GaBI Educational Workshops

3rd Colombian Educational Workshop on
REGULATORY ASSESSMENT OF BIOSIMILARS

30 April 2019, Hilton Bogotá, Colombia

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- CHMP member of the Committee of Advanced Therapies and the Paediatric Committee

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

PPCI
Pro Pharma Communications International

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Quality assessment of biologicals/ biosimilars – most relevant quality attributes: case study on monoclonal antibody

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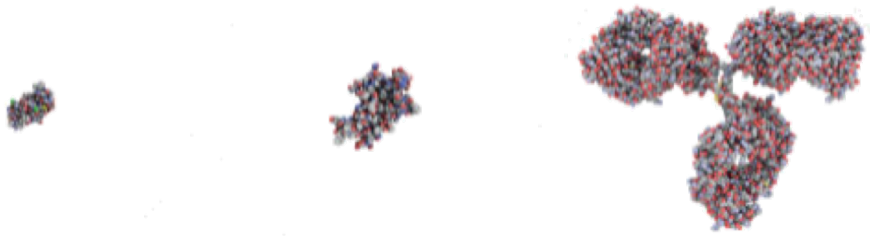
Quality assessment of biologicals/biosimilars

Most relevant quality attributes with case studies

Professor John J Borg



Disclaimer

Disclaimer Statement

- The views expressed in this presentation are the personal views of the presenter and may not be used or quoted as being made on behalf of, or reflecting the position of, the EMA or one of its committees or working parties or any University.

Competing Interests

- The presenter declares no conflicts of interest.

Contents

1) Basics
2) Quality of biological products – The Pillar for granting a marketing Authorisation
3) Experiences of Evaluating Quality Dossiers in the EU
4) Examples

Basic Concepts of the Biosimilar Definitions

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WHO

- Similar biotherapeutic product (SBP) is a biotherapeutic product which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product. *(ref: WHO, Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), 2009)*

EMA

- 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) A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise. *(ref: EMA, Guideline on similar biological medicinal products, 2014)*

US FDA

- The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components, and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product. *(ref: Section 7002(b)(3) of the Affordable Care Act, adding section 351(i)(2) of the PHS Act)*

Comparability Studies and Quality of biological products

The Pillar for granting a marketing Authorisation

- The standard generic approach (demonstration of bioequivalence with a reference medicinal product by appropriate bioavailability studies) is normally applied to chemically derived medicinal products.
- Due to the complexity of biological/biotechnology-derived products the generic approach is scientifically not appropriate for these products.
- The “similar biological medicinal products” approach, based on a comparability exercise, will then have to be followed.

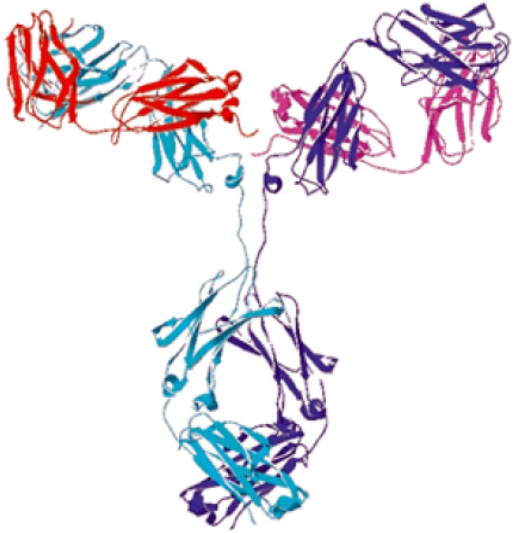
Basic Concepts of the Biosimilar

- Biosimilars are **similar but not identical products**
- Biological medicines produced in a living system or organism
- The (complex) manufacturing process is a determining factor
  - Larger molecules, complex (three-dimensional structure) and heterogeneous (e.g. isoforms and multimers)
  - Difficult to characterise
  - Impurities: Both Product-related and Process-related
  - Low stability

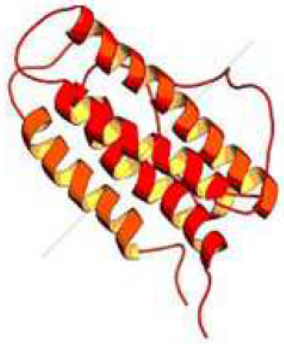
Basic Concepts of the Biosimilar

Antibody based biosimilars - challenges

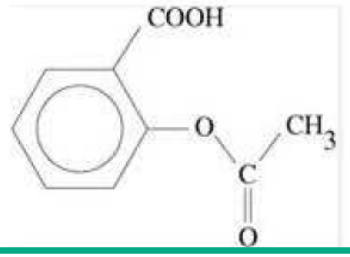
IgG M_W ~ 145 000 D



Epoetin M_w – 18 000 D



Acetylsalicylsyra M_W – 180 D



Basic Concepts of the Biosimilar

Quality part

Complete Module 3 (Quality dossier)

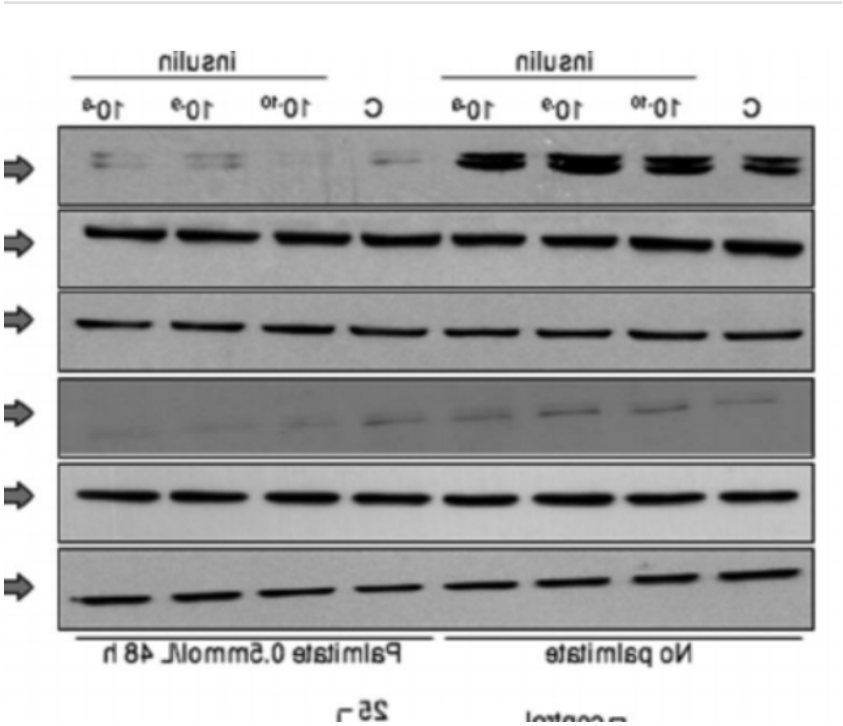
- ***Plus* Comparability Exercise**

– After ***process change***

– ***During development***

– ***Biosimilar***

- Reference product
  - Identical primary structure (AA order)
  - Post-translational differences (incl. glycosylation)
  - E.g. Non-PEGylated vs. PEGylated not accepted
- Physicochemical characterisation
- Biological activity
- Impurities
- Stability studies



Basic - Concepts of the Biosimilar

The Biosimilar “Stepwise approach”

Stepwise approach

a) Demonstration of similarity of a biosimilar and a reference product in terms of quality is a prerequisite for reducing the nonclinical and clinical data set required for licensure.

b) Move onto the next level to address a residual uncertainty if any.

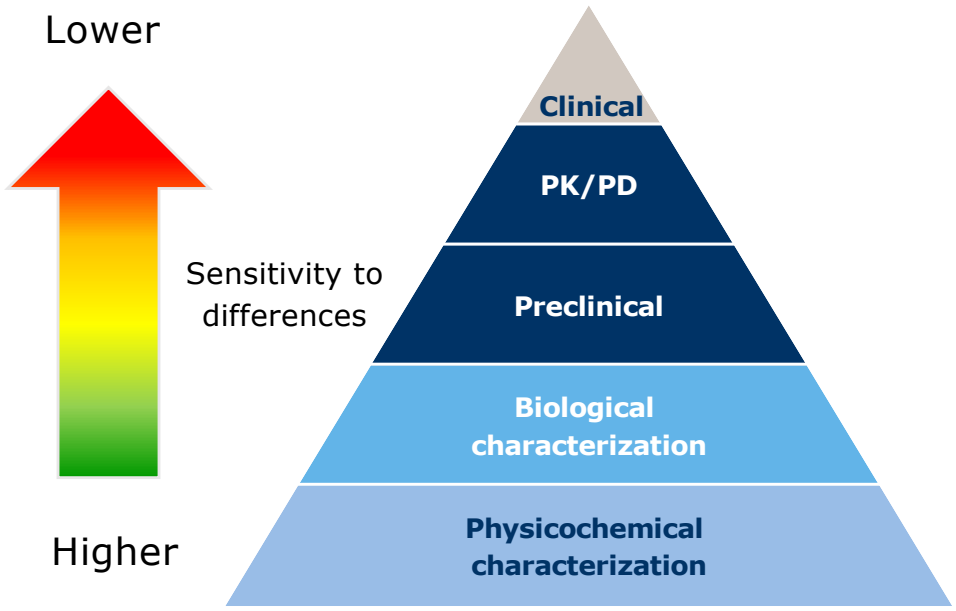
Totality of evidence

a) The decision to license a biosimilar product should be based on comprehensive evaluation of the whole data package for each of Quality, Non-Clinical and Clinical parameters to demonstrate similarity to a Reference Product.

How is this done?

- Abbreviated application
- Comparability (quality, non-clinical, clinical including PK/PD study)
- Differences supported by additional Non-clinical /Clinical data
- Case-by-Case
- Same indication as reference product
- Immunogenicity

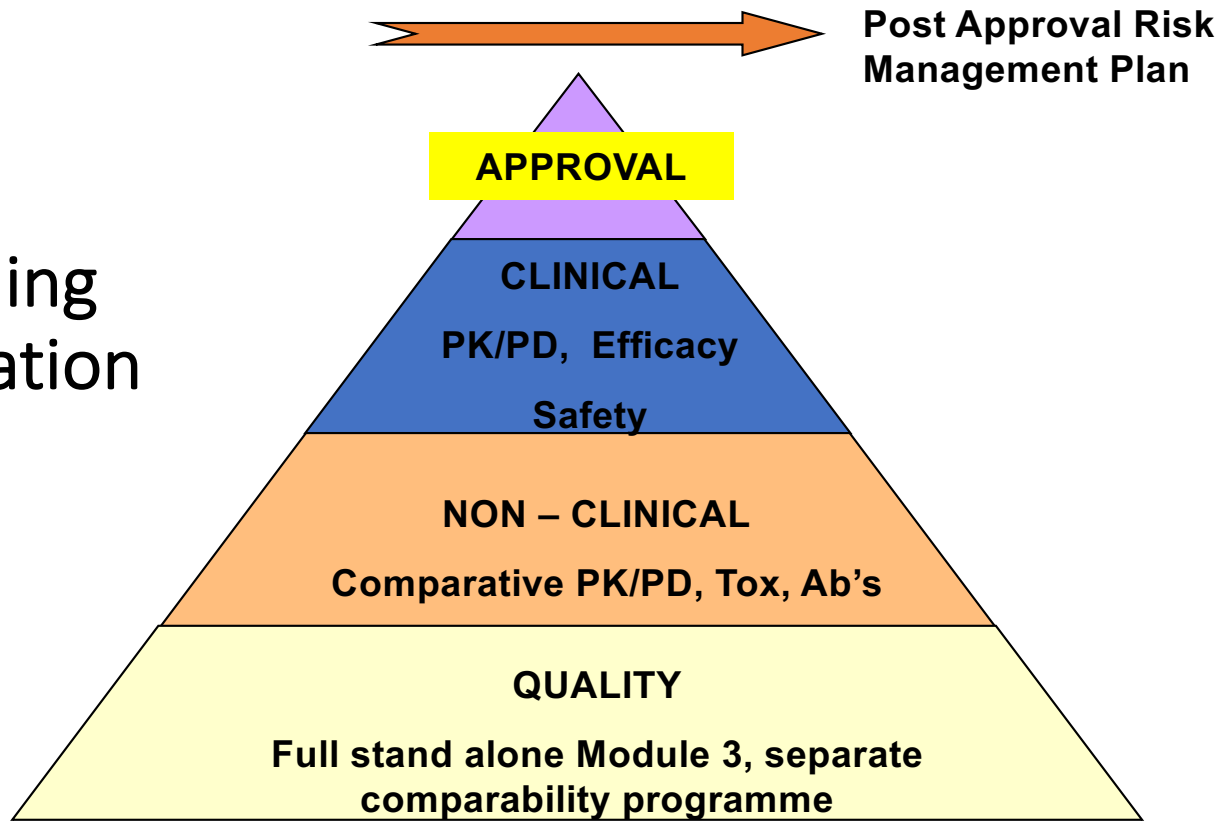
Quality – The foundation of biosimilars
Highly structured development – THE PILAR OF COMPARABILITY



Quality

- Define Target Profile
- State of art analytical tools
- Structured development: QbD
- Critical Quality Attributes – systematically Controlled
- Non-critical attributes – greater tolerance

Biosimilar Building Blocks for application dossier



Comparability Evaluation

- Production step where changes are introduced
- Type of change
- Potential impact on
  - Purity
  - Physicochemical and biological properties

- Take into account:
  - Complexity
  - Degree of knowledge of the product (e.g., impurities, product related substances)
  - Availability of suitable analytical techniques to detect potential product modifications
  - known relationship between quality attributes and safety and efficacy

The nature and level of knowledge of product

- Product complexity, including heterogeneity and higher order structure
- Structure-activity relationship and strength of the association of quality attributes with safety and efficacy;
- Relationship between the therapeutic protein and endogenous proteins and the consequences for immunogenicity;
- Mode(s) of action (unknown vs. known, single vs multiple active sites).

Immunogenicity

- Antibodies to therapeutic protein
- Consequences: from non-significant to serious life-threatening
- Immunogenicity an issue for all biologicals (both innovators and biosimilars)
- Immunogenicity also after process change!!

Risk Factors for Immunogenicity (1)

Product-related

- Protein structure, e.g. Glycosylation, oxidation, deamidation
- Formulation (albumin removal)
- Aggregation
- Excipients
- Impurities

Patient-related

- Genetic factors modulating the immune response
- Age (“children are not small adults“)
- Previous infections

Risk Factors for Immunogenicity (2)

Disease

Autoimmunity / chronic infection as ”adjuvant“

Failure to mount immune response in severe conditions

Indication-specific differences

Concomitant treatment

Immunosuppressives decrease immunogenicity

Monotherapy: No extrapolation to combination therapy

Duration, route of administration, treatment modalities

s.c. / i.m. > i.v.

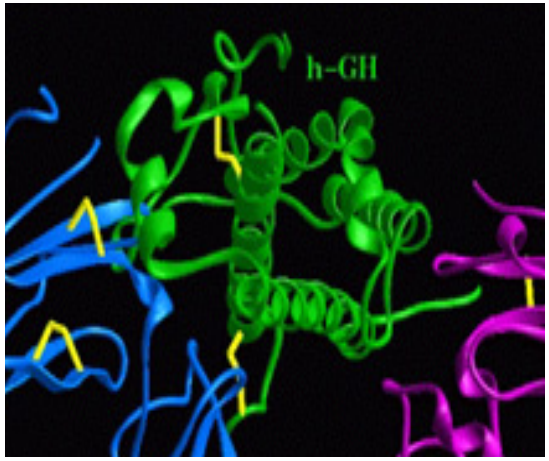
Short-term > long-term (but: re-exposure!)

Quality of Biological Products

The Pillar for granting a marketing Authorisation

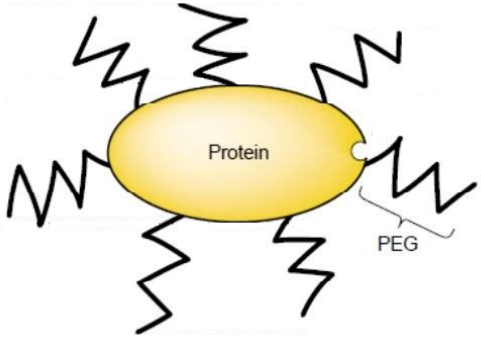
- Importance of the proteic structure:
  - Somatropin as an example
    - Substitution of Gly120 by Arg 120

    ⇨ hGH becomes a R-GH antagonist



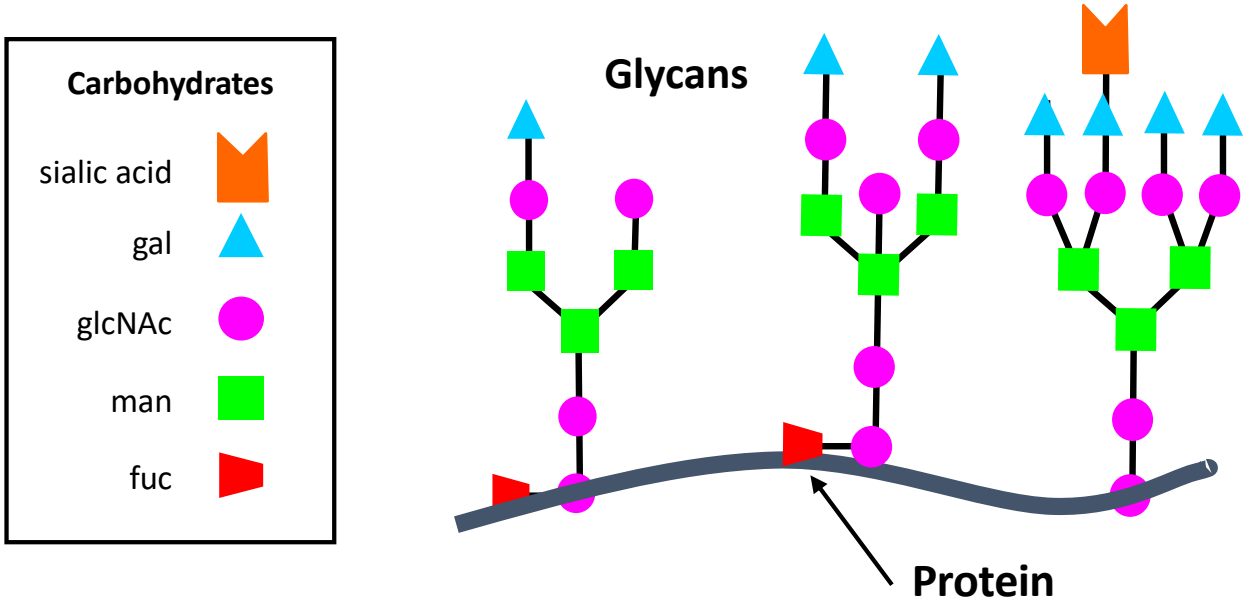
Post-translational Modification

- Many proteins are further processed in the cell:
  - Glycosylation
  - Sulphatation, Amidation, etc.
- Glycosylation is also complex: more than one glycosylation pattern (isoform)
- Sometimes, proteins are chemically modified (post-production modification)
  - PEGylation
  - Conjugation



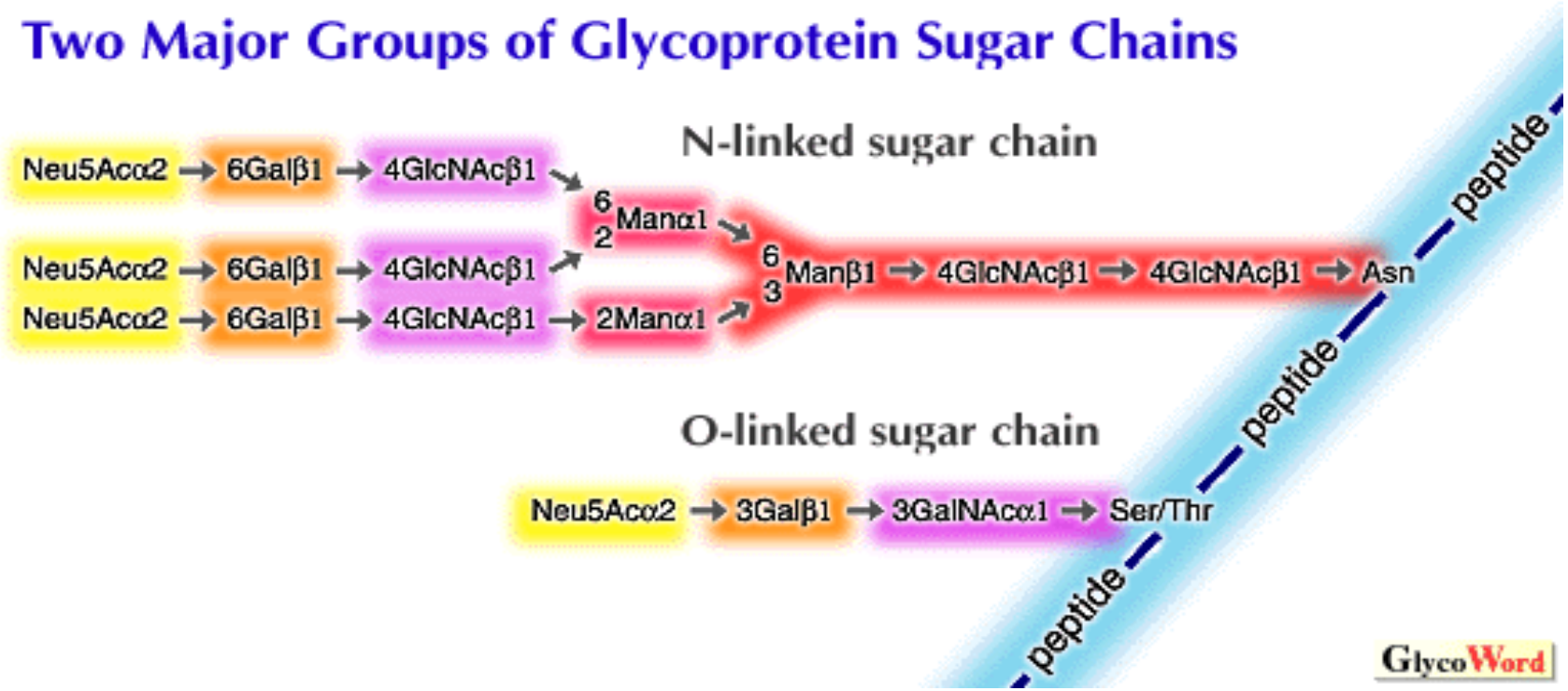
Glycosylation

Complex carbohydrate structures (1)



Glycosylation

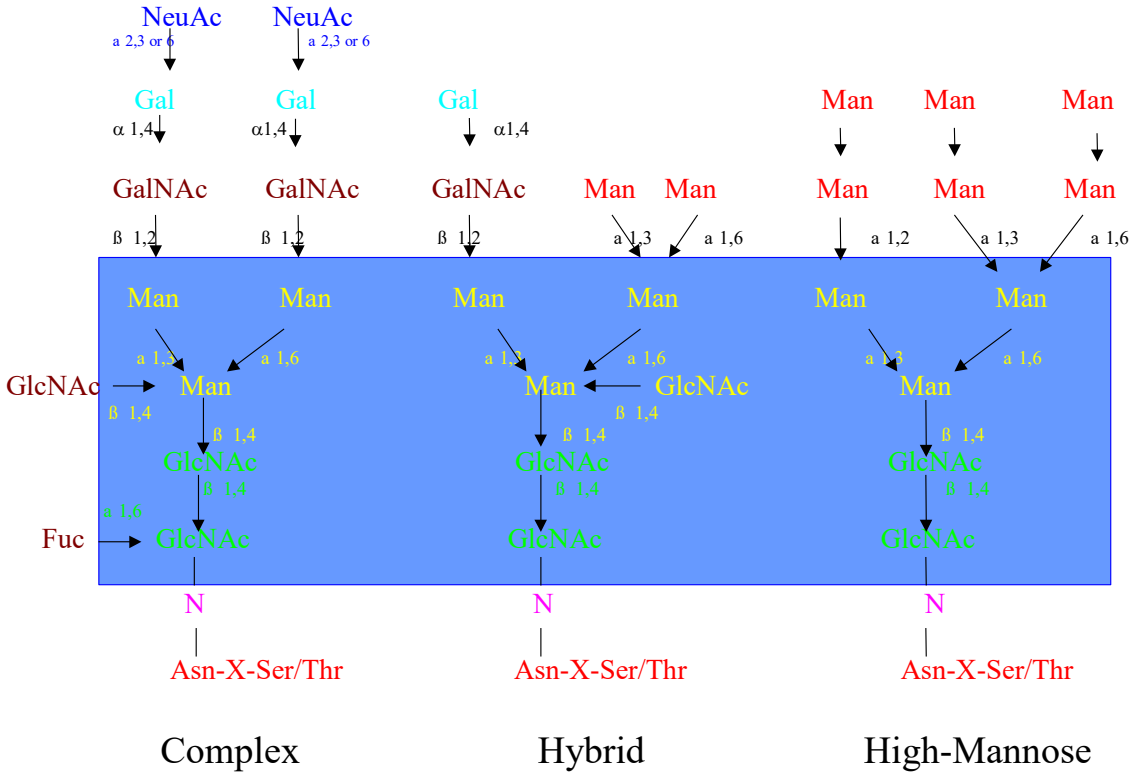
Complex carbohydrate structures (2)



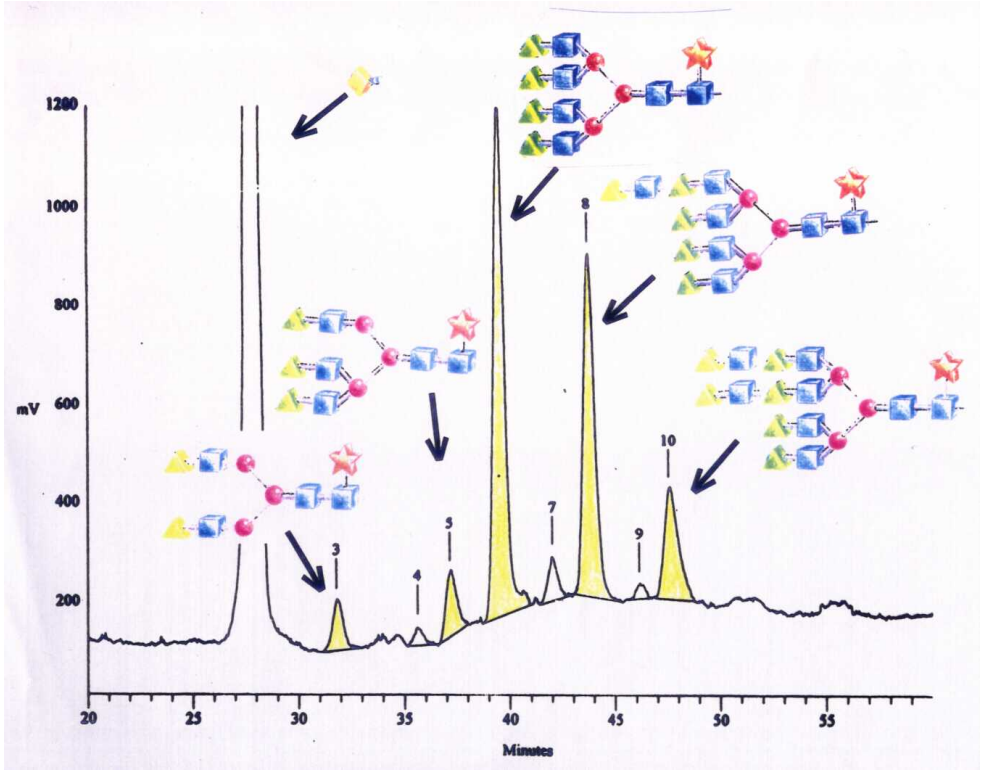
www.glycoforum.gr.jp

Glycosylation

Complex carbohydrate structures (3)

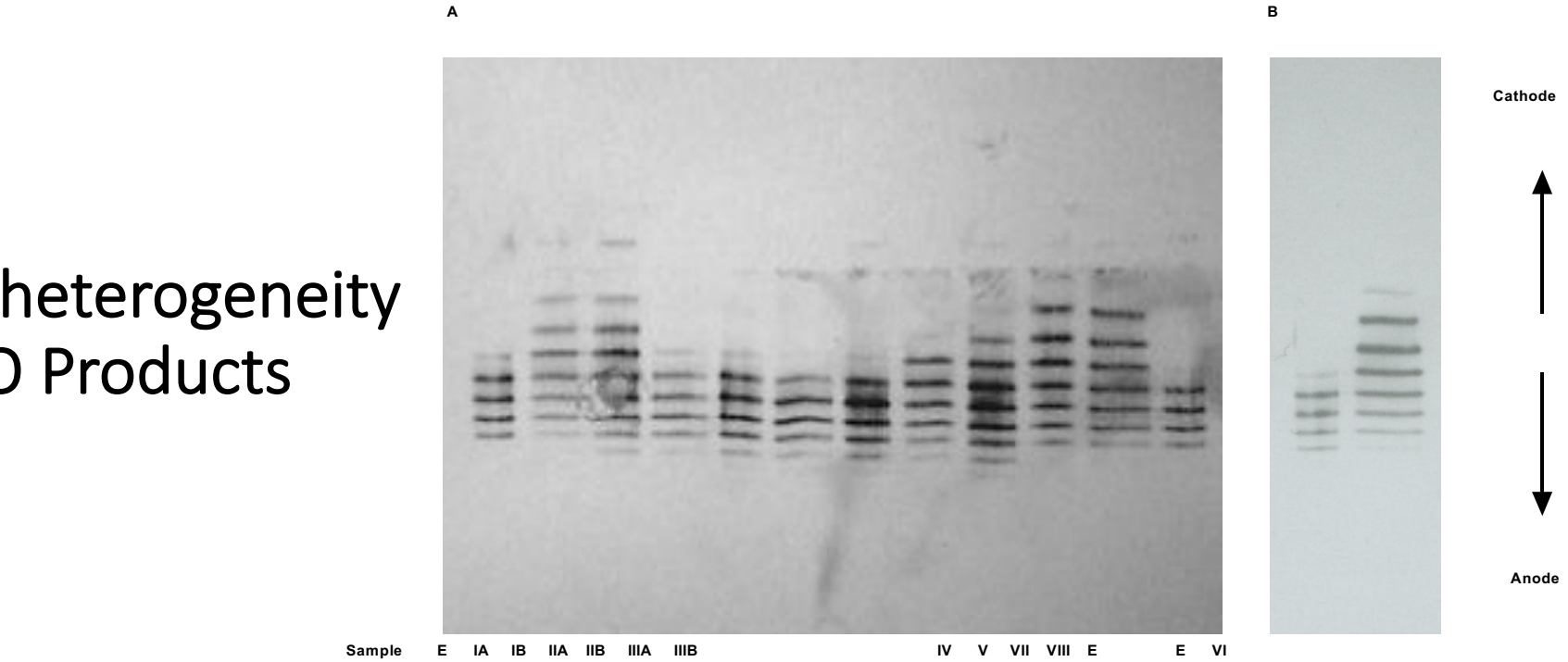


Chromatographic analysis (HPAZED-PAD)



Source: Burg, J. et al. 1998
PCT/EP/98/07876

Microheterogeneity of EPO Products



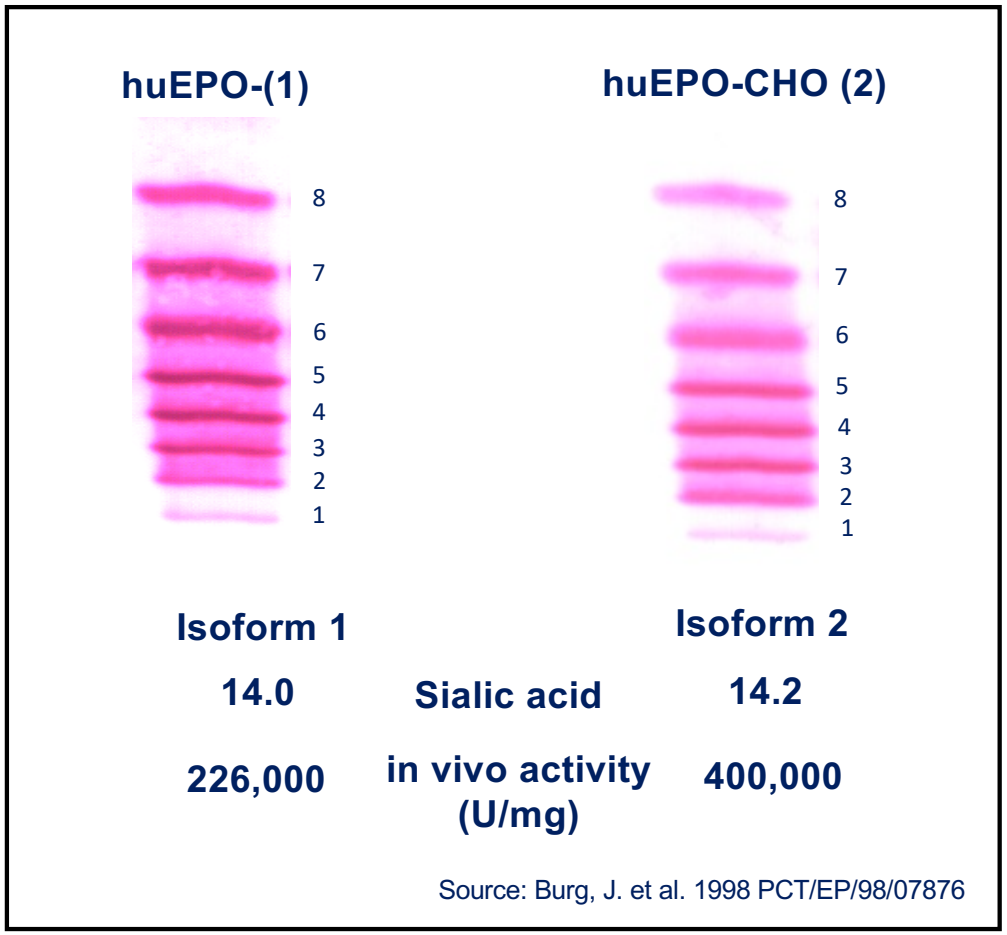
Isoelectric focussing profiles of EPO preparations from various manufacturers

Source: H. Schellekens (2004) Eur. J. Hosp. Sci. **3**, 43-47

Microheterogeneity

Isoelectric focusing (IEF) pattern and sialic acid content of the two EPO isoform preps are very similar but

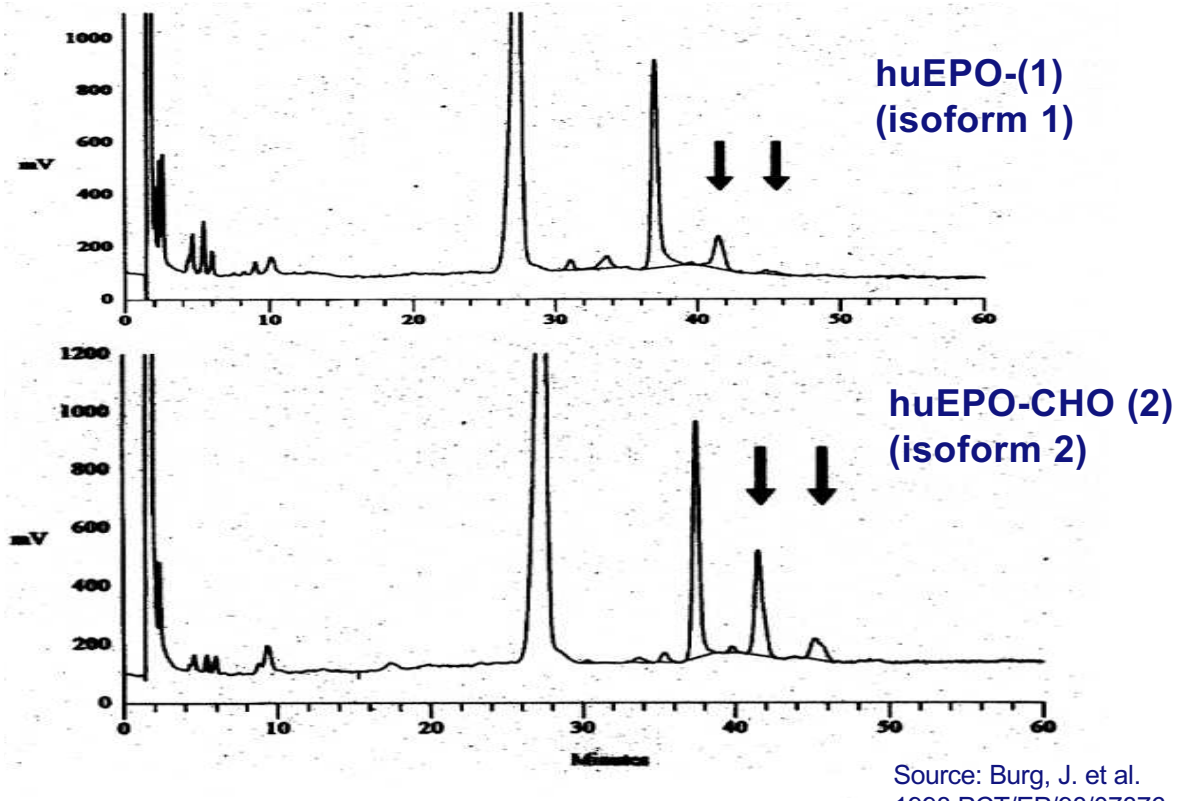
Bioactivity is different



Microheterogeneity

Carbohydrate structures of two EPO isoforms

Carbohydrate structures

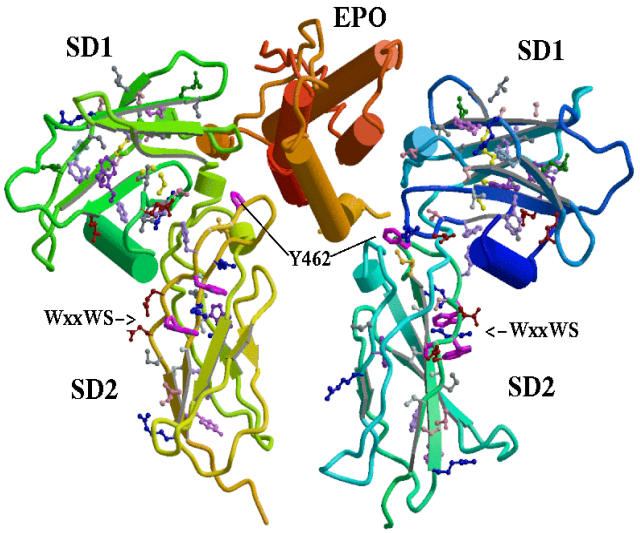


Source: Burg, J. et al. 1998 PCT/EP/98/07876

Quality of biological products

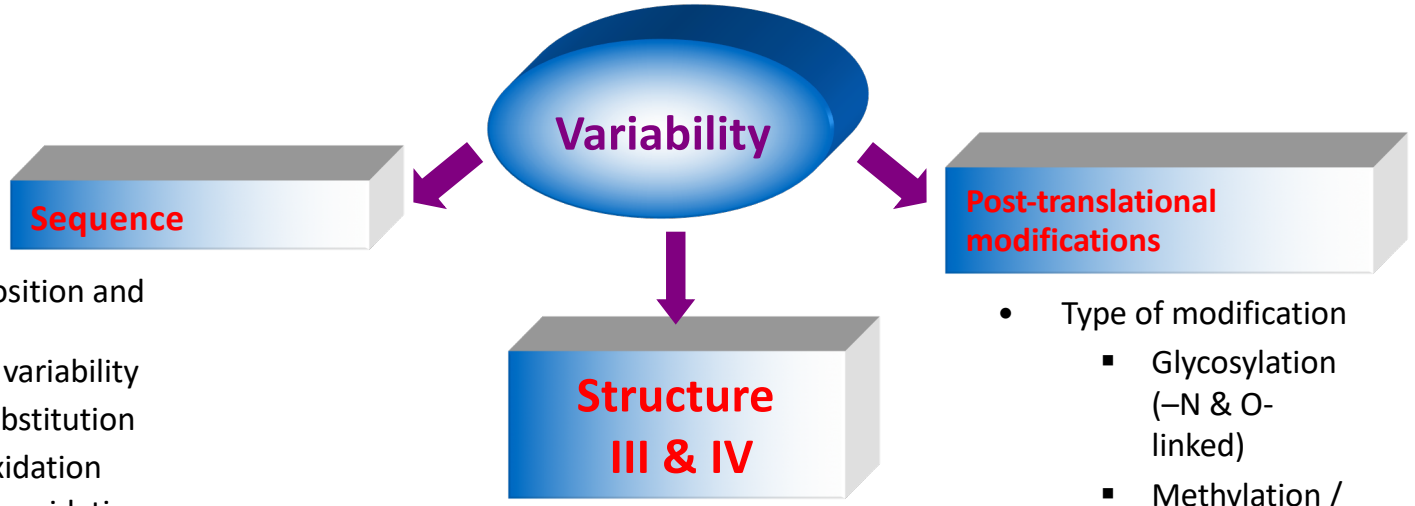
- Importance of post-translational modifications
  - EPO as an example
    - Modification of glycosylation

    ⇨ decrease or increase in the *in-vivo* biological activity



Quality of biological products

The Pillar for granting a Marketing Authorisation



- AA composition and sequence
- Source of variability
  - Substitution
  - Oxidation
  - Deamidation
  - Truncated form
  - N- and C-terminal heterogeneousness

…

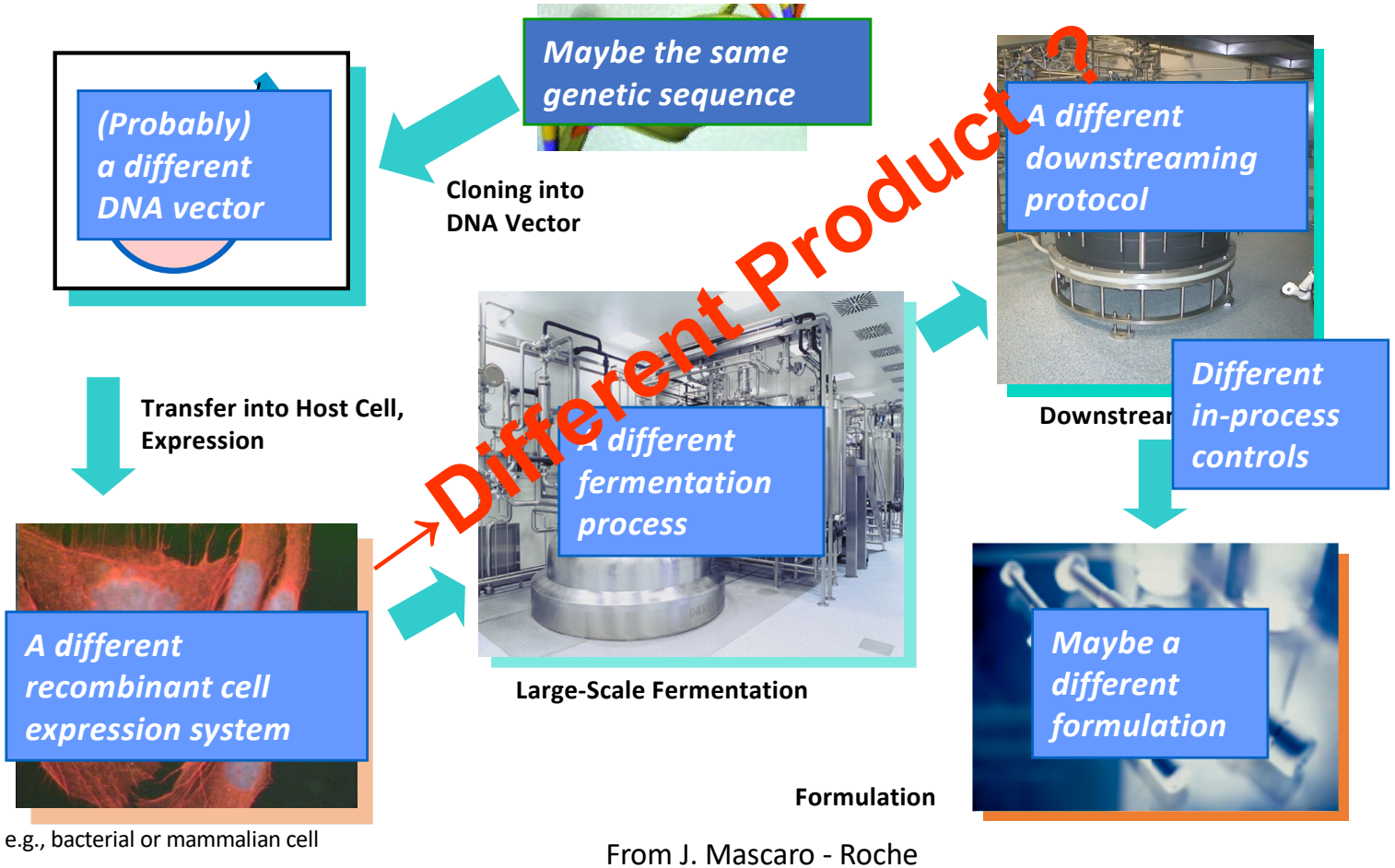
- Type of variability
  - Conformation
  - Aggregates
  - Dissociation

…

- Type of modification
  - Glycosylation (–N & O-linked)
  - Methylation / Acetylation / Acylation
  - Phosphorylation / Sulfatation

…

Biosimilars Manufacturers - Different Process



From J. Mascaro - Roche

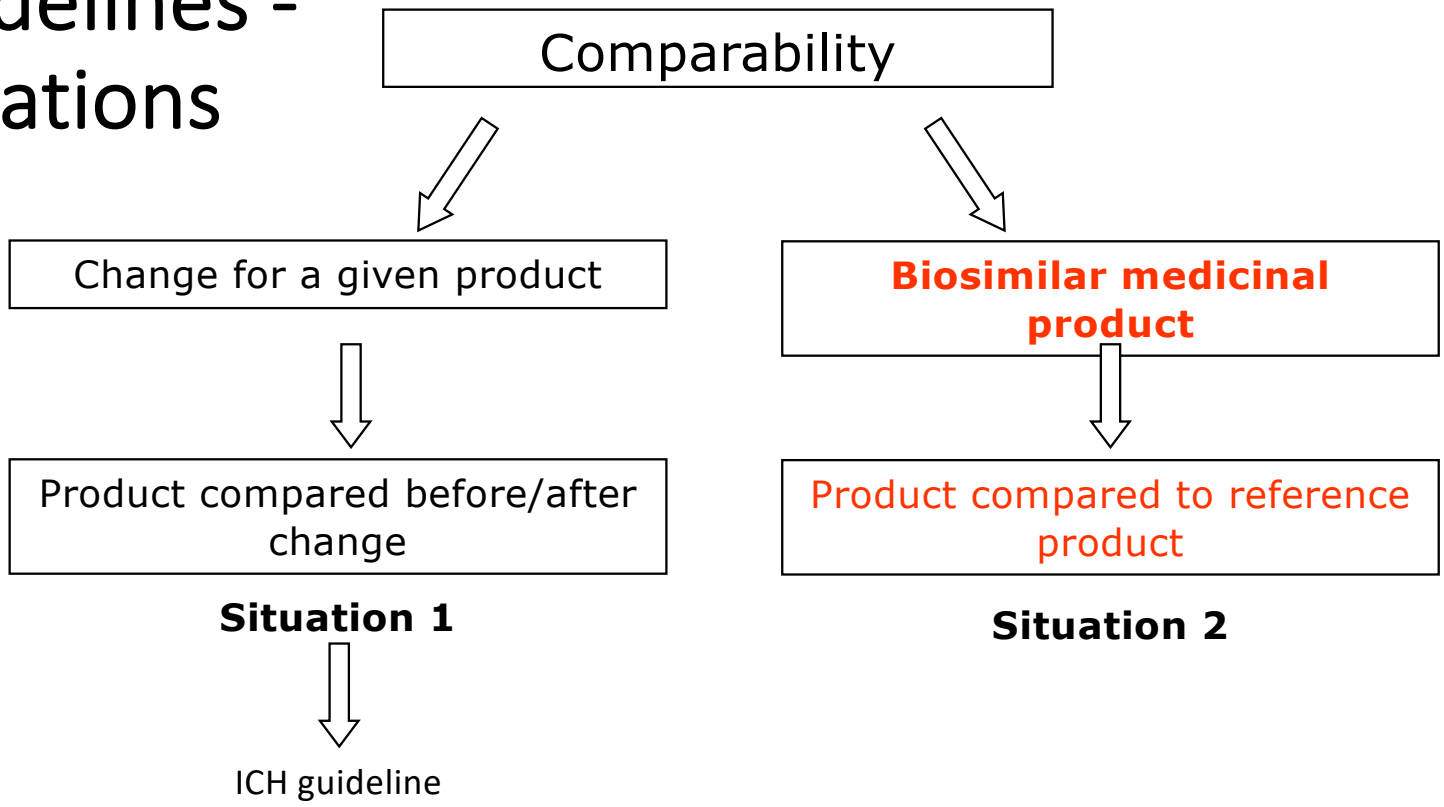
Back to Biosimilars - The context

- For biologics, the quality is highly depending on the manufacturing process which is very complex:
  - Each biotechnology-derived protein is defined by its production process and its formulation
  - Equipment, raw materials, process parameters and in-process controls contribute to the product characteristics
- Acceptability of the product: is not only depending on quality criteria, but has also to be validated with safety and efficacy data

Critical Quality Aspects (not exhaustive list)

The extent of information needed about the structure of a molecule and the quality characteristics of the drug substance
Information needed on cell banks
The extent of characterisation needed for process and product related impurities
The extent of information needed on the manufacturing process, the control of critical steps and in-process controls
The extent of development and/or validation of the manufacturing process that is required prior to and during clinical development.
The extent of qualification/validation required for the analytical procedures
Setting and justification specifications
The requirements for container closure and stability data

CHMP guidelines - two situations



Principles of the "Comparability Exercise" (1)

- “Comparability” in terms of
  - Quality
  - Safety
  - Efficacy

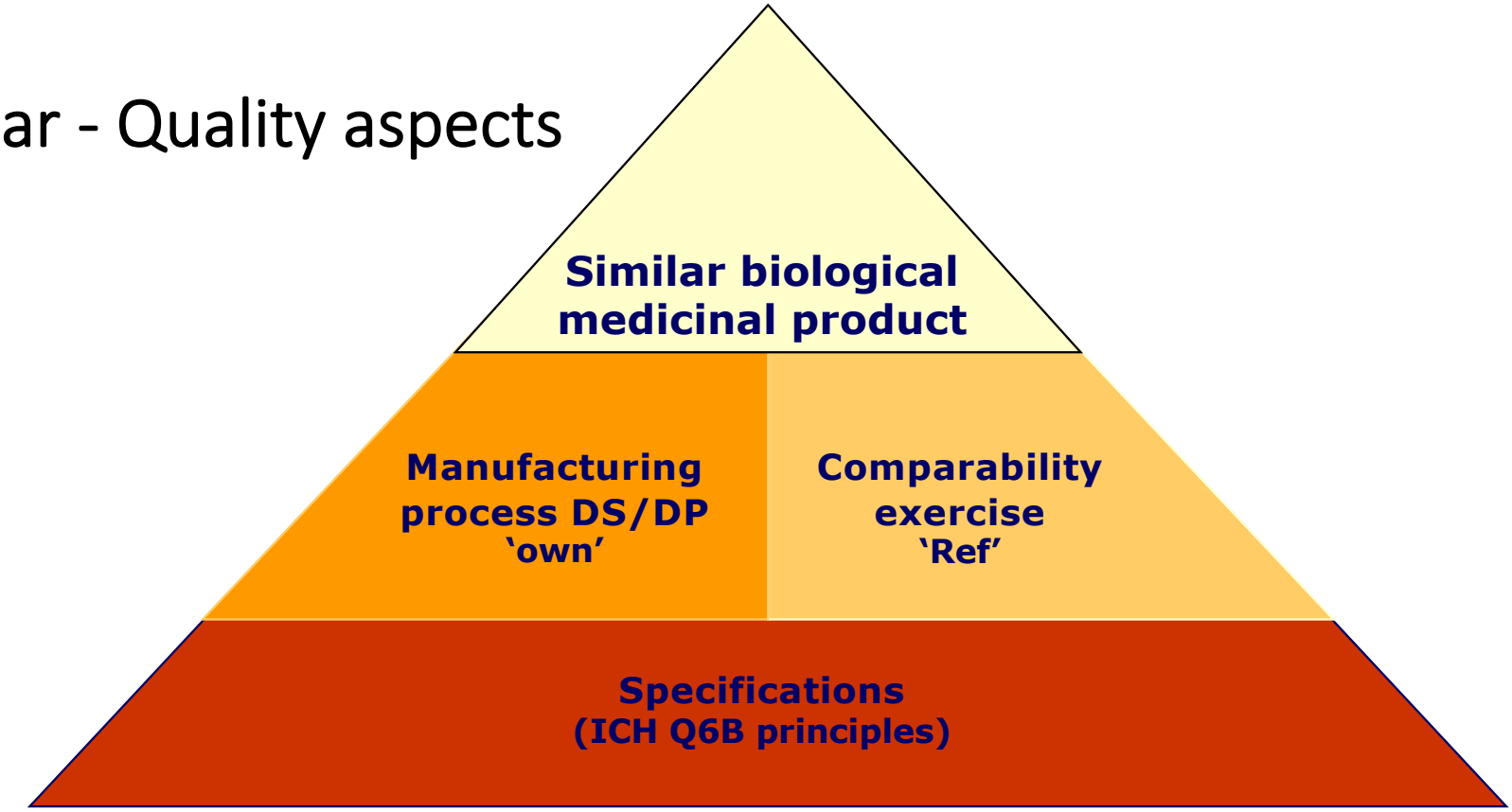
- Generally, same pharmaceutical form, strength and route of administration

- (Pre)-Clinical data requirement depends on:
  - Extent of possible characterisation
  - Observed / potential differences
  - Clinical experience with substance class
  - Case by case approach

Principles of the "Comparability Exercise" (2)

- Studies principally comparative
- Reference product must be authorized
- Same reference product for all aspects of the comparability exercise
- Pivotal studies: use final formulation derived from final process material (otherwise justification and adequate additional data needed)

Biosimilar - Quality aspects



Understanding the key quality critical attributes of the Reference Product

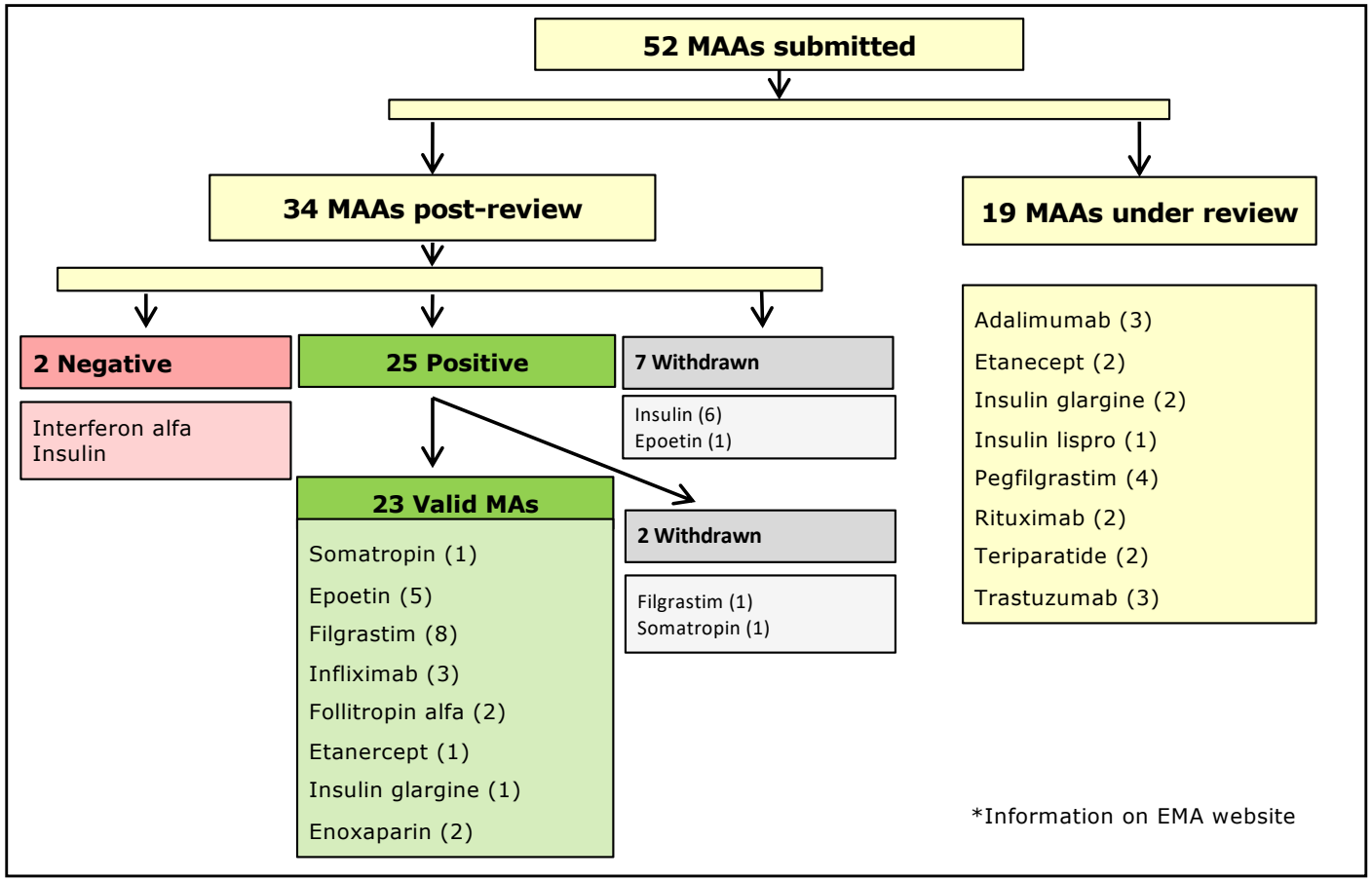
The majority of the regulations necessarily require demonstration of comparability to a local reference product approved in their jurisdiction.

- Possibility of geographic divergence of reference products in quality attributes
  - Variations from different supply chain, e.g. Difference of manufacturing sites
  - Variations after separation of license holders & independent change
  - Variations from sequential application of a manufacturing process change

The Use of a Foreign Reference Product

- To facilitate global development, most NRAs accept the use of non-local reference products by demonstrating the equivalence of the local and foreign reference products **(Bridging study).**

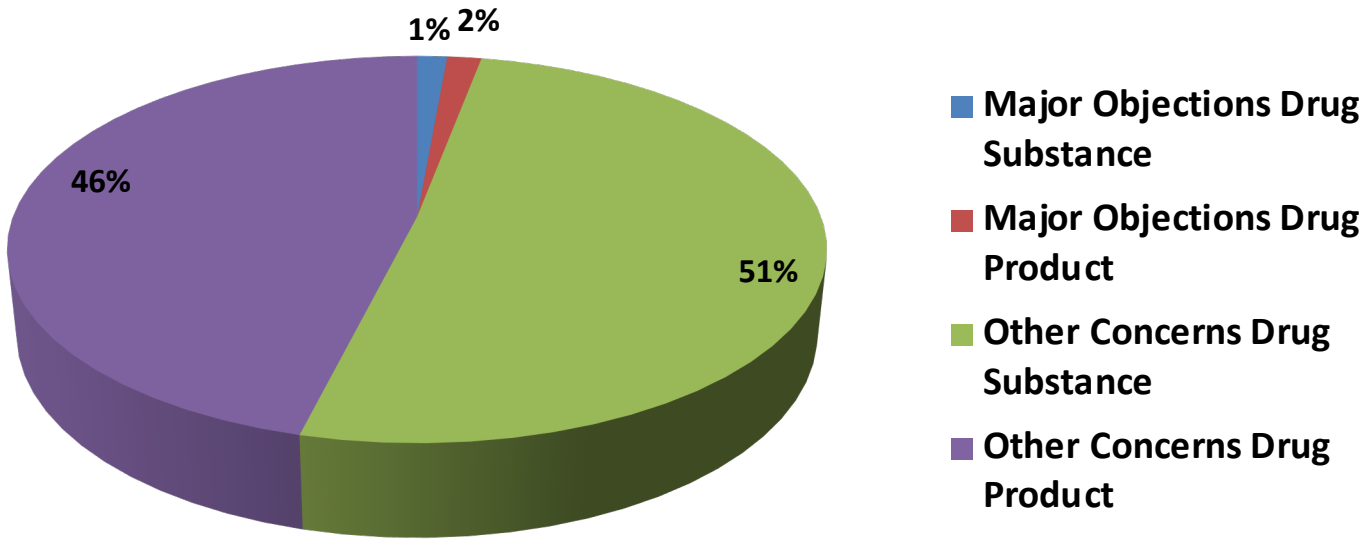
Biosimilar Product Review (Nov 2016)*



A review of quality concerns

What's the story?

CHMP Day 120 LOQs sorted per DS and DP
Cut off date: December 2015



Major Objections as deficiencies for Drug Substance

Category description of deficiency (Major Objection)	Number of Major Objections
Inadequate evidence of biocomparability between product substance and reference product substance due to lack of supporting data.	4
Insufficient data/evidence or incomplete exercise for analytical validation.	2
Missing information or documentation and ill-defined or characterised reference standards and materials used.	2
Insufficient or inadequate stability data or methods used to support the proposed shelf life.	2
Process control strategy used was not clear since it was not fully explained, and not enough data was submitted to support the design space approach used.	1
Specifications of drug substance were not sufficiently justified and were impaired by insufficient validation of the analytical method used.	1
Two different but similar manufacturing processes were used whose comparability was not adequately shown.	1
Reference product used was not authorised in the EU and the same reference product was not used throughout the comparability study.	1
Characterisation of the drug substance was inadequate for a number of given reasons.	1

Major Objections for Drug Product

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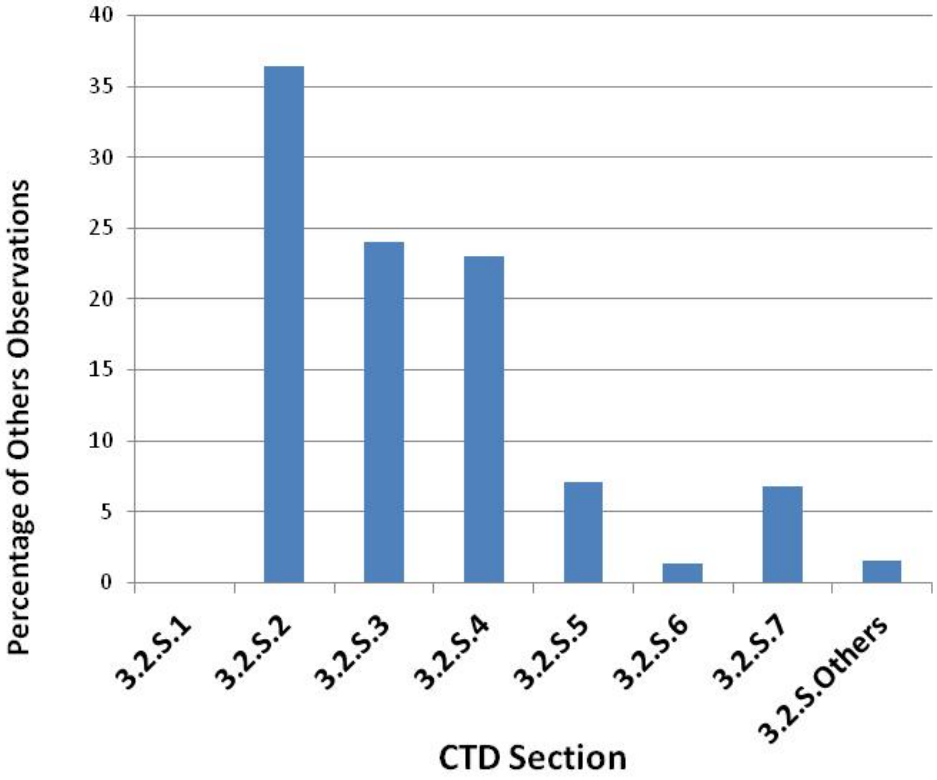
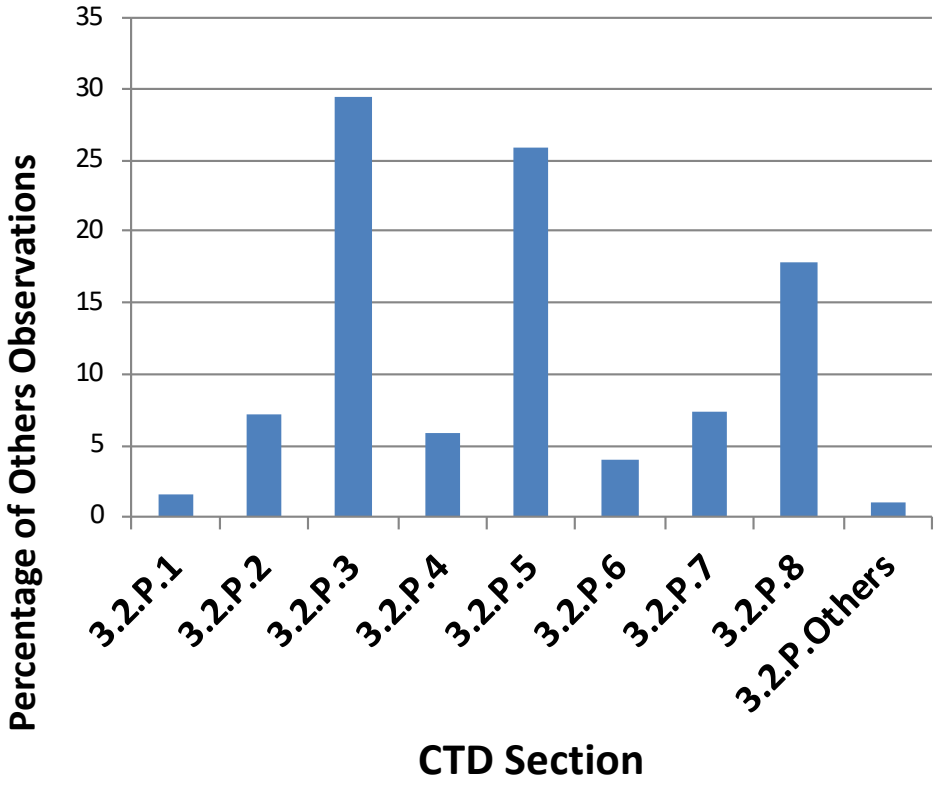
Category description of deficiency (Major Objection)	Number of Major Objections
Insufficient data and evidence for process validation.	3
There were diverse issues with the reference standards and materials used.	3
Insufficient data and evidence or incomplete method and exercise for the validation of analytical methods used.	2
Insufficient data for drug product comparability, namely insufficient structural characterisation data or comparisons done on drug product.	2
Insufficient or inadequate stability data to support the proposed shelf life of finished drug product.	2
Biosimilarity between product and reference product were not considered as established due to lack of supporting data.	2
Specifications of the drug product were not acceptable as they were inadequately justified.	1
Different plungers were used in production to those used in clinical trials, having also a higher impurity profile and this without any justification whatsoever.	1
There was lack of GMP compliance evidence throughout the dossier both for the clinical batches used in the clinical trials and for batches used in all validation studies.	1



Percentage of Others Concerns for Drug Substance

3.2.S.1 General Information
3.2.S.2 Manufacture
3.2.S.2.6 Manufacturing Process Development
3.2.S.3 Characterization
3.2.S.4 Control of Drug Substance
3.2.S.5 Reference Standards or Materials
3.2.S.6 Container Closure System
3.2.S.7 Stability



3.2.P.1 Description and Composition of the Drug Product
3.2.P.2 Pharmaceutical Development
3.2.P.3 Manufacture
3.2.P.4 Control of Excipients
3.2.P.5 Control of Drug Product
3.2.P.6 Reference Standards or Materials
3.2.P.7 Container Closure System
3.2.P.8 Stability

Biosimilar guidelines: Evolution in EU
Totality of evidence founded on quality data

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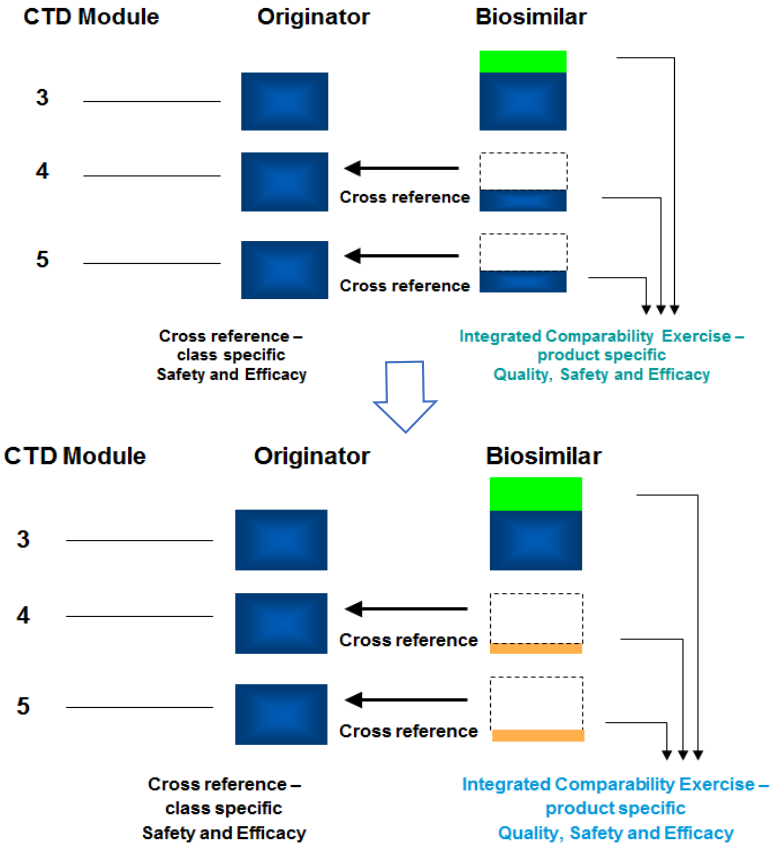
Initially: conservative on clinical, e.g. epoetin: 2 studies required in titration and maintenance + emphasis on animal studies.

Now: use of PD markers for clinical, relevant non-clinical in-vivo study + increased value from detailed quality (characterisation).



EXAMPLE

CMC Documents for Monoclonal Antibodies derived from a Monoclonal Cell Line

i.e MAs for therapeutic and prophylactic use and *in vivo* diagnostic use.

Monoclonal Antibody CMC

- Development of Mab
  - Justification of structure with regards to mechanism of action, biological activity, stability and immunogenicity
  - Information on procedures used during development, e.g. viral transformation, use of in-silico technology…
  - Hybridoma and human B-lymphocyte immortalisation **not excluded**, but specific requests included.
- Production of Mab
  - General consideration (Validation studies, IPC…)
  - Viral safety and TSE

Monoclonal Antibody CMC

- Characterisation of Mab (Q6B headings)
  - Physicochemical characterisation
    - Detailed analysis of glycosylation required
  - Immunochemical properties
    - **Includes detailed recommendations on cross-reactivity**
  - Biological activity
    - justification with regards to mechanism of action and effector functions
  - Purity, impurity and contaminant
  - Quantity

Monoclonal Antibody CMC

- Specifications (Q6B headings)
  - Identity
  - Purity and impurity
    - Glycosylation monitoring requested even if MoA does not require the use of effector functions.
  - Potency
  - Quantity
  - General tests
    - visible and sub-visible particulates analysis required

Remsima

- Remsima is a ‘biosimilar medicine’.

  This means that Remsima is similar to a biological medicine (the ‘reference medicine’) that is already authorised in the EU and that Remsima and the reference medicine contain the same active substance.

  The reference medicine for Remsima is Remicade.

Remsima
Biosimilar Comparability

Remsima – Biosimilar Comparability

MALTA MEDICINES AUTHORITY

Summary of Physicochemical Test Methods for Comparability of CT-P13 Active Substance and Finished Product with Remicade

Test Method	Purpose	Drug Substance Tested	Drug Product Tested	RMP Tested
Primary Structure				
Amino Acid Analysis	Determination of amino acid composition	–	√	√
Peptide Mapping (LC-MS) in combination with MS/MS	Comparison of peptide coverage and chemical modifications	√	√	√
Peptide mapping (HPLC)	Comparison of tryptic peptide map by visual inspection	√	√	√
N-terminal Sequencing	Comparison of N-terminal sequences	√	√	√
C-terminal Sequencing	Comparison of C-terminal sequences	√	√	√
Reduced Mass	Comparison of molecular weights by mass spectrometry	√	√	√

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Summary of Physicochemical Test Methods for Comparability of CT-P13 Active Substance and Finished Product with Remicade (cont..)

Test Method	Purpose	Drug Substance Tested	Drug Product Tested	RMP Tested
Higher Order Structure				
Disulphide Bonds	Comparison of disulphide bonds location	√	√	√
Free Thiol Analysis	Comparison of the amount of free sulph-hydryl groups	√	√	√
FTIR	Comparison of secondary structures	√	√	√
CD	Comparison of secondary structure	√	√	√
DSC	Comparison of thermal stability and determination of thermal transition temperatures	√	√	√
Purity/ Impurity				
SEC-HPLC	Comparison of aggregate content and monomeric purity	√	√	√
CE-SDS (Reduced/Non-Reduced)	Comparison of electrophoretic mobility and purity under non-reducing and reducing conditions	√	√	√

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Summary of Physicochemical Test Methods for Comparability of CT-P13 Active Substance and Finished Product with Remicade (cont..)

Test Method	Purpose	Drug Substance Tested	Drug Product Tested	RMP Tested
Charged Isoforms				
IEF	Comparison of isoelectric point(s)	√	√	√
IEC-HPLC	Comparison of charge variant distribution	√	√	√
Glycosylation				
Sialic Acid Analysis	Comparison of sialic acid content	√	√	√
Monosaccharide Analysis	Comparison of neutral and amino sugar composition	√	√	√
Oligosaccharide Profiling	Comparison of glycosylation pattern (ex. G0F, G1F, G2F)	√	√	√
N-linked Glycan Analysis	Comparison of oligosaccharide structures, attachment sites and distribution	√	√	√

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Summary of Studies Comparing Biological Activity between Remsima and Remicade

Test Method	Key Findings
Fc Receptor related	
Comparative binding to Fcγ receptors: FcγRI, FcγRIIa, FcγRIIb, and FcRn using Surface Plasmon Resonance [SPR]	The relative binding affinities of Remsima and Remicade to Fcγ receptors (FcγRI, FcγRIIa, FcγRIIb and FcRn) were comparable.
Comparative binding to Fcγ receptors: FcγRIIIa (V and F hemizygotes) and FcγRIIIb using SPR	Differences in the relative binding affinity of Remsima and Remicade FcγRIIIa and FcγRIIIb were detected; reduced binding to FcγRIIIa (V and F hemizygotes) and FcγRIIIb was detected in Remsima lots.
Comparative binding to Fcγ receptors: *Ex vivo* assay using NK cells and neutrophils to assess FcγRIIIa and FcγRIIIb binding, respectively	There was a difference in mean relative binding affinities to isolated NK cells of healthy donors and Crohn's disease (CD) patients (between Remsima and Remicade, which was shown to be FcγRIII genotype dependent (V/V and V/F genotypes, respectively). No differences were shown with F/F genotype. In the presence of diluted CD patient serum all differences in binding for Remsima and Remicade lots were abrogated.
	The mean relative binding affinities of Remsima and Remicade to isolated neutrophils (*ex vivo*) from a healthy donor or CD patient were shown to be comparable.

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Test Method	Key Findings
F(ab')2 related	
Comparative binding of Remsima and Remicade to hTNFα using ELISA	The relative binding affinities of Remsima and Remicade were shown to be comparable. Remsima and Remicade demonstrated comparable binding activity to both monomeric and trimeric hTNFα.
Comparative binding of Remsima and Remicade to hTNFα using Surface Plasmon Resonance [SPR]	Similar equilibrium binding affinities (K_D) toward the intact trimeric form of hTNFα. The binding affinity of Remsima and Remicade to monomeric and trimeric hTNFα was comparable. The relative binding affinities of Remsima and Remicade were shown to be comparable for hTNFα. Remsima and Remicade demonstrated comparable binding to both monomeric and trimeric hTNFα.
Comparative transmembrane (tm) hTNFα binding affinity of Remsima and Remicade using cell-based ELISA	The relative binding affinities of Remsima and Remicade were shown to be comparable.
The human TNFβ binding specificities of Remsima and Remicade	Neither Remsima nor Remicade had binding affinity for hTNFβ.

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Summary of Studies Comparing Biological Activity between Remsima and Remicade (cont..)

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Test Method		Key Findings
F(ab')2 related		
Human tissue cross-reactivity of Remsima and Remicade using immunohistochemistry		The tissue cross-reactivity of biotinylated Remsima and biotinylated Remicade were shown to be comparable using a panel of human tissues.
Comparative TNFα binding affinity from different species of Remsima and Remicade using SPR		For Remsima and Remicade, neither product displayed binding affinity for mouse, rat, canine, porcine, or rhesus monkey TNFα.
Comparative hTNFα neutralisation assay of Remsima and Remicade		The neutralising activities of Remsima and Remicade on a TNFα sensitive cell line were shown to be dose dependent and comparable and within ≤15% of assay variance.
Comparative apoptosis of Remsima and Remicade		The apoptotic effects by reverse signalling through tmhTNFα for Remsima and Remicade were comparable. No statistically significant differences were detected at any time point.
Comparative Reverse signalling		Blockade of pro-inflammatory cytokine production by reverse signalling through tmhTNFα for Remsima and Remicade were comparable, using peripheral mononuclear blood cells (PBMC) from either healthy donors or CD patients.
Effect of blocking soluble TNFα in ***in vitro*** IBD model	Suppression of cytokine secretion in epithelial cell line by blocking soluble TNFα	Suppression of pro-inflammatory cytokine (IL-6 and IL-8) secretion from co-stimulated epithelial cell line was shown to be comparable and dose dependent for Remsima and Remicade; no statistical difference in pro-inflammatory cytokines suppression was found.
	Suppression of apoptosis in epithelial cell line cells by blocking soluble TNFα	Suppression of epithelial cell line apoptosis was shown to be comparable for Remsima and Remicade.

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Summary of Studies Comparing Biological Activity between Remsima and Remicade (cont..)

Test Method		Key Findings
Fc-F(ab')2 related		
Comparative C1q binding affinity of Remsima and Remicade using ELISA		The relative binding affinities of Remsima and Remicade were shown to be comparable.
Comparative complement-dependent cytotoxicity (CDC) of Remsima and Remicade		CDC effects of Remsima and Remicade against tmhTNFα-Jurkat cells by lysis were comparable. No statistically significant differences were detected in relative CDC activity.
Comparative antibody-dependent cell-mediated cytotoxicity (ADCC) of Remsima and Remicade using tmhTNFα-Jurkat cells as target cells and human PBMC as effector cells		Remsima and Remicade had comparable ADCC activity and no statistically significant differences were detected.
Comparative ADCC of Remsima and Remicade using tmhTNFα-Jurkat cells as target cells and NK cells from healthy donor as effector cells		Comparable ADCC for Remsima and Remicade when NK cells from a healthy donor (genotype V/F) were used as effector cells.
Evaluation of Regulatory Macrophage Function	Suppression of T cell proliferation by induced regulatory macrophages in mixed lymphocyte reaction (MLR) assay	Inhibition of T cell proliferation of PBMCs from healthy donors and CD patients was shown to be comparable and dose dependent for Remsima and Remicade.
	Quantitation of the induced regulatory macrophages by FACS analysis	Induction of regulatory macrophages in a 2-way allogenenic MLR using FcγRIIIa genotype matched PBMCs, from either healthy donors or CD patients, was shown to be comparable for Remsima and Remicade.
	Induced regulatory macrophage-mediated wound healing of colorectal epithelium cells	Promotion of ***in vitro*** wound healing of colorectal epithelial cells by regulatory macrophages from healthy donors and CD patients (induced by Remsima or Remicade) in the MLR assay was comparable.

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Summary of Studies Comparing Biological Activity between Remsima and Remicade (cont..)

Test Method	Key Findings
F(ab')2 related	
Comparison of ADCC activity between Remsima and Remicade using transfected Jurkat cells as target cells and either PBMCs or NK cells from CD patients as effector cells	No differences in ADCC activity were detected using PBMC from CD patients (V/F or F/F genotype). Differences in ADCC with Remsima and Remicade were seen when NK cells from CD patients were used as effector cells. Effect was FcγRIIIa genotype specific; differences were observed with V/V and V/F, but not F/F genotypes.
Comparison of ADCC effect between Remsima and Remicade using transfected Jurkat cells as target cells and whole blood from healthy donor or CD patients as effector cells	No differences in ADCC were seen between various batches of Remsima and Remicade.
Comparison of ADCC between Remsima and Remicade using LPS-stimulated monocytes from healthy donor or CD patient as target cells and PBMC as effector cells	No ADCC activity was seen with Remsima and Remicade when PBMCs from a healthy donor (V/F) or a CD patient (V/F) were used as effector cells and LPS-stimulated monocytes were used as target cells.

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Thank you
John Borg