



Making Medicines Affordable

Manufacturing and Quality Aspects for Biosimilars

Copenhagen, 24 Oct 2011

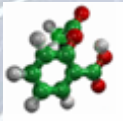
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Biopharmaceuticals



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Biopharmaceuticals are Complex...



Aspirin®



Calcitonin



Monoclonal
Antibody (IgG)

small chemical molecule



peptide



complex biologic

Molecular weight
= 180 Daltons
0 amino acids

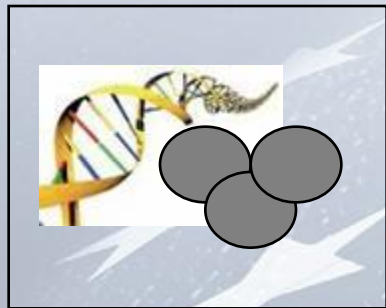
Molecular weight
= 3,455 Daltons
~ 32 amino acids

Molecular weight
= 150,000 Daltons
~ 1300 amino acids

- w/o host cell modifications
- produced in yeast, bacteria

- w/host cell modifications (glycosylations, etc)
- produced in mammalian cells

...and are Produced from Living Organisms



Modify host cells
(e.g., bacteria, yeast
mammalian cells) to
produce
recombinant
proteins



Grow cells
under
controlled
conditions
(fermentation)



Extract, refold,
purify
(downstream) -
generate drug
substance



Formulate to
stable finished
drug product
(vial, syringe,
cartridge)

What is a Biosimilar (Follow-on Biologic)?

Description

Overview

- Successor to a biologic medicine that has lost exclusivity & patent protection
- Not a simple generic due to complexity: size, structure and manufacturing
- Identical sequence. Differences in post-translational modification.

Regulatory Definition

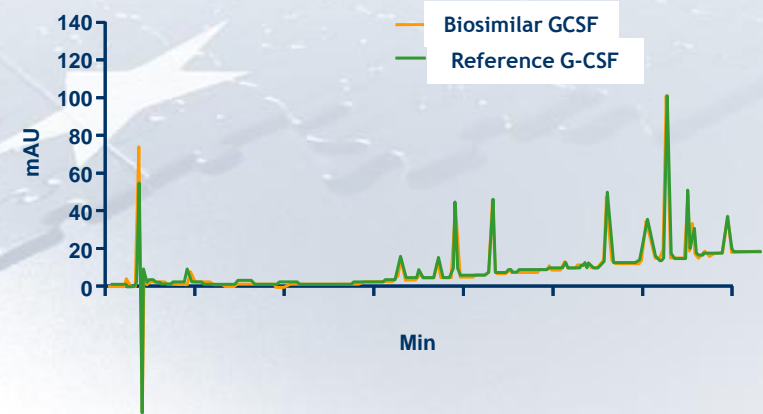
- A biologic approved via a stringent regulatory defined pathway demonstrating comparability with licensed originator at multiple levels

Comparability Approach

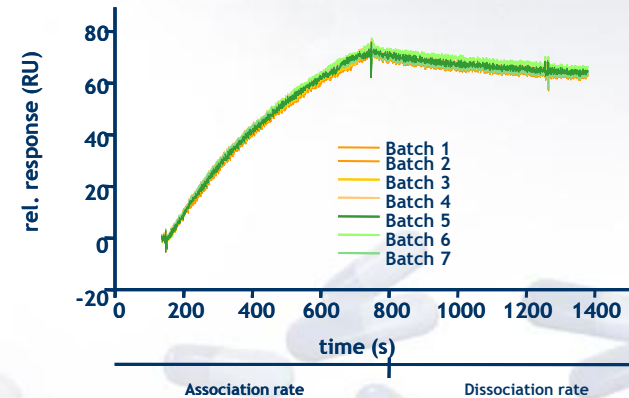
- Highly analogous structure (via robust analytical characterization)
- Comparable quality, safety and efficacy to reference product
- Extrapolation to all indications of originator if same MoA

Robust analytical characterization

GCSF Peptide Mapping



Determination of Receptor Binding: Surface Plasmon Resonance (SPR) spectroscopy



Innovation is required in Technical and Clinical Development of Biosimilars

Key challenges

Time & Investment

- Significant expense (USD 75 - 250m)
- Long time to develop (7-8 years)

Technical Development

- Achieving “highly similar” to match originator molecule profile
- Matching final dosage form of originator or innovative dosage form

Clinical Development

- Use of novel endpoints and populations to confirm biosimilarity (not *de novo* safety/efficacy)
 - Clinical trial design to support extrapolation across indications, interchangeability & commercial success
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Approvable Biosimilars are Systematically Engineered to Match the Reference Product

Define target

Development of
Manufacturing process
Target directed approach

Confirmation:
Final comparability
exercise



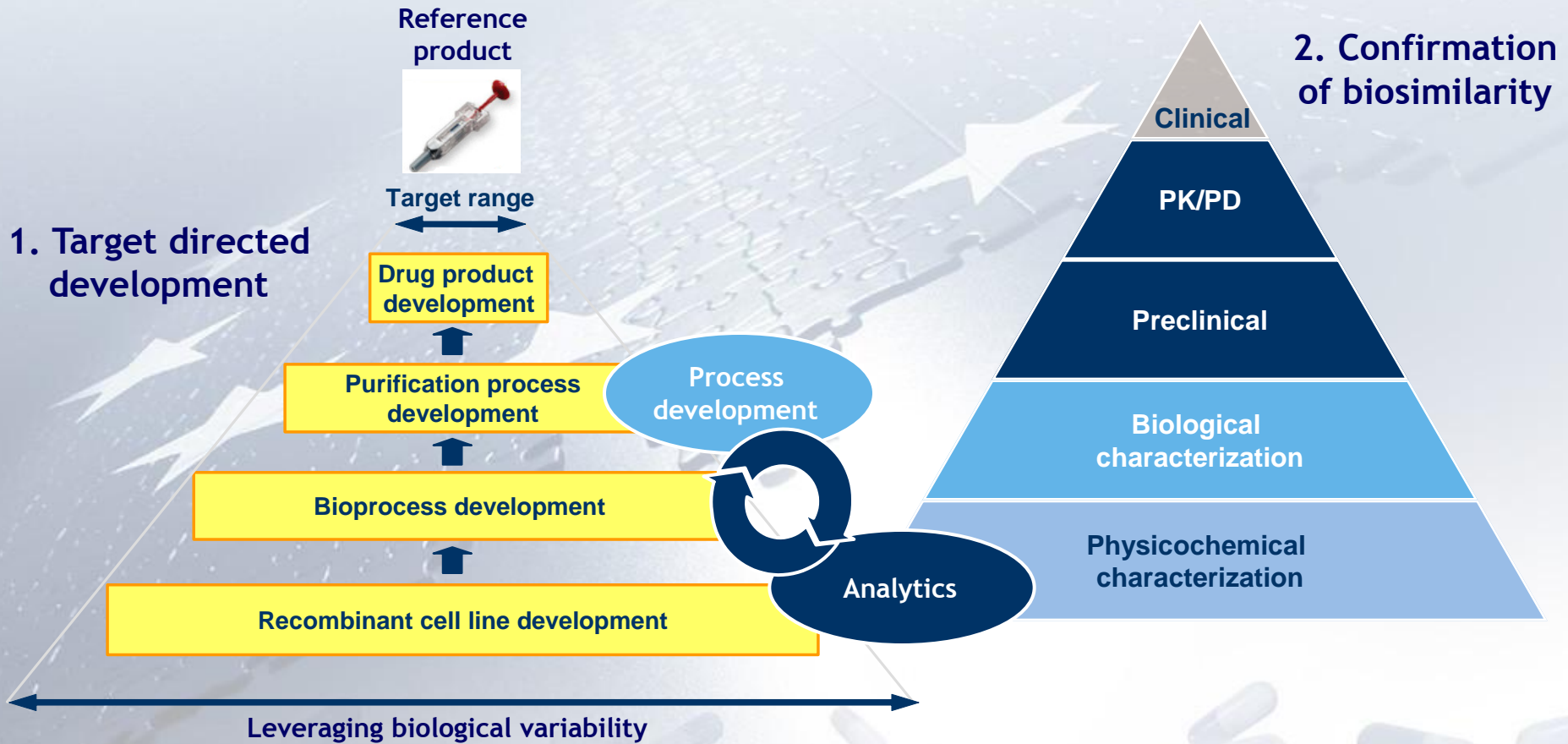
- Characterize multiple lots of the Reference Product
- Variability in the reference product over time provides 'goal posts'
- Iterative optimization of all process steps using
- sophisticated analytical tools

Our experience:

- Risk based approach
- Rank quality attributes for their criticality

“Quality cannot be tested into a product, it has to be built in by design”; International Guideline ICH Q8

Target Directed Development and Confirmation of Biosimilarity





Biosimilars are Produced under the Same Stringent cGMP Requirements

... as innovative Biopharmaceuticals:

- Quality-by-Design based process development
- Quality Assurance approved documentation
- State-of-the-art manufacturing facilities
- Quality Assurance systems to detect deviations, out-of-specification and out-of-trend results

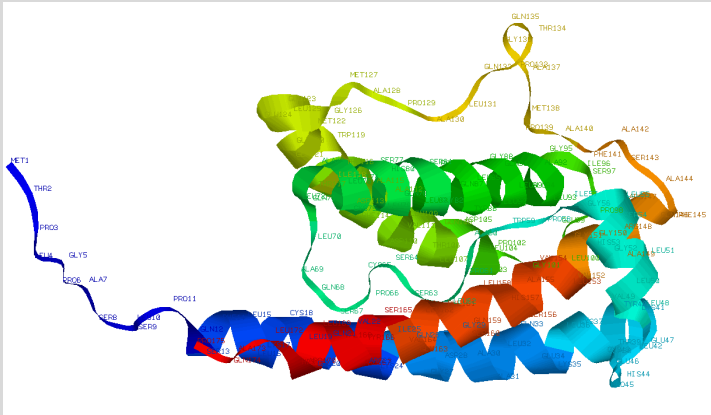
GMP



Example of Biosimilar Targeted Development (G-CSF, Filgrastim)

Granulocyte-Colony Stimulating factor

- *E. coli* expressed (INN: Filgrastim, r-Meth G-CSF)
- Molecular Mass: 18798.9
- 175 amino acids

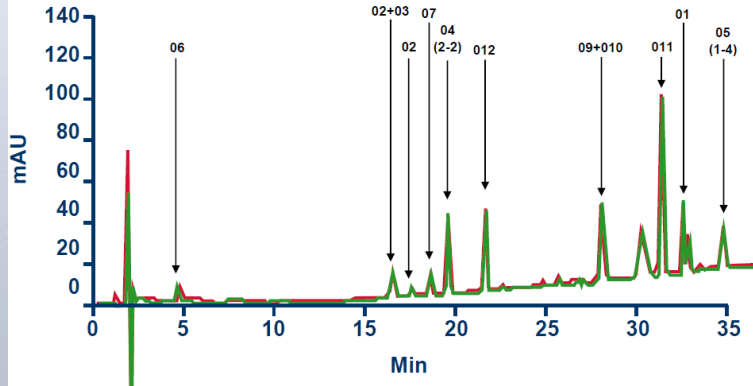


Background of development

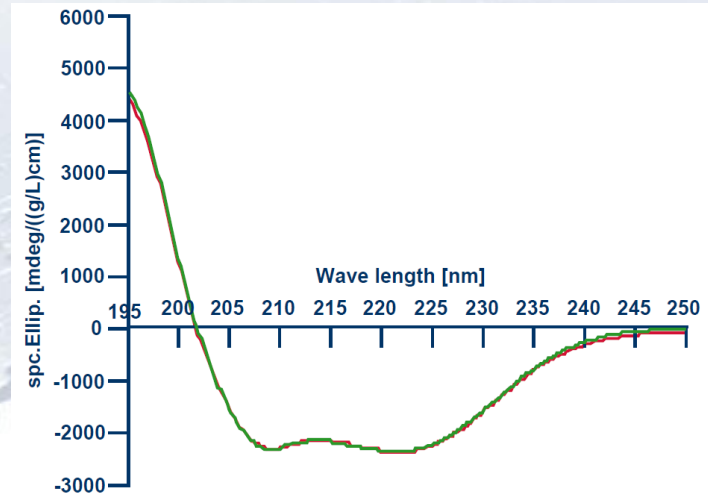
- Properties
 - No post-translational modification (e.g glycosylation, PEGylation)
 - Produced in a host cell, which is very well known
 - Mode of action well understood
- State-of-the-art analytical methods can characterize this molecule very thoroughly
- Decades of experience exist in *E. coli* fermentation and also production of proteins

Example of a Biosimilar Filgrastim: Highly Similar to Reference Product

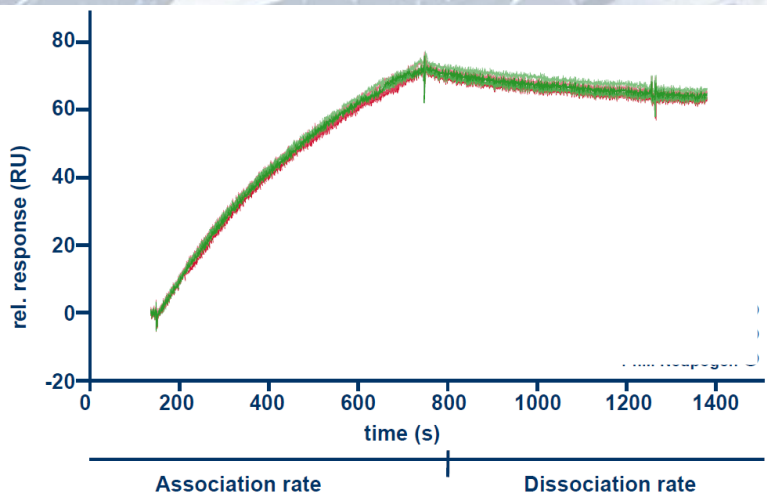
Primary structure – peptide mapping



Higher order structure – UV CD spectroscopy

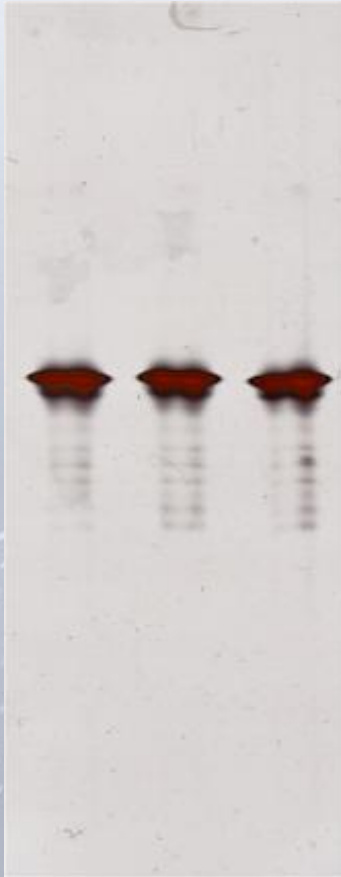


Bioactivity – Surface plasmon resonance spectroscopy

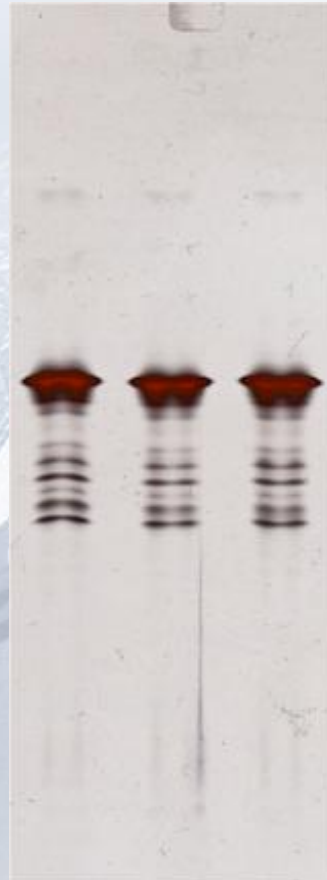


Comparability performed for EU Biosimilar application showed highly similar results with state of the art methods

Determination of Isoelectric Point and Charged Variants



Three batches of
Biosimilar product



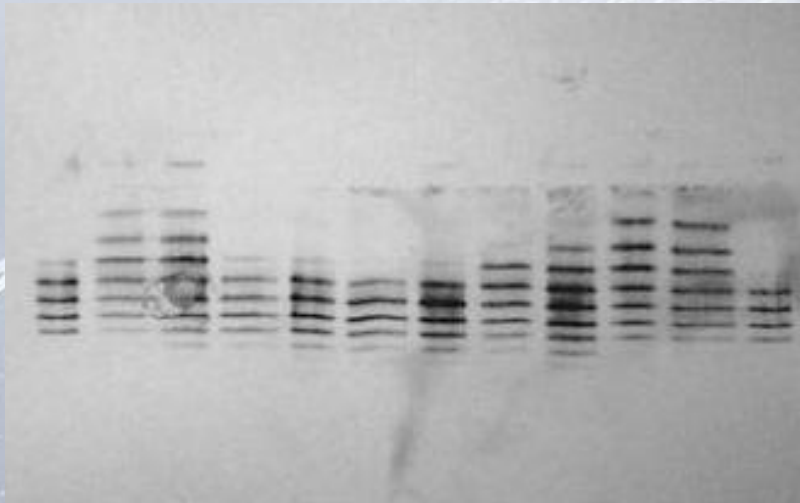
Three batches of
Reference product

- Proteins separated according to isoelectric point (charge)
- Same isoelectric points found for this biosimilar Filgrastim and the reference product
- The Biosimilar Filgrastim has high purity and low variability

“Non-Comparable Biologics” are NOT Biosimilars

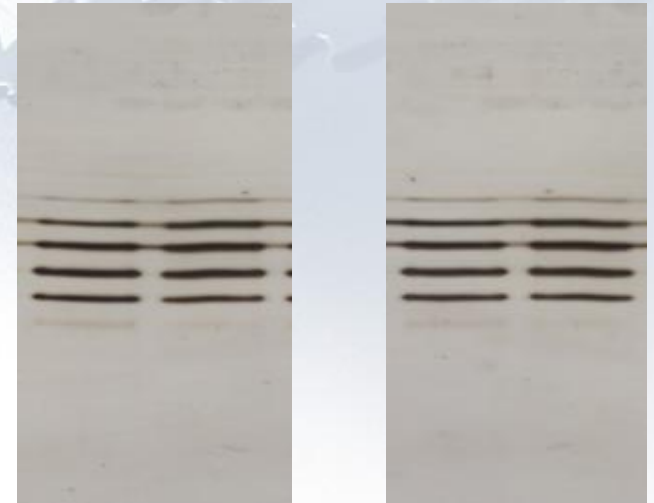
Isoelectric focusing gels

Alternative biologics \neq biosimilar
NOT similar to Reference E



Sample E IA IB IIA IIB IIIA IIIB IV V VII VIII E

Approved biosimilar in EU
NO difference to originator



Sample 1 2 3 4

Schellekens H *et al.* *Eur J Hosp Pharm Pract* 2004;3:43-7

Brockmeyer C, Seidl A *et al.* *Eur J Hosp Pharm Pract* 2009;15:34-40

These products are not considered as Biosimilars

Risk Management Plans and Traceability/Identification

Safety Risk Management Plans (RMPs)

- All Biosimilars in EU are scientifically assessed centrally by the European Medicines Agency and have RMPs.
- All biologics should be treated in the same consistent and scientifically valid manner, and this also applies to any post-approval regulatory requirements

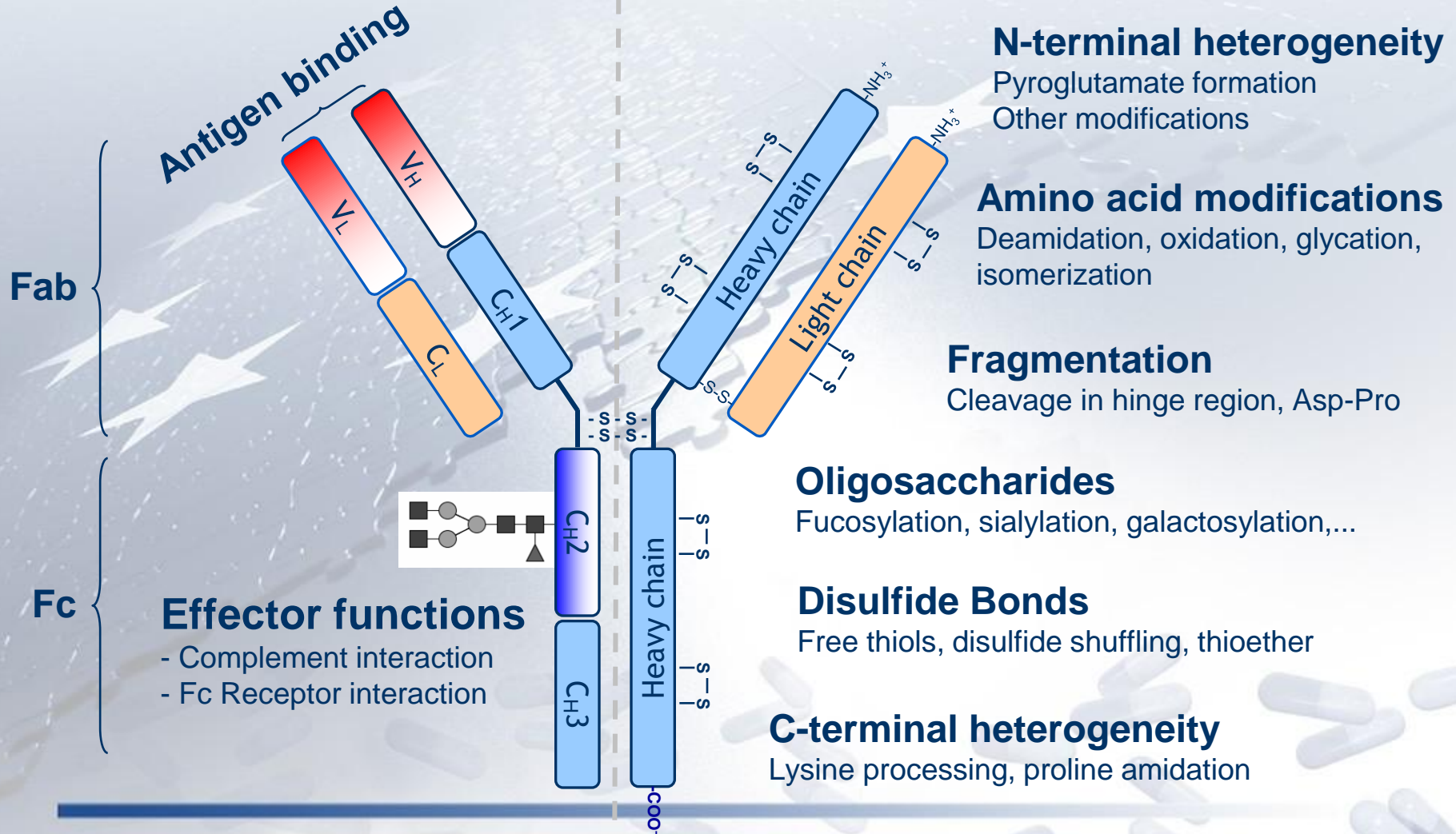
Traceability and adverse event reporting: same as any biologic

- Clear identification of biosimilars via approved trade name
 - ADR reporting: name and batch number
 - Traced via controlled systems/processes
-

Even Monoclonal Antibodies can be Thoroughly Characterized Today

Biological characteristics

Physicochemical characteristics





Use of Orthogonal Methods Provides Understanding of the Overall Picture

Attributes:

- Primary structure
- Mass
- Disulfide bridging
- Free cysteines
- Thioether bridging
- Higher order structure
- N- and C-terminal heterogeneity
- Glycosylation (isoforms, sialic acids, NGNA, fucosylation, alpha gal, site specific)
- Glycation
- Fragmentation
- Oxidation
- Deamidation
- Aggregation

Proteins can be well characterized at least up to the complexity of monoclonal antibodies

- Primary structure determined from recombinant DNA sequence and fully accessible to analytical verification
- Set of orthogonal analytical methods available to characterize the identity and amount of related variants with high sensitivity
- Glycosylation profile can be comprehensively determined with regard to identity and content of individual glycans with high sensitivity
- Accurate and relevant bioassays for pivotal biological functions available

Methods e.g.:

- MS (ESI, MALDI-TOF/TOF, MS/MS)
- Peptide mapping
- Ellman's
- CGE
- SDS-PAGE
- CD
- H-D exchange
- FT-IR
- HPLC
- HPAEC
- IEF
- 2AB NP-HPLC
- SE-HPLC
- FFF
- AUC
- DLS
- MALLS



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Summary

- Development of Biosimilars has to follow the Quality by Design (QbD) approach from the very beginning
 - Manufacturing of Biosimilars is done according to the same stringent cGMP requirements as for other biopharmaceuticals
 - Intrinsic and acceptable batch-to-batch variability of biopharmaceuticals sets the 'goals posts' for biosimilar development
 - Targeted process development allows the control of quality attributes under manufacturing conditions
 - Significant clinical experience with Biosimilars is available in highly regulated markets
 - Pharmacovigilance / Risk-management plans (RMP) are in place as for other biopharmaceuticals
 - Biosimilars have demonstrated over the past 5 years to be safe and efficacious as the reference products
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