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EAHP 2015 Synergy Satellite MAbs and biosimilars
1

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MONOCLONAL ANTIBODIES AND BIOSIMILARS
production, naming, pharmacovigilance and other pharmaceutical quality aspects
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2

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Conflict of Interest Disclosure
Jos Kosterink, Pharm D, PhD

- Consulting Fees (eg, advisory boards): Amgen Europe, MSD, BMS
- Contracted Research: MSD, Genentech, Pfizer

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Outline

- Facts and Figures Biopharmaceuticals Monoclonal antibodies
- Mabs characteristics
- Manufacturing
- Quality aspects
- Immunogenicity
- Formulation
- Comparibility
- Pharmacovigilance and traceability
- Concluding remarks

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Biopharmaceuticals vs Biologicals

- **Biopharmaceuticals**: drugs produced through biotechnology technology and methods (hybridoma technolgy; recombinant DNA-synthesis)
- **Biologicals**: drugs produced through extraction from biologic source

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Biopharmaceuticals

Most common classes of Biopharmaceuticals:

- Vaccines
- Therapeutic proteins
- Monoclonal antibodies
- Gene therapies

Most common administration routes:

- Intravenously (IV)
- Subcutaneously (SC)
- Intramuscularly (IM)

Medicines do not have to pass the Gastrointestinal Barrier

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Small Chemical Drugs vs Biopharmaceuticals

	Small Chemical Drugs	Biopharamceuticals
Size	Small	Large
Structure	Simple	Complex
Stability	Stable	Unstable
Modification	Well defined	Many options
Manufacturing	• Predictable chemical process • Identical copy can be made	• Unique line of living cells • Impossible to ensure identical copy
Characterization	Easy to characterize fully	Difficult to characterize fully due to a mixture of related molecules
Immunogenicity	Nonimmunogenic	Immunogenic

7

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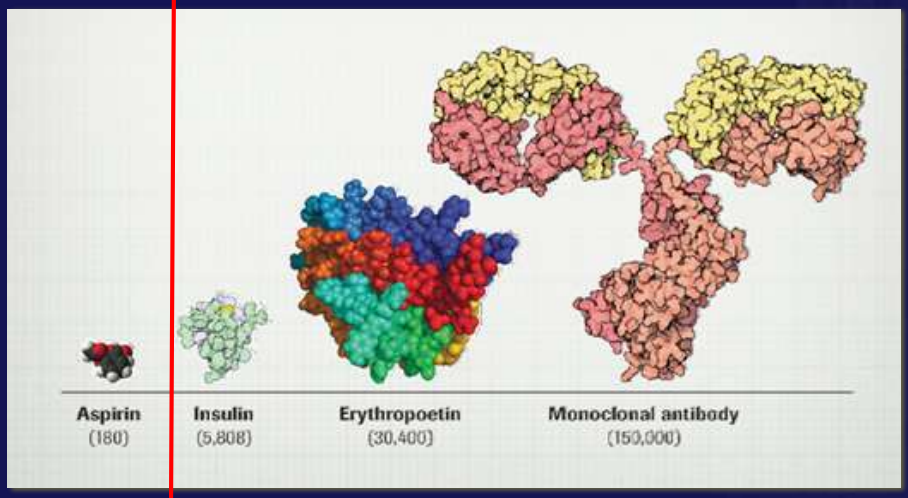
Biopharmaceuticals Are More Complex Than Small Molecule drugs



Small molecule drug

'Simple' biologics

'Complex' biologics

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Impact of Blockbuster Mab's

Demand for existing commercial antibody products will nearly double by 2016

- ~8.3 metric ton ➡ ~13.4 metric tons
- Current annual requirements for top five monoclonal antibody products range from 1,003 kg to 1,431 kg
- Total demand for all other monoclonal antibody products is approximately 2,169 kg
- Anticipated demand for new antibody products approved between now and 2016 expected to be ≤5 metric tons/year/MAb

Ransohoff, 2011

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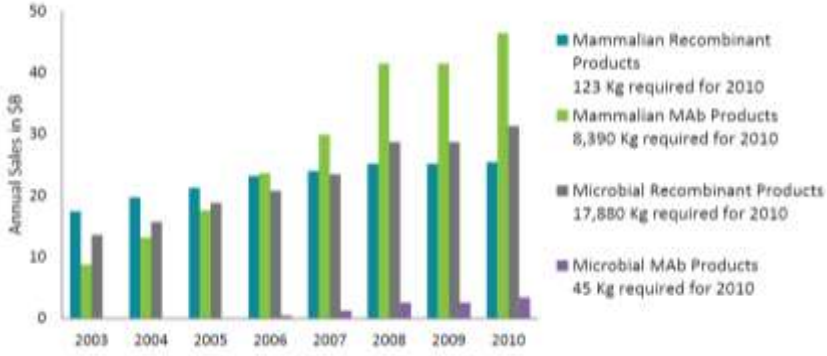
Relevance of Monoclonal Antibodies



Ransohoff, 2011

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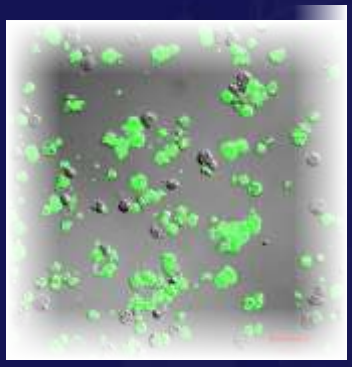
Biopharmaceutical Manufacturing

The work horses for biological manufacturing of glycosylated proteins are **mammalian cells**:

- Chinese Hamster Ovary (CHO)
- Murine Myeloma (NS0)
- Primary Human Retina (Per.C6)
- Canine Kidney (MDCK)
- African Green Monkey Kidney (Vero)



Stained MDCK cells in culture

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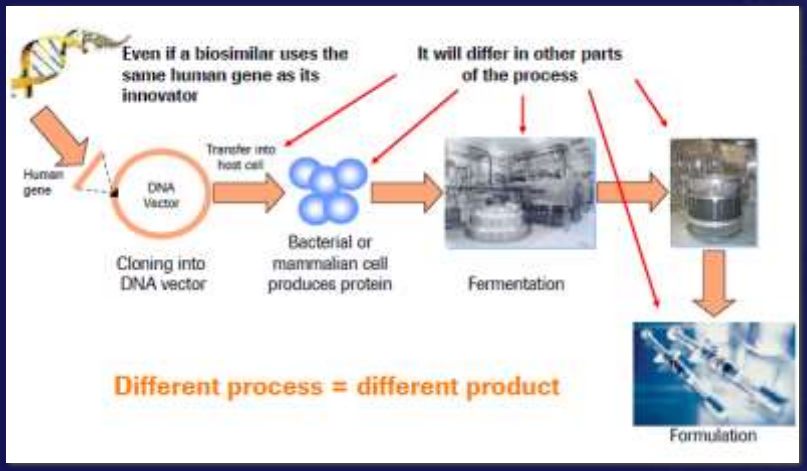
Manufacture of Biopharmaceuticals: Unique and Complex Process



It is impossible to make an exact copy

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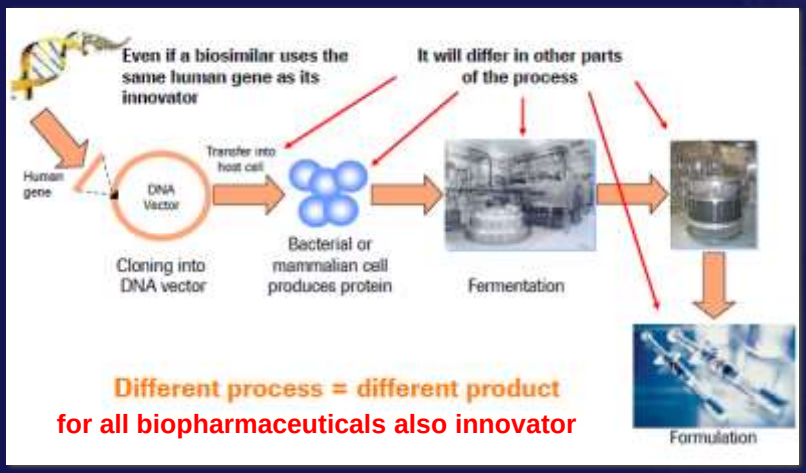
Manufacture of Biopharmaceuticals: Unique and Complex Process



Different process = different product

for all biopharmaceuticals also innovator

It is impossible to make an exact copy

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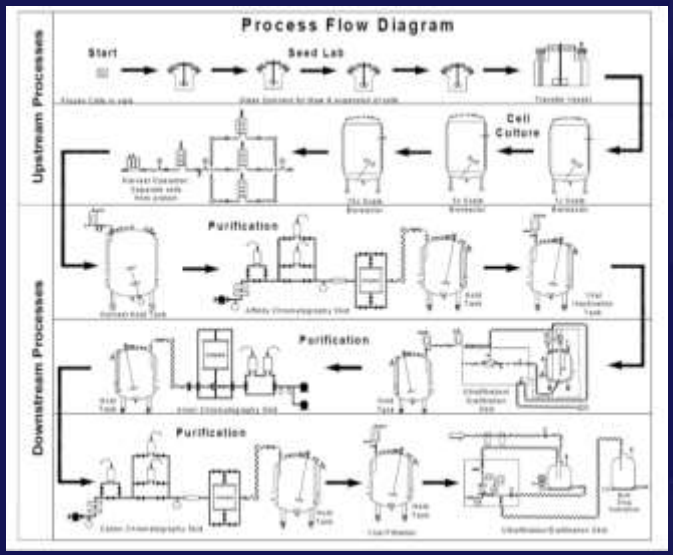
Mab production process



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Production Scheme – USP

Upstream Processing:

- **Preculture: Expand cells from the Working Cell Bank (WCB) to the Production Bioreactor (through a cascade of shaker flasks and batch bioreactors)**
- **Production: Produce large amounts of cells and allow expressed product to accumulate in the culture broth**
- **Most common production scheme is fed-batch**

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USP – Seed Train

Large scale seed train at Biogen-Idec, Berthold, 2008

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Production Scheme – DSP

Global overview:

- Clarification (centrifugation and filtration)
- Capture chromatography
- Viral inactivation
- Polishing steps
- Viral filtration
- Concentration & Preformulation
- Sterile filtration

Large scale chromatography columns

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DSP – Capture Chromatography

Main features:

•Specific binding of any monoclonal antibody to chromatography media due to affinity ligand (Protein A)

•Elute monoclonal antibody with lower pH buffer

•Reduce contaminants with 3-logs

•The work horse in MAb purification

•Expensive chromatography media (€ 10,000 per liter)

Large scale Protein A chromatography columns

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DSP – Polishing Chromatography

Purpose **removal of impurities**:

- Trace amounts of host cell proteins
- Residual rDNA
- Leached protein A
- Viral contaminants

Process related impurities

- High-molecular weight aggregates
- Product isomers

Product related impurities

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Safety and Efficacy

Efficacy:

•Attributes of the active ingredient or drug substance (and the formulation);

•As long as we don't alter the molecule, biomanufacturing will not affect efficacy (but, this is less trivial than you may think);

Safety:

•Attributes of the product itself (mainly immunogenicity) and its environment (impurities);

•Includes (but is not limited to) sterility, viral safety, process related impurities and product related impurities;

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Ensuring Safety and Efficacy

current Good Manufacturing Practice (cGMP)

Robust Manufacturing Process should be designed to:

- Remove process related impurities
- Remove product related impurities
- Retain therapeutic effect
- High yield
- Acceptable costs

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Quality Control in Biomanufacturing

Quality Control:

- Not every product quality attribute can be measured directly
- Production process has direct impact on the product quality
- Process validation: demonstrate process capability to deliver if operated within specified range

Overall quality envelope:

- Written procedures
- Training
- Testing
- Regulatory Inspections

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Quality Control: Cell Banking

- **MCB: Master Cell Bank**
- **WCB: Working Cell Bank**
- **PPCB: Post Production Cell Bank**

	MCB	WCB	PPCB
Viability	☑	☑	☑
Identity	☑	☑	
Purity	☑	☑	☑
Stability	☑		☑
Sterility	☑	☑	☑
Mycoplasma	☑	☑	☑
Adventitious viruses	☑		☑

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Quality Control: Viral Safety

Potential sources for adventitious viruses:

- Cell substrates (particularly animal cell systems)
- Raw materials, including cell culture reagents
- Environment (water, operators, air)

Avoiding the use of Animal Derived Ingredients is a key element of all viral safety strategies

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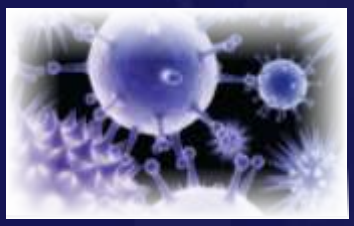
Quality Control: Viral Safety

Virus Removal relies on **Multiple Orthogonal steps**, typically**:**

- Viral inactivation
- Anion exchange (flow through)
- Viral filtration (nanofiltration)



- Total removal efficiency of viruses normally is 10^6 – 10^{15} (LRV = 6 – 15)
- Process capability is demonstrated with spiking studies on small scale using carefully selected model viruses (enveloped/non-enveloped, RNA/DNA, varying sizes, etc.)

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Quality Control: Product Testing

	Drug Substance	Drug Product
Identity	☑	☑
Purity (process and product related impurities)	☑	☑
Safety (bioburden, sterility, endotoxin)	☑	☑
Potency (biological activity)	☑	☑
Strength (protein content)	☑	☑
Stability	☑	☑
Container Closure		☑

This looks like a fairly comprehensive list…

but it could easily involve 30 assays or more.

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Immunogenicity: The Key Issue for Protein Drugs

Factors Contributing to Immunity

- **Host related**
  - Genetic predisposition (major histocompatibility complex alleles)
  - Concomitant therapy (interferon)
  - Immunosuppression (cancer)
  - Activated immune system due to infection
  - Ethnic sensitivity
  - Prior treatments
- **Product related**
  - Structural properties
  - Glycosylation
  - Impurities
  - Formulation
  - Storage
  - Aggregates
- **Treatment related**
  - Route of administration
  - Dose
  - Length of treatment

27

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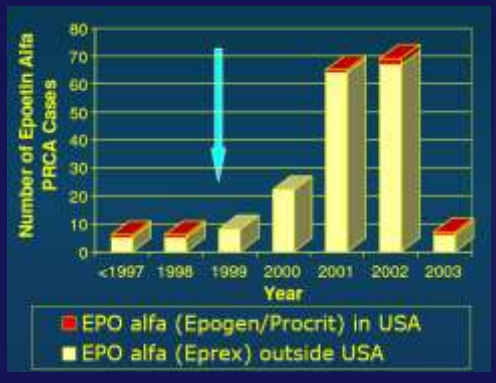
Formulation

- **Albumin replaced by Tween 80/glycine in epoetin alpha formulation (outside USA)**



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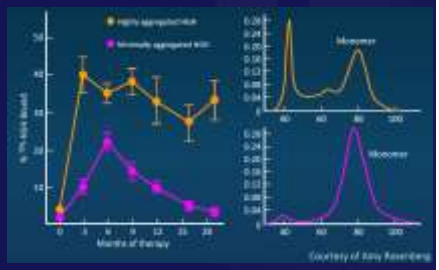
Aggregates and immunogenicity

- Intravenous immunoglobulins (1950s, 1960s)
  - Aggregate removal resulted in less immunogenic products
- Human growth hormone purified from formalin-fixed pituitary glands (1950s)
  - The higher the aggregate levels (up to 70%!) the more immunogenic
- Betaseron
  - Contains substantial aggregate levels and is more immunogenic than other interferon-beta products
- Interleukin 2
  - Aggregated formulation induced antibodies in most patients
- Interferon-alfa
  - Formulation with oxidized and aggregated products was more immunogenic than other formulations



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Comparibility Biopharmaceuticals

Pharmacotherapy. 2005 Jul;25(7):954-62.

Biosimilar epoetins: an analysis based on recently implemented European medicines evaluation agency guidelines on comparability of biopharmaceutical proteins.

Combe C, Tredree RL, Schellekens H.

Department of Nephrology, Hôpital Pellegrin and Université Victor Segalen, Bordeaux, France.

Abstract

Patents of innovator biopharmaceutical products, such as epoetin, are expiring, and biosimilar versions of these products may soon enter European and American markets. Copies of these products, termed biosimilars or follow-on biologics, are not truly equivalent and cannot gain market approval through the procedure typically applied to generic drugs. We evaluated literature reports of both analytic and clinical studies conducted with biosimilar epoetin products currently marketed outside the United States and Europe in light of recently implemented European Medicines Evaluation Agency guidelines. The analytic studies reported that products differed widely in composition, did not always meet self-declared specifications, and exhibited batch-to-batch variation. Although several clinical studies demonstrated correction of anemia with biosimilar epoetins by using an open-label or placebo-controlled study design, only 4 of 22 studies were competitor controlled. Most of the studies were small (median 41 patients, range 18-1079 patients) and of short duration (median 12 wks, range 6 wks-1 yr). Clinical experience with epoetin shows that the dosage required to achieve similar hemoglobin levels varies among patients, making it impossible to demonstrate bioequivalence without a comparator. The analytic reports did not demonstrate comparability of biosimilar epoetin products with innovator epoetin alfa, and the clinical studies were not rigorous enough to show equivalent safety and efficacy of a biopharmaceutical product. The variation between products illustrates the challenge in replicating and consistently producing biopharmaceutical proteins. Immunogenic reactions with epoetin indicate that large, long-term studies are needed to adequately monitor safety.

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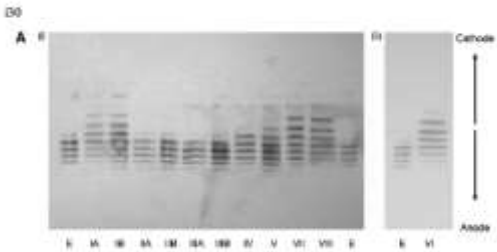
Non-innovator erythropoietins



Sample	Concentration (IU/mL)	Country
IA	2000	Korea
IB	4000	Korea
IIA	2000	Korea
IIB	10 000	Korea
IIIA	2000	Korea
IIIB	10 000	Korea
IV	2000	Argentina
V	10 000	Argentina
VI	4000	India
VII	10 000	China
VIII	6000	China

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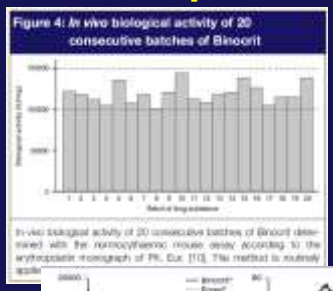
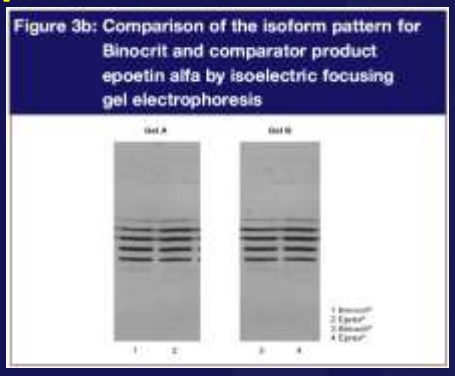
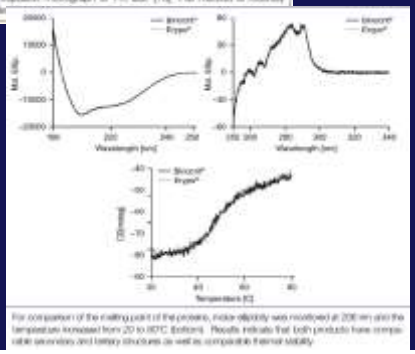
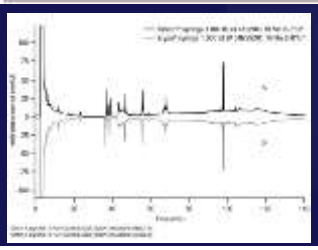
Comparibility Biopharmaceuticals









Brockmeyer and Seidel, EJHP 2009

32

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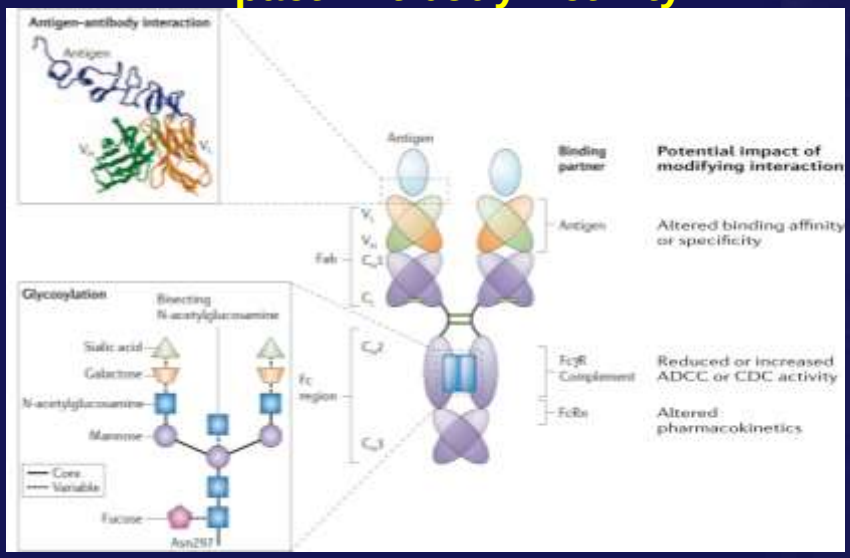
Post-translational Modifications May Impact Antibody Activity



Carter PJ. *Nat Rev Immunol.* 2006;6(5):343-357.

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Comparibility Biopharmaceuticals

REPORT

Physicochemical characterization of Remsima®

Soon Kwan Jung[1], Kyoung Hoon Lee[1], Jae Won Jeon[1], Joon Won Lee[1], Byoung Oh Kwon[1], Yeon Jung Kim[1], Jin Soo Bae[1], Dong-Il Kim[2], Soo Young Lee[1], and Shin Jae Chang[1,*]

[1]R&D Division, Celltrion Inc., Incheon, Korea; [2]Department of Biological Engineering, Inha University, Incheon, Korea

Keywords: infliximab, biosimilar, CT-P13, characterization, comparability, Remsima®, Remicade®, reference medicinal product (RMP)

Remsima® (infliximab) was recently approved as the world's first biosimilar monoclonal antibody (mAb) in both the European Union and Korea. To achieve this, extensive physicochemical characterization of Remsima® in relation to Remicade® was conducted in order to demonstrate the highly similar properties between the two molecules. A multitude of state-of-the-art analyses revealed that Remsima® has identical primary as well as indistinguishable higher order structures compared with the original product. Monomer and aggregate contents of Remsima® were also found to be comparable with those of Remicade®. In terms of charge isoforms, although Remsima® was observed to contain slightly less basic variants than the original antibody, the difference was shown to be largely due to the presence of C-terminal lysine. On the other hand, this lysine was found to be rapidly clipped inside serum in vitro and in vivo, suggesting it has no effect on the biological potency or safety of the drug. Analysis of the glycan contents of the antibodies showed comparable glycan types and distributions. Recent results of clinical studies have further confirmed that the two antibody products are highly similar to each other. Based on this research as well as previous clinical and non-clinical comparability studies, Remsima® can be considered as a highly similar molecule to Remicade® in terms of physicochemical properties, efficacy, and safety for its final approval as a biosimilar product to Remicade®.

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Pharmacovigilance and traceability

- **Same rules apply to biosimilar as to all biologicals**

this is specifically addressed in the pharmacovigilance legislation

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Pharmacovigilance and Traceability

- Post approval, biosimilars must undergo at least one year of **post-marketing surveillance** to detect incidence of immunogenicity and other adverse events
- This includes detailed **risk management plans** that should be followed by both physicians and pharmacists
- Because biosimilars are given the international nonproprietary name (INN) as the originator, additional information including brand name should be used when prescribing

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Risk-Management Plan (RMP)

- Risk Management Plan of the biosimiar is required to guide PV activities (as for all biologics)
- Enhanced PV monitoring is important for biosimilars due to limited size of the pre-marketing clinical trial population
- Safety-related post-marketing commitments:
  - Safety in indications that are claimed on extrapolation
  - Rare and SAEs predicted based on pharmacology of reference product
  - Detection of new safety signals
  - Activities to obtain additional immunogenicity data (immunogenicity testing)

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RMP for Biosimilar Antibodies

- **Proactive PV activities**
  - Targeted questionnaire
  - Phase IV studies
  - Registries
  - Specialized follow-up for long-term use
- **Individual RMPs are available in the European public assessment report (EPAR)**
- **Physicians should be informed about RMPs (close collaboration with hospital pharmacists)**

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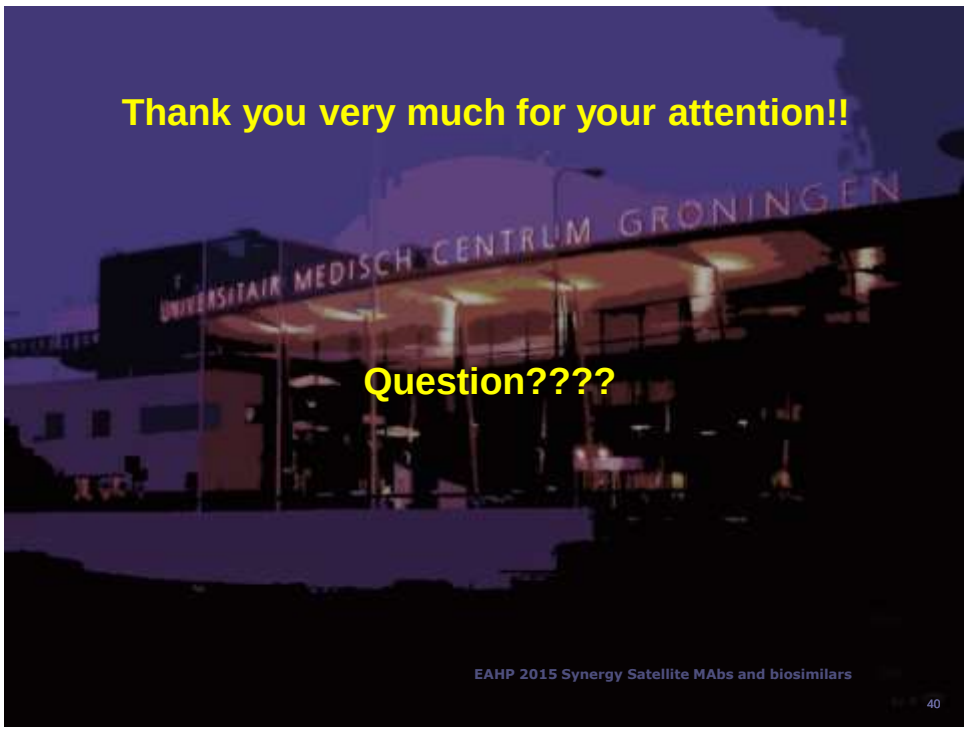
Concluding remarks

- Differences in production process can influence characteristics of the end product
- Physicochemical characterisation is the basis for biosimilar development
- Step-wise approach is highly recommended
- (Remaining) uncertainties are tackled by non-clinical and clinical studies
- Biosimilarity is concluded based on integral evidence
- Tracebility and pharmacovigilance is of high importance for all biopharmaceuticals including biosimilars

Biosimilars are similar to the reference product