrite R* in *water R* and dilute to 1000.0 mL with the same solvent.

For the preparation of reference solution (b), use a pipette previously rinsed with reference solution (a).

Reference solution (b). Dilute 1.00 mL of reference solution (a) to 50.0 mL with *water R*.

Before preparing reference solutions (c), (d) and (e), rinse all pipettes with reference solution (b).

Reference solution (c). Dilute 1.00 mL of reference solution (b) to 100.0 mL with *water R* (corresponding to 1 ppm of nitrite in the test sample).

Reference solution (d). Dilute 3.00 mL of reference solution (b) to 100.0 mL with *water R* (corresponding to 3 ppm of nitrite in the test sample).

Reference solution (e). Dilute 5.00 mL of reference solution (b) to 100.0 mL with *water R* (corresponding to 5 ppm of nitrite in the test sample).

The chromatographic procedure may be carried out using:

- a column 0.125 m long and 4.3 mm in internal diameter packed with a strong anion-exchange resin,
- as mobile phase at a flow rate of 1.0 mL/min a solution consisting of 13.61 g of *sodium acetate R* dissolved in *water R*, adjusted to pH 4.3 with *phosphoric acid R* and diluted to 1000 mL with *water R*;
- as detector an appropriate electrochemical device with the following characteristics and settings: a suitable working electrode, a detector potential of +1.00 V versus *Ag/AgCl* reference electrode and a detector sensitivity of 0.1 µA full scale.

Inject 100 µL of reference solution (d). When the chromatograms are recorded in the prescribed conditions, the retention time for nitrite is 3.3 to 4.0 min. The test is not valid unless:

- the number of theoretical plates calculated for the nitrite peak is at least 7000 per metre per column (dalteparin sodium will block the binding sites of the stationary phase, which will cause shorter retention times and lower separation efficiency for the analyte; the initial performance of the column may be partially restored using a 58 g/L solution of *sodium chloride R* at a flow rate of 1.0 mL/min for 1 h; after regeneration the column is rinsed with 200 mL to 400 mL of *water R*);
- the symmetry factor for the nitrite peak is less than 3;
- the relative standard deviation of the peak area for nitrite obtained from 6 injections is less than 3.0 per cent.

Inject 100 µL each of reference solutions (c) and (e). The test is not valid unless:

- the correlation factor for a linear relationship between concentration and response for reference solutions (c), (d) and (e) is at least 0.995;
- the signal-to-noise ratio for reference solution (c) is not less than 5 (if the noise level is too high, electrode recalibration is recommended);
- a blank injection of *water R* does not give rise to spurious peaks.

Inject 100 µL of the test solution. Calculate the content of nitrite from the peak areas in the chromatogram obtained with reference solutions (c), (d) and (e).

Boron. Not more than 1 ppm, determined by inductively coupled plasma atomic emission spectroscopy.

Boron is determined by measurement of the emission from an inductively coupled plasma (ICP) at a wavelength specific to boron. The emission line at 249.733 nm is used. Use an appropriate apparatus, whose settings have been optimised as directed by the manufacturer.

Test solution. Dissolve 0.2500 g of the substance to be examined in about 2 mL of *water for chromatography R*, add 100 µL of *nitric acid R* and dilute to 10.00 mL with the same solvent.

Reference solution (a). Prepare a 1 per cent V/V solution of *nitric acid R* in *water for chromatography R* (blank).

Reference solution (b). Prepare a 11.4 µg/mL solution of *boric acid R* in a 1 per cent V/V solution of *nitric acid R* in *water for chromatography R* (STD_{cal}).

Reference solution (c). Dissolve 0.2500 g of a reference dalteparin sodium with no detectable boron in about 2 mL of *water for chromatography R*, add 100 µL of *nitric acid R* and dilute to 10.00 mL with the same solvent (STD_0).

Reference solution (d). Dissolve 0.2500 g of a reference dalteparin sodium with no boron detected in about 2 mL of a 1 per cent V/V solution of *nitric acid R* in *water for chromatography R*, add 10 µL of a 5.7 mg/mL solution of *boric acid R* and dilute to 10.00 mL with the same solvent (STD_1). This solution contains 1 µg/mL of boron.

Calculate the content of boron in the substance to be examined, using the following correction factor:

$$f = \frac{(STD_1 - STD_0) \times 2}{(STD_{cal} - blank)}$$

Loss on drying (2.2.32). Not more than 5.0 per cent, determined on 1.000 g by drying in an oven at 60 °C over *diphosphorus pentoxide R* at a pressure not exceeding 670 Pa for 3 h.

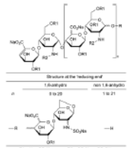
Identification

Test A, C and D + Anion exchange chromatography (**including 26 derivatives**)

01/2014:1097

ENOXAPARIN SODIUM

Enoxaparinum natricum



Example 3:
Product specific vs Class specific monograph

CLASS SPECIFIC LMM HEPARINS	PRODUCT SPECIFIC 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?

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

IFPMA

- 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 emerged[1].
  - 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 syringe[2].

[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

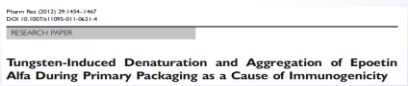
Despite high analytic similarity and clinical similarity in intravenous use study, subcutaneous use study revealed clinically important difference in immunogenicity.

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/s11095-011-0621-4
RESEARCH PAPER
Tungsten-Induced Denaturation and Aggregation of Epoetin Alfa During Primary Packaging as a Cause of Immunogenicity

Industry Expectations/Perspectives

Ph.Eur. General Monograph (**Product Class**)

- List of appropriate Quality Attributes
- List of methods (for identification, characterization and quantification…)

Ph.Eur. General Text (**Product Class** Testing)

Provide guidance and description for one or more of several methodology for the selection of suitable:

- sample preparation
- parameters and conditions of the analytical technique
- as well as system suitability

For different type of testing as identification and/or characterisation and/or quantification

BLA/CTD file

Product Specification

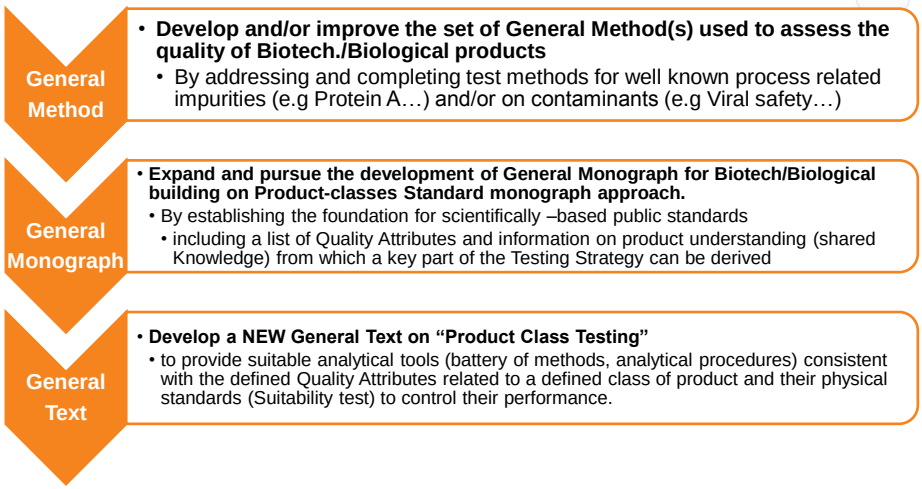
The ability/suitability of the test in the presence of the product to be tested must be confirmed.

Set/Justify Acceptance criteria

The combination of the Product Class Monograph(s) and Product Class General Text should replace Product-specific monograph(s)

efpia

Industry Expectations/Perspectives



efpia ebe Roche

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

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

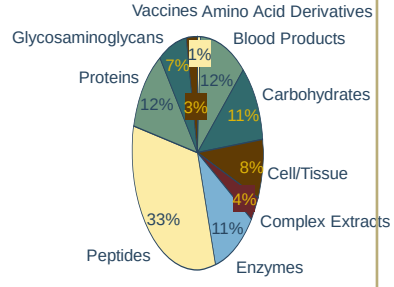
USP's long-term investment in biologics has led to the development of a broad set of standards

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

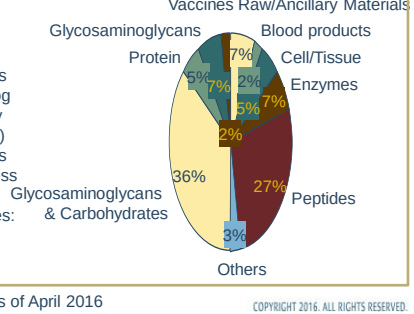
Documentary standards (monographs)

112 documentary standards split across 8 categories:



Physical (Reference) Standards

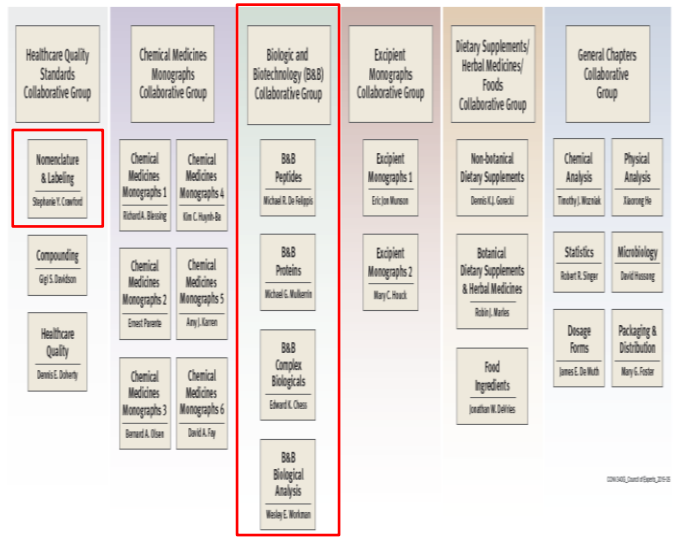
130 physical standards (in catalog or readily available) standards split across 10 categories:



As of April 2016

USP Biologics – Council of Experts & Expert Committees

2015–2020 Council of Experts
Expert Committees and Collaborative Groups

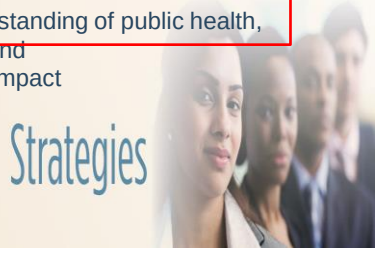


USP Biologics Strategy

2015–2020 Strategies

Continue to develop and improve USP's portfolio of quality standards for biological medicines:

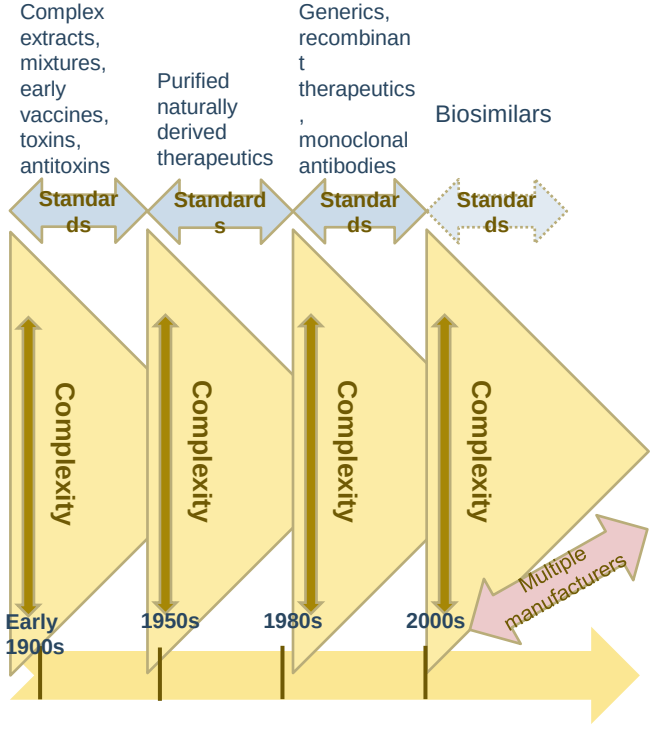
- Continue to modernize standards for legacy products
- Continue to eliminate animal-based bioassays
- Grow portfolio of ancillary and raw materials standards
- Grow portfolio of procedural and system suitability tools for the analysis of all biologics
- Development new standards for biologics based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



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

MTPLGPASSL PQSFLLKCLE QVRKIQGDGA ALQEKLCATY KLCHPEELVL
LGHSLGIPWA PLSSCPSQAL QLAGCLSQLH SGLFLYQGLL QALEGISPEL
GPTLDTLQLD VADFATTIWQ QMEELGMAPA LQPTQGAMPA FASAFQRRAG
GVLVASHLQS FLEVSYRVLR HLAQP

$C_{845}H_{1339}N_{223}O_{243}S_9$ 18,799 daltons
[121181-53-1].

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⟩.)

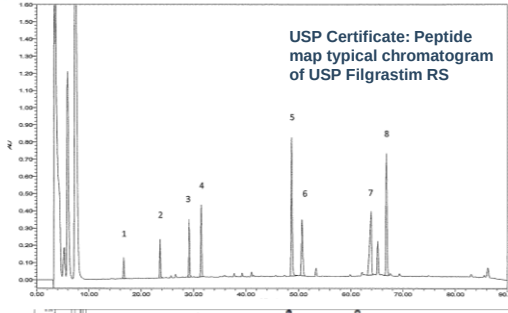
In addition to the originator, 2 recent products are licensed in the US:

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

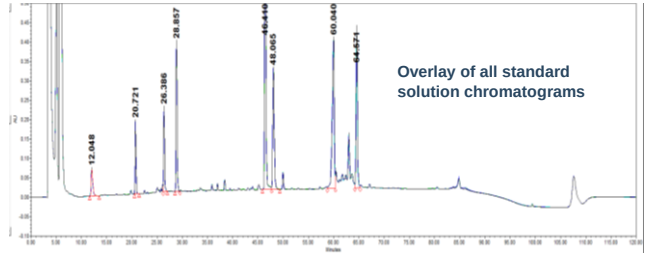
USP tested 3 batches from filgrastim-sndz; these meet the USP Filgrastim drug substance monograph criteria for:

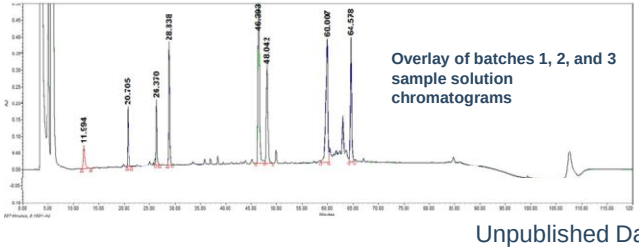
- Identification *(data on next slide)*
- Assay
- Impurities
- Other requirements

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

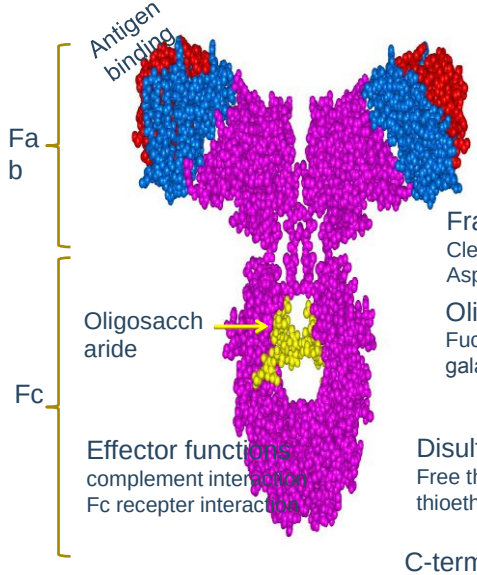
Case Study 2: Approach to Quality Attributes Across Product Classes

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

Which Quality Attributes to Consider?

Biological characteristics

Physico-chemical characteristics



N-terminal heterogeneity
pyroglutamate formation
Other modifications

AA modifications
deamidation, oxidation, glycation, isomerization

Fragmentation
Cleavage in hinge region, Asp-Pro

Oligosaccharides
Fucosylation, sialylation, galactosylation…

Disulfide bonds
Free thiols, disulfide shuffling, thioether

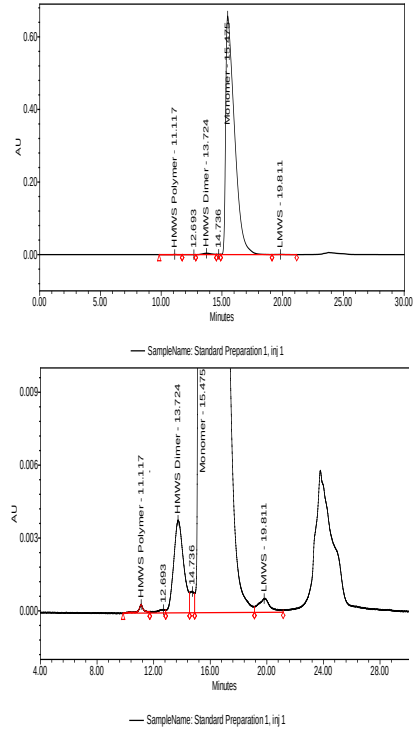
C-terminal heterogeneity
Lysine processing, proline amidation

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*

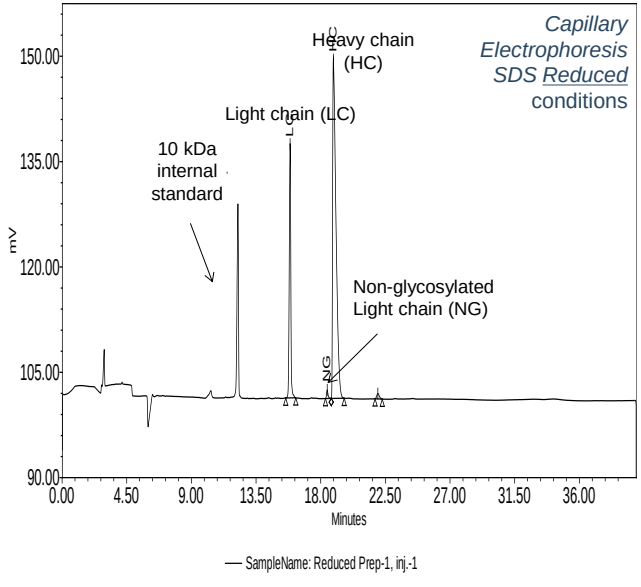
Example: Monoclonal IgG System Suitability

SEC-HPLC Chromatograms



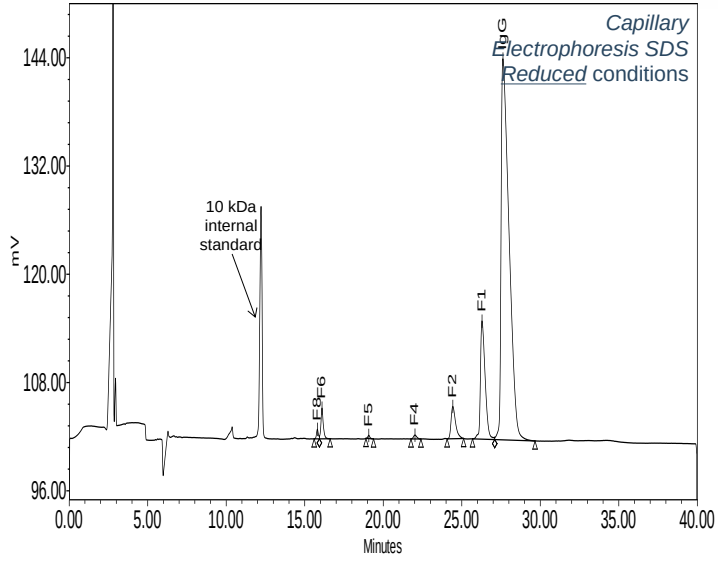
- RS chromatograms must be consistent with the typical chromatogram provided in the USP certificate
- The area percent for the high molecular weight species (HMWS), the main peak, and the low molecular weight species (LMWS) must meet the criteria.

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 nonglycoslylated HC and intact HC must be met

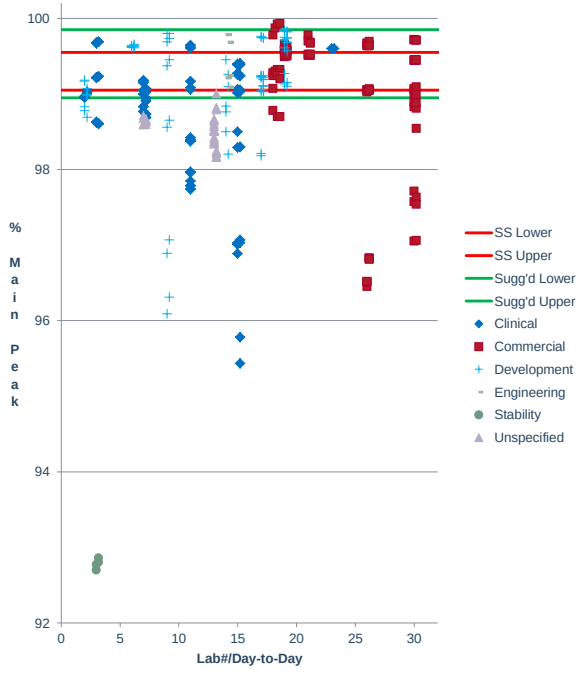
Example: Electropherogram for Monoclonal IgG System Suitability



- 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

SEC Participant Samples: % Main Peak by Sample Type



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

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.

USP U.S. Pharmacopeial Convention
Global Expertise
Trusted Standards
Improved Health

Thank You