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University Medical Center Rotterdam

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10 - 14 September

Understanding the Similarity Exercise: The Basis for Biosimilar Acceptance

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Honorary Professor KU Leuven, Belgium

Vs17i13

Conflict of Interest Statement

Generics and Biosimilars Initiative
Building trust in cost-effective treatments
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- I declare no personal financial interest in any pharmaceutical business.
- My hospital receives financial compensation for the time I consult / lecture for 3rd parties, like speaking bureaus and pharmaceutical companies.
- I entertain friendly relationschips with all innovative and generic / biosimilar companies and I help them all where I can. I don't receive personally any payment for that.
- Companies / Organisations involved are: AbbVie, Amgen, Biogen, EGA (Medicines for Europe), Mundipharma, Pfizer/Hospira, Roche, Sandoz
- I am the co-founder of the Generics & Biosimilars Initiative (GaBi), The Dutch Initiative Group on Biosimilars (IBN) and the KULeuven – EramusMC MABEL Research Fund

Who is Arnold Vulto?

- A practising hospital pharmacist, not a lawyer nor regulator
- Member of ErasmusMC Medical Ethical Review Board
  - In the pharmacy we see and run all drug trials
- Qualified Person (QP) for biotechnology medicines
- Got involved in biosimilars as early as 2004 via European Journal of Hospital Pharmacy
  - How to guide hospital pharmacists in this difficult area
- 2008 Founder of GaBI, together with Huub Schellekens and Lasia Tang
  - To provide transparency to cost-effective medicines
- 2013 Co-founder of the Dutch Biosimilar Initiative
  - Independent platform to promote efficient use of medicines
- 2015: Co-founer of the MABEL-research fund (KU Leuven / ErasusMC)

My motto: *For each patient the best medicine at the best price*

Agenda

1. Introduction
2. A new drug development paradigm
3. Critical quality attributes of biological medicines
4. Variability is inherent to biological medicines
5. What needs to be done in biosimilar develpment
    1. Fingerprinting the originator (reference product)
    2. Compare with biosimilar fingerprint
6. Take Home Message

What are biosimilars?

- How I see biosimilars as of September 2017
  - A biosimilar medicinal product is a licensed medicinal product which is similar to a biological medicinal product that has already been authorised (the ‘biological reference medicinal product’).
- What does that mean?
  - It is a ***version*** of an already licensed rec-DNA drug product, for which similarity has been proven in an extensive ***comparability exercise***, encompassing **physical, chemical, biological and pharmacological properties**, including efficacy and safety
  - This excludes all kinds of *bio-questionables* in existence in other regions of the world that have not been endorsed via the WHO pathway as a biosimilar. *Reference to such products as if biosimilars may be inferior is thus WRONG*.

Prescribing a drug requires understanding all details of the drug

- Biosimilars are not *identical* but *similar:* what does that mean?
- All biological medicines have inherent variability
- What are then the differences and what could be the consequence?
- A deep understanding of bioequivalence and “biosimilarity” is not easy
- But pharmacists should be able to explain to doctors and other HCP’s
- It starts with understanding the innovator medicine / reference product

Only if pharmacists can explain the background of the similarity exercise, they can successfully manage transition programs

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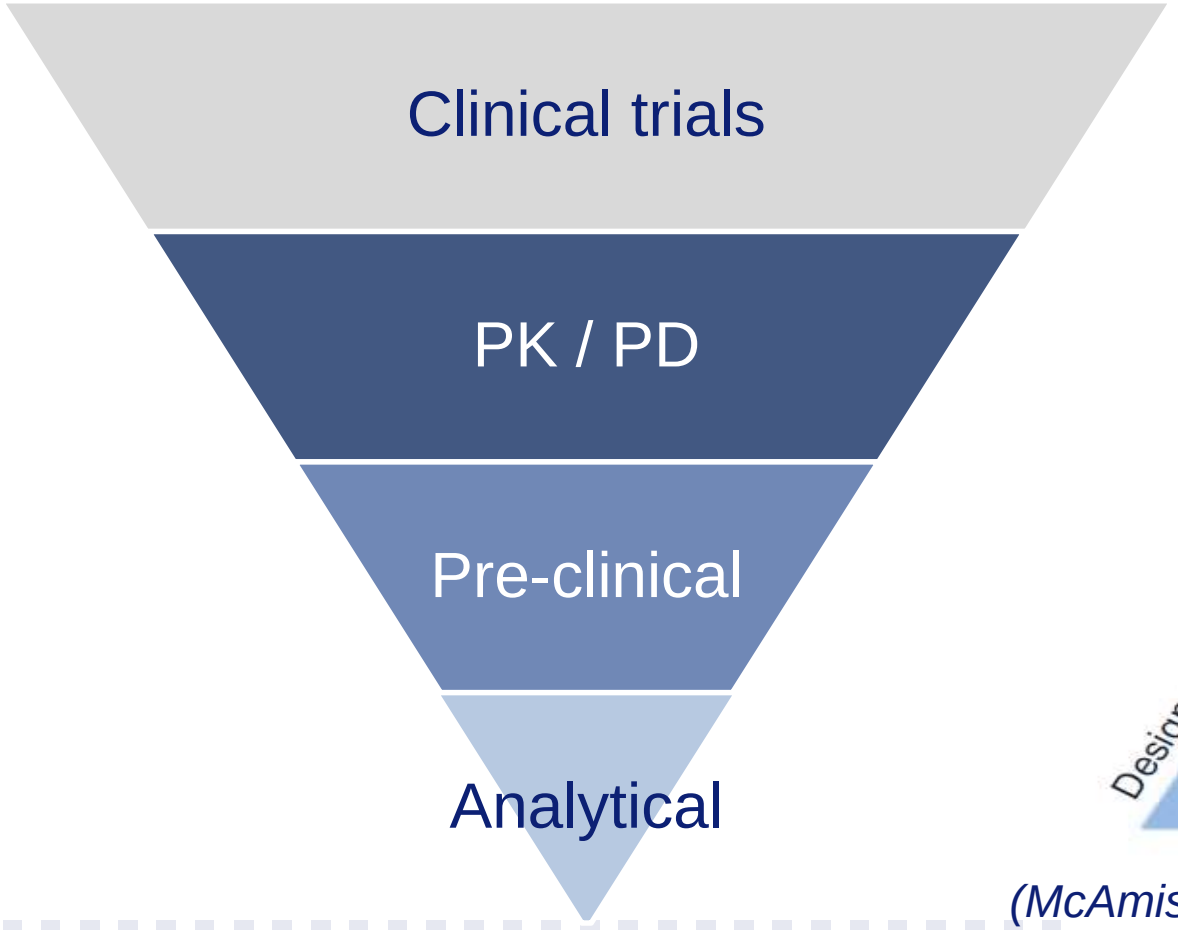
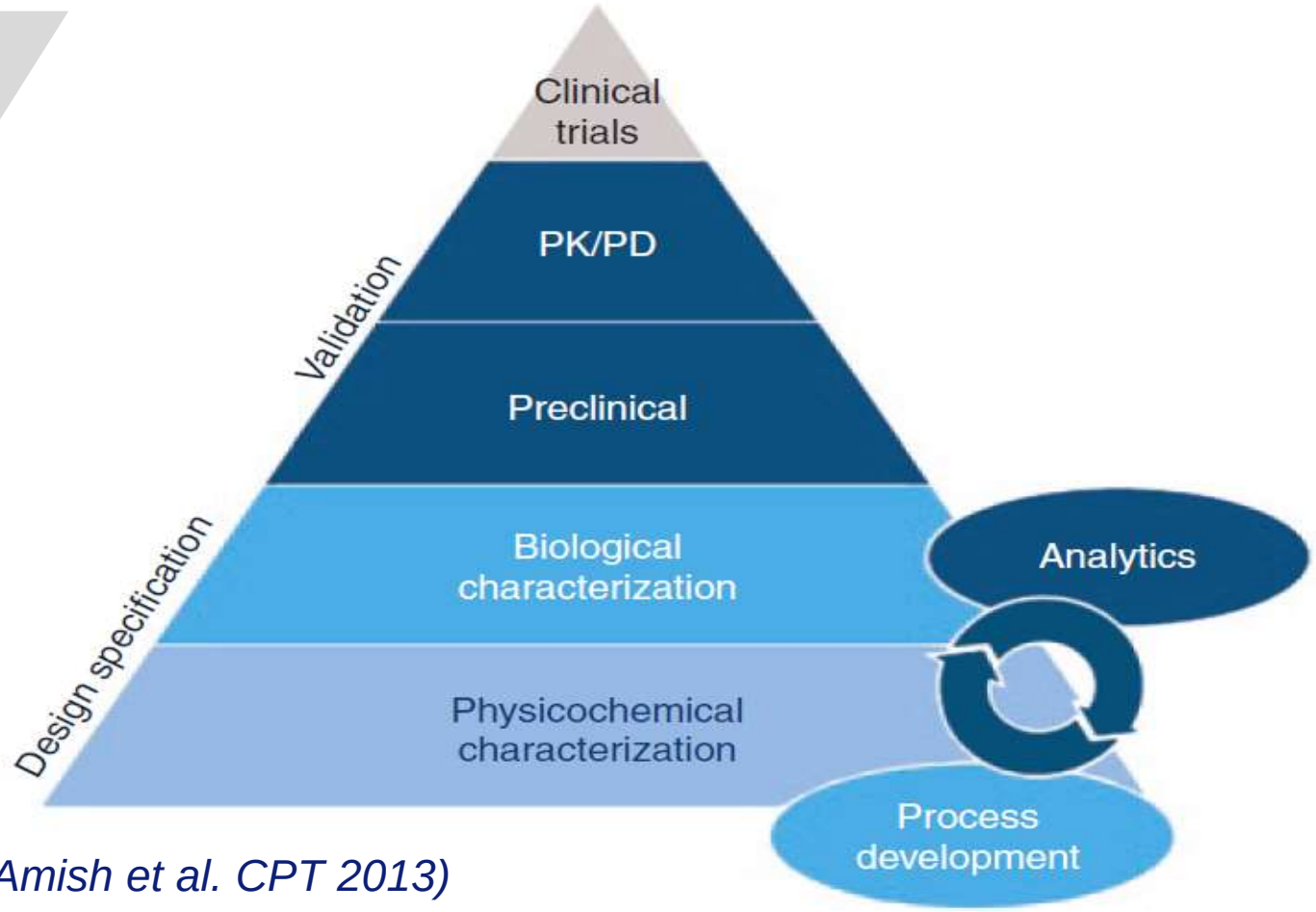
A new drug development paradigm, based on an all encompassing *comparability excercise*

traditional



biosimilar

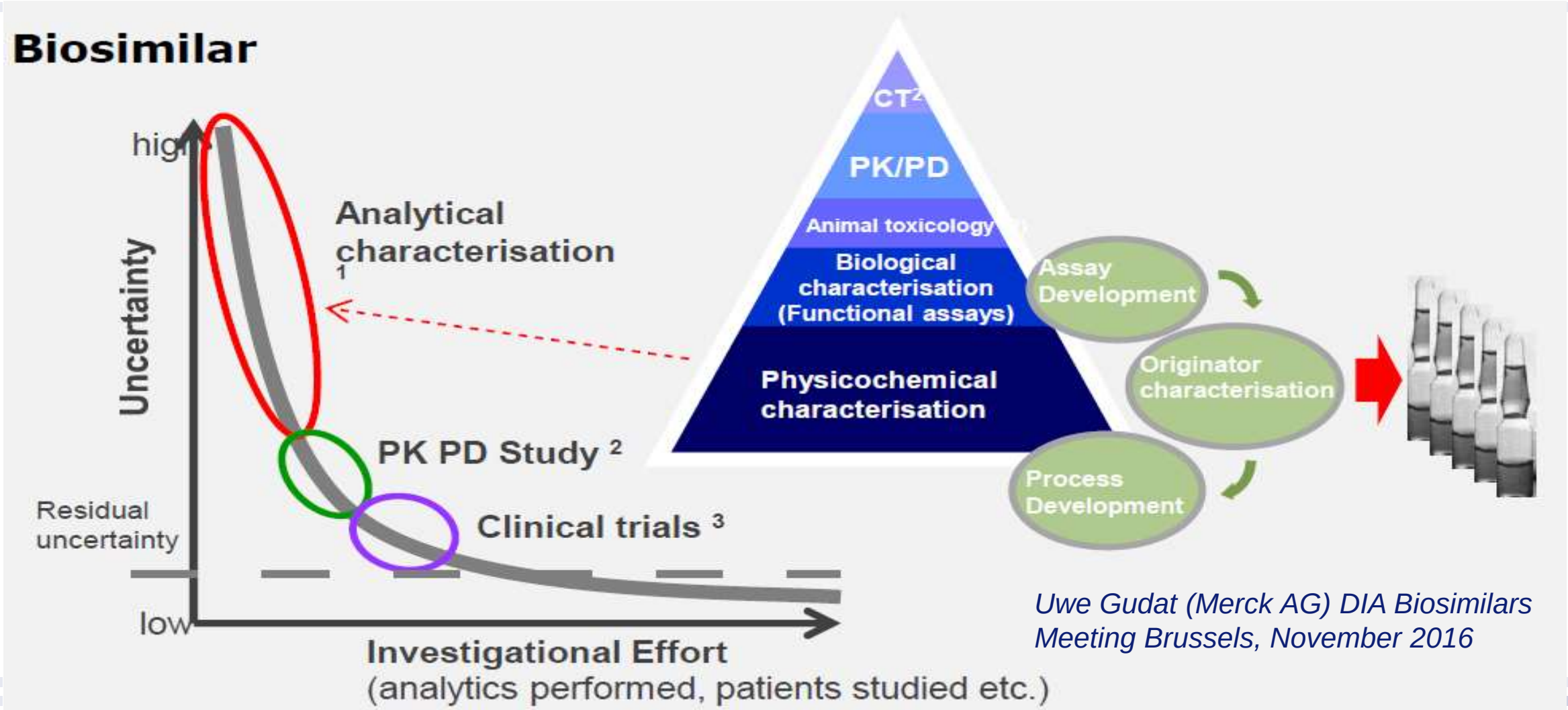


(McAmish et al. CPT 2013)

Stepwise approach in the development of biosimilars

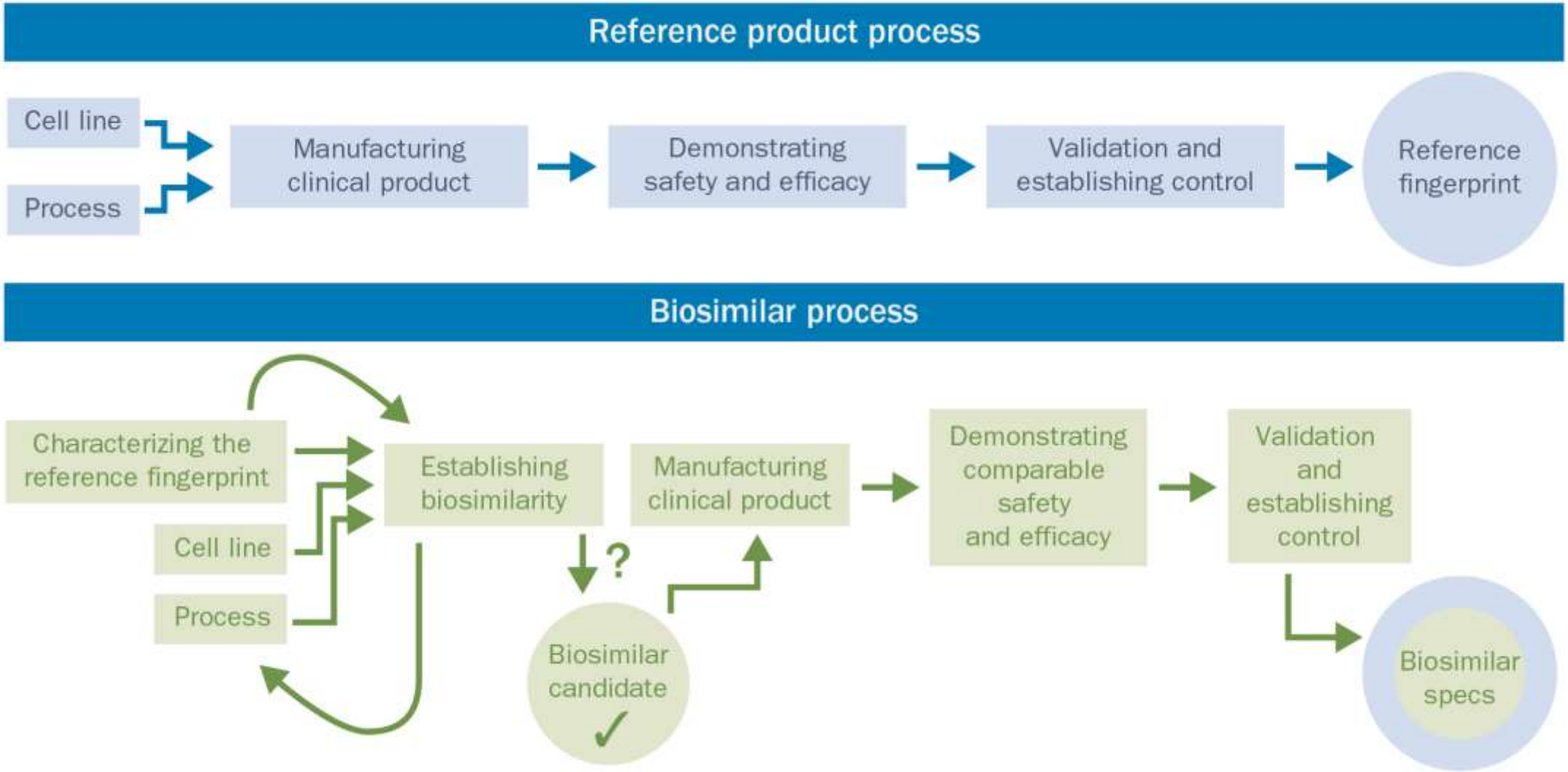
1. technical qualifications of reference product → biosimilar candidate
2. bioassays (for instance, on human cells)
3. non-clinical tests in animals
4. at least 2 clinical trials in humans: one PK/PD, one Phase III trial in the most sensitive population with sensitive endpoints (i.e. *able to detect a difference* if there is one)
5. specific post-marketing surveillance ("*Risk Management Plan*"), e.g. check for unexpected immunogenicity

Trust in similarity is being developed in a reversed "totality of evidence"

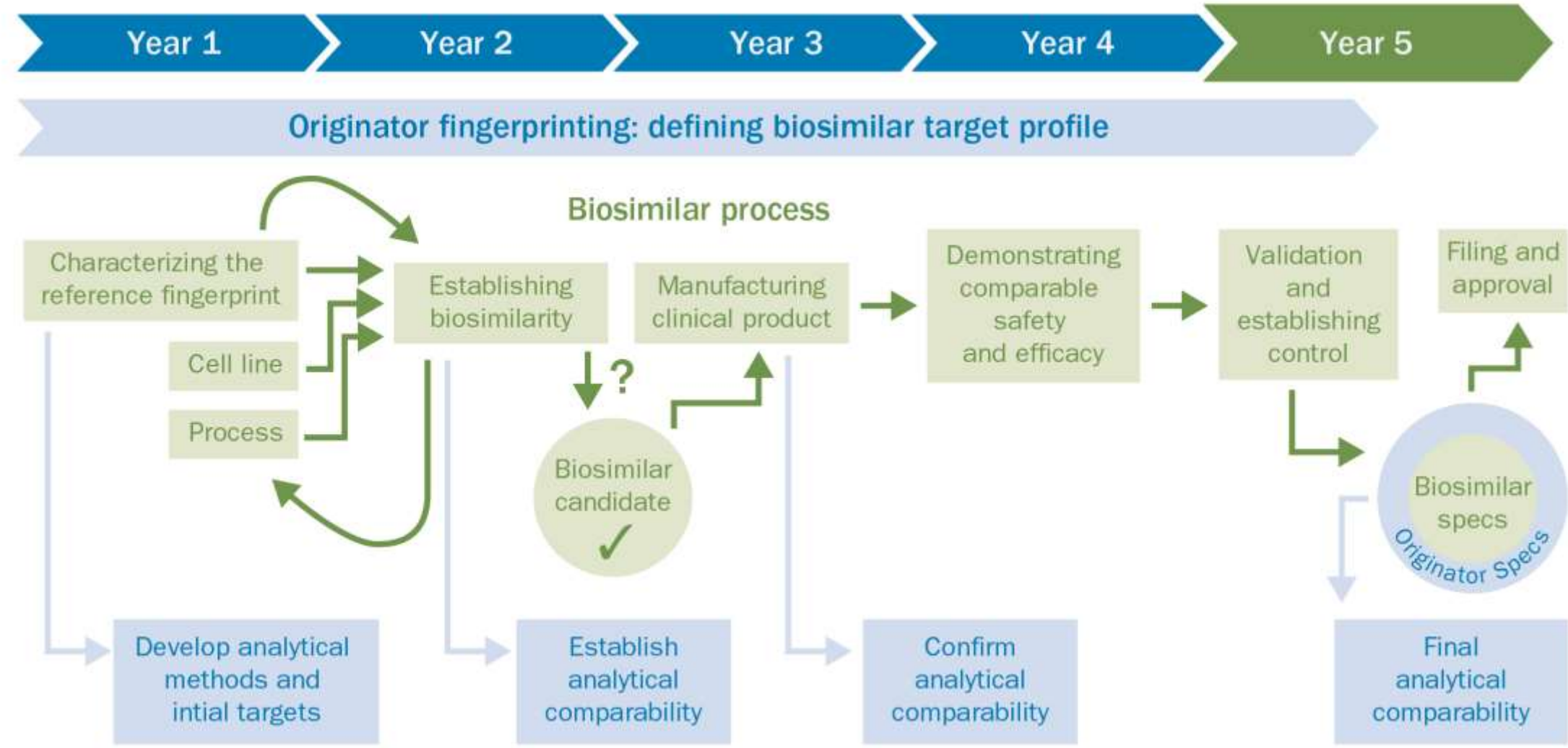


Uwe Gudat (Merck AG) DIA Biosimilars Meeting Brussels, November 2016

Comparison of the developmental processes for a reference (originator) product and a biosimilar



Comparability of the biosimilar with the originator attributes (fingerprint) during the biosimilar development process



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RHEUMATOLOGY

Rheumatology 2017;56:iv14–iv29
doi:10.1093/rheumatology/kex278

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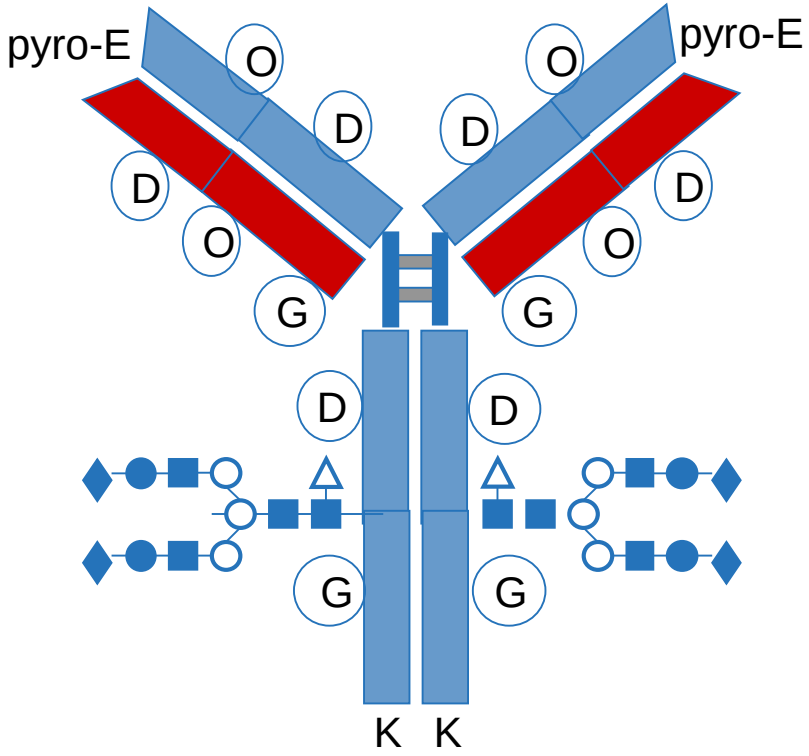
The process defines the product: what really matters in biosimilar design and production?

Arnold G. Vulto[1] and Orlando A. Jaquez[2]

- It's all about "***critical quality attributes***":
  - Which moieties in the molecule have what kind of action / effect
  - Once you know that, the " fingerprinting" can start

A biologic is a mixture of isoforms and is inherently variable



- ***Chemical modifications***
  - *Pyro-Glutamate (2)*
  - *D=Deamidation (3 × 2)*
  - *O=Methionine oxidation (2 × 2)*
  - *G=Glycation (2 × 2)*
- ***Biosynthetic or enzymatic modifications***
  - *High mannose, G0, G1, G1, G2 (5)*
  - *Sialylation (5)*
  - *K=C-terminal Lysine (2)*

$(9{,}600)^2 \approx 10^8$

$2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9{,}600$

Kozlowski S, et al. *Adv Drug Deliv Rev* 2006;58:707–722

Clinical relevance of quality attributes is well understood

Potentially clinically relevant attributes

Efficacy

- Amino acid sequence
- Folding, disulphide bridges, free cysteines
- Degradation
- Deamidation
- Glycation
- Glycosylation: fucosylation, mannose X, sialylation, galactose

Immunogenicity

- Amino acid sequence
- Aggregates
- Folding, disulphide bridges, free cysteines
- Degradation
- Host cell proteins
- Leachables / extractables
- Glycosylation
- Galactose-α1,3-Galactose

- **Quality attributes are assessed systematically and for each indication separately**

Brocchini S, et al. Adv Drug Deliv Rev 2008;60(1):3–12; Chung CH, et al. N Engl J Med 2008;358:1109–17; Dashivets T, et al. PLoS One 2015;10:e0143520; Goetze AM, et al. MAbs 2010;2(5):500–7; Kennedy DM, et al. Clin Exp Immunol 1994;98:245–51; Liu H, May K. Mabs 2012;4:17–23; Markovic I. Expert Opin Drug Saf 2007;6:487–91; Rathore N, Rajan RS. Biotechnol Prog 2008;24(3):504–14; Ripple DC, Dimitrova MN. J Pharm Sci 2012;101:3568–79; Wang X, et al. Biotechnol Bioeng 2009;103:446–58; Weber CA, et al. Adv Drug Deliv Rev 2009;61:965–76; Wright A, et al. EMBO J 1991;10:2717–23

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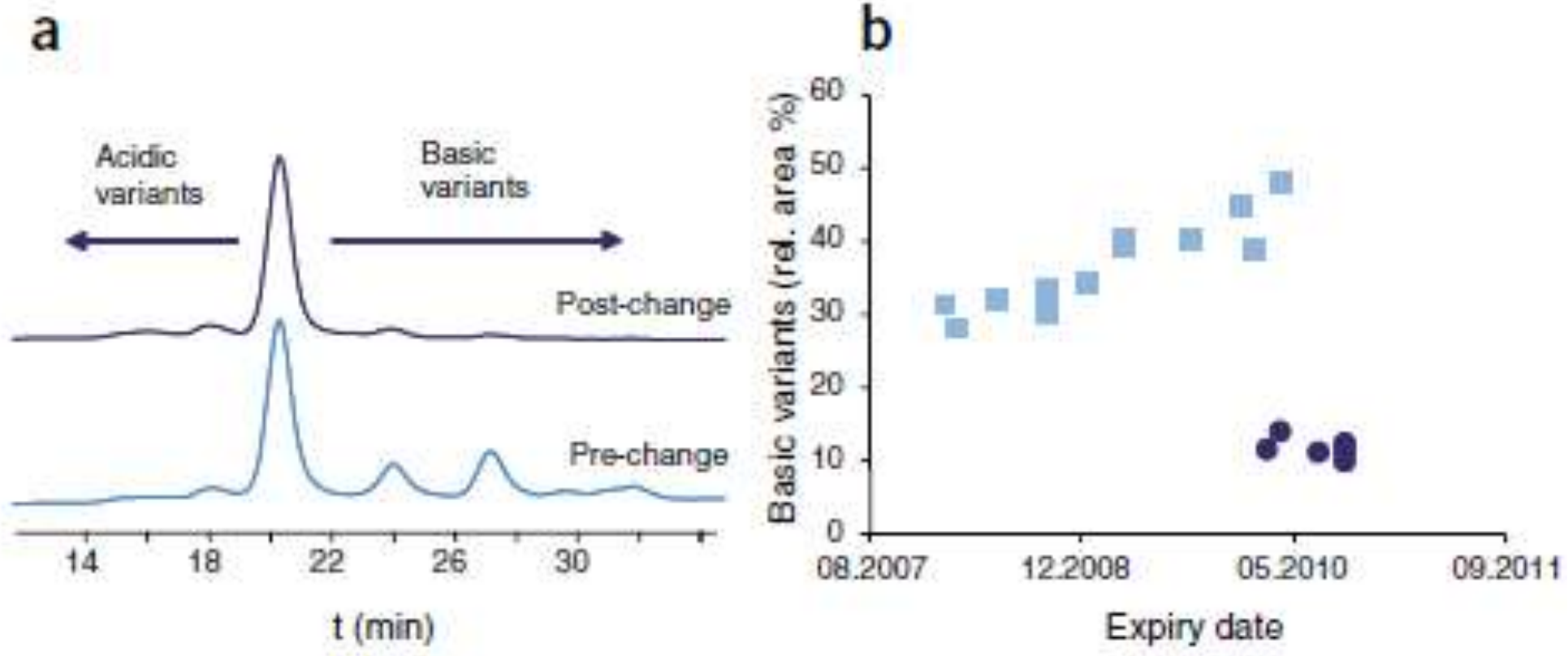
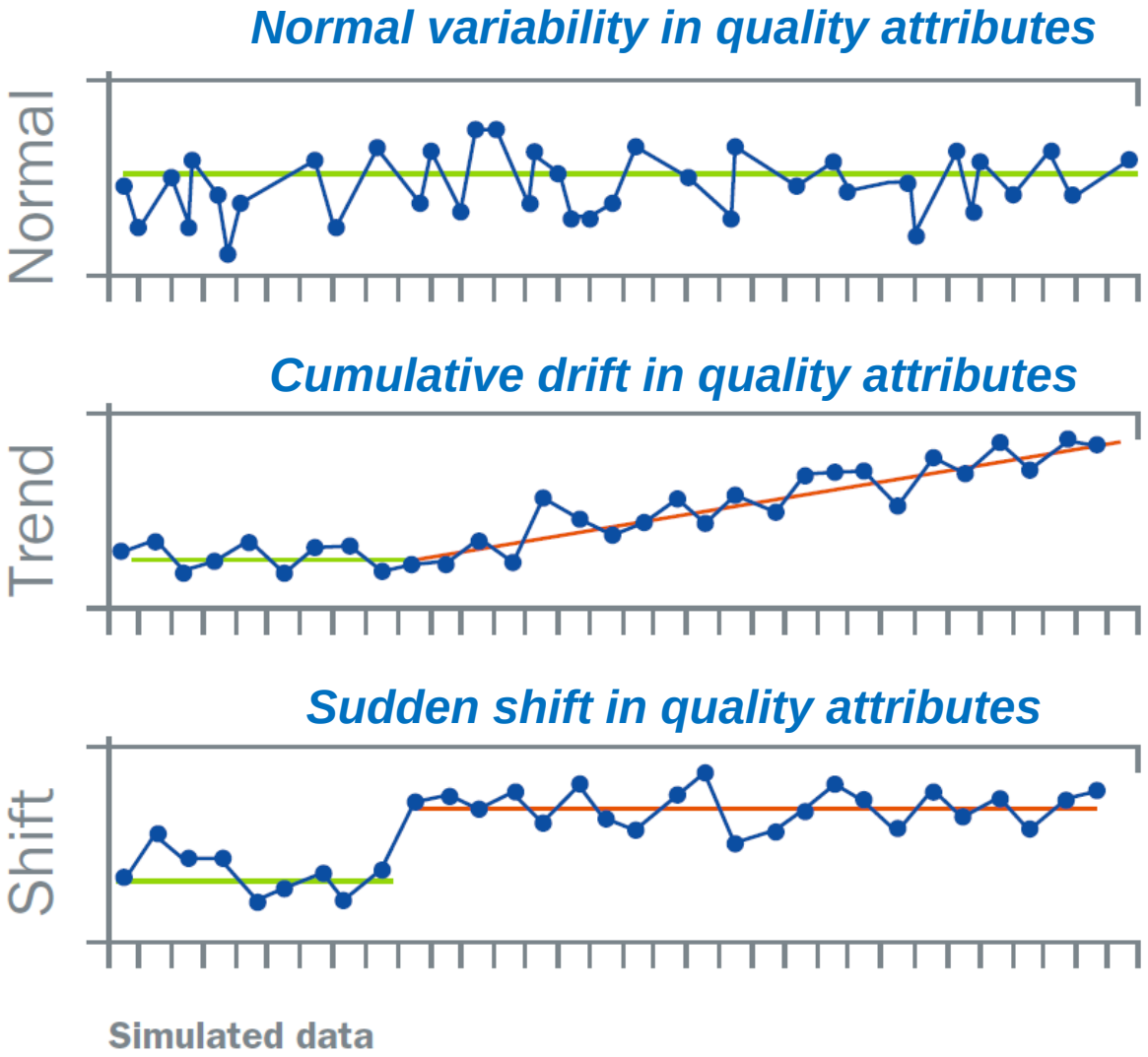
It was Dr. Martin Schiestl (Sandoz) who made us aware of the batch-to-batch variations in biological medicines



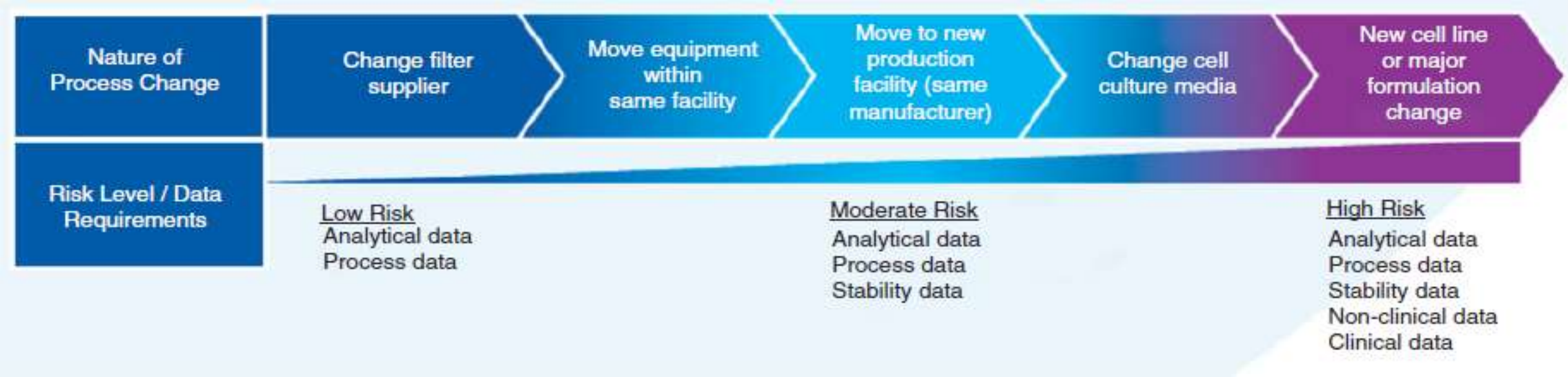
Schiestl M, et al. Nature Biotechnology 2011;29:310–312

Process variability is inevitable for reference products and biosimilars: no two lots are the same



1. Ramanan S, et al. *BioDrugs* 2014;28:363–372
2. Schiestl M, et al. *Nature Biotechnology* 2011;29:310–312

Post-approval manufacturing changes to monoclonal antibody therapeutics



Vezer B, et al. *Curr Med Res Opin* 2016;32:829–834

Number post-approval changes

Vezer et al. 2016

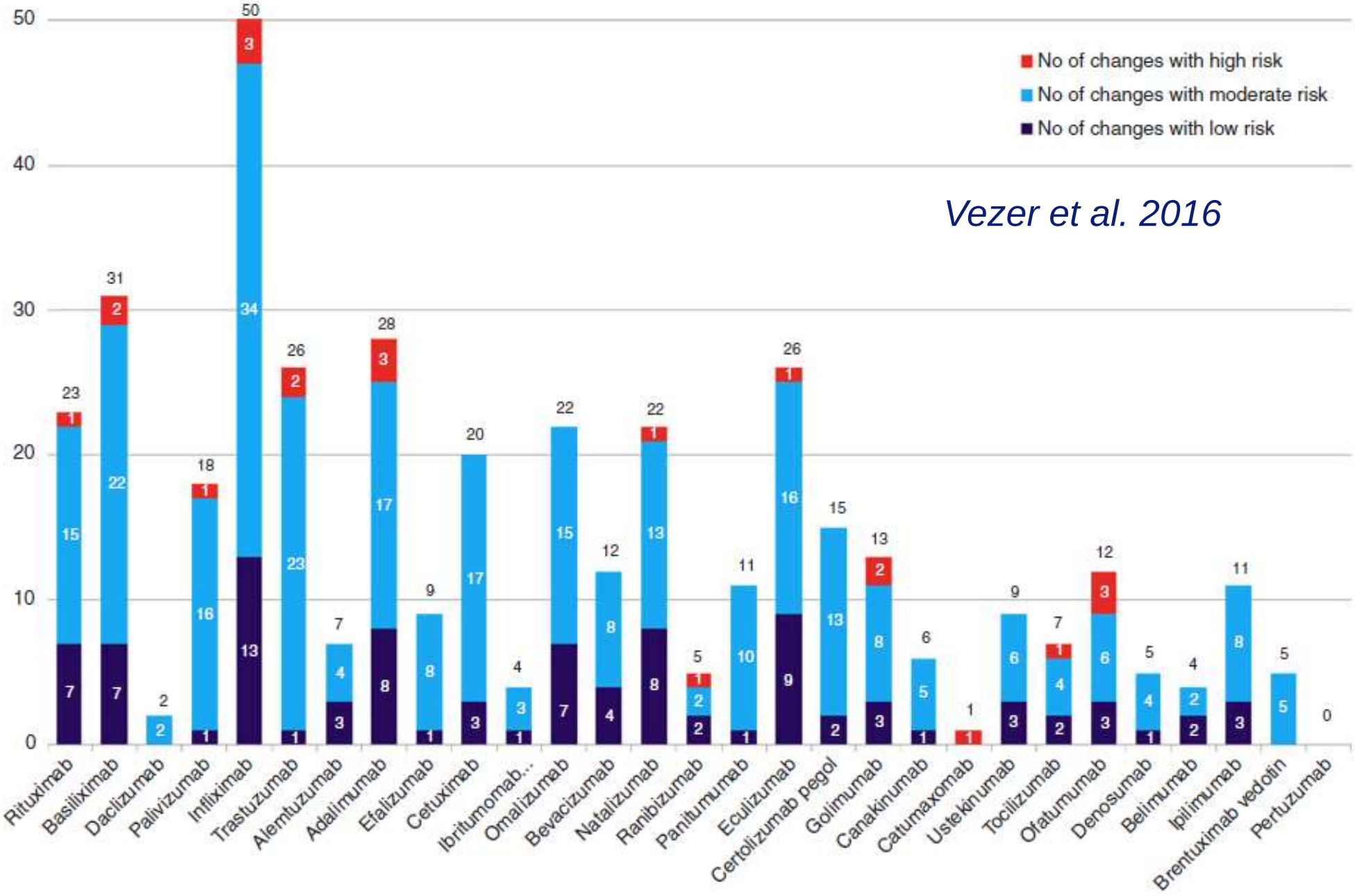


Figure 2. Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

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http://dx.doi.org/10.1080/19420862.2017.1305530

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REPORT

OPEN ACCESS

Drifts in ADCC-related quality attributes of Herceptin®: Impact on development of a trastuzumab biosimilar

Seokkyun Kim*, Jinsu Song*, Seungkyu Park, Sunyoung Ham, Kyungyeol Paek, Minjung Kang, Yunjung Chae, Heewon Seo, Hyung-Chan Kim, and Michael Flores

Quality Evaluation Team, Samsung Bioepis, Incheon, South Korea

ABSTRACT

A biosimilar product needs to demonstrate biosimilarity to the originator reference product, and the quality profile of the latter should be monitored throughout the period of the biosimilar's development to match the quality attributes of the 2 products that relate to efficacy and safety. For the development of a biosimilar version of trastuzumab, the reference product, Herceptin®, was extensively characterized for the main physicochemical and biologic properties by standard or state-of-the-art analytical methods, using multiple lots expiring between March 2015 and December 2019. For lots with expiry dates up to July 2018, a high degree of consistency was observed for all the tested properties. However, among the lots expiring in August 2018 or later, a downward drift was observed in %afucose (G0+G1+G2). Furthermore, the upward drift of %high mannose (M5+M6) was observed in the lots with expiry dates from June 2019 to December 2019. As a result, the combination of %afucose and %high mannose showed 2 marked drifts in the lots with expiry dates from August 2018 to December 2019, which was supported by the similar trend of biologic data, such as FcγRIIIa binding and antibody-dependent cell-mediated cytotoxicity (ADCC) activity. Considering that ADCC is one of the clinically relevant mechanisms of action for trastuzumab, the levels of %afucose and %high mannose should be tightly monitored as critical quality attributes for biosimilar development of trastuzumab.

ARTICLE HISTORY
Received 16 December 2016
Revised 6 March 2017
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KEYWORDS
ADCC; biosimilar; FcγRIIIa; Herceptin®; N-glycan; trastuzumab; quality drift

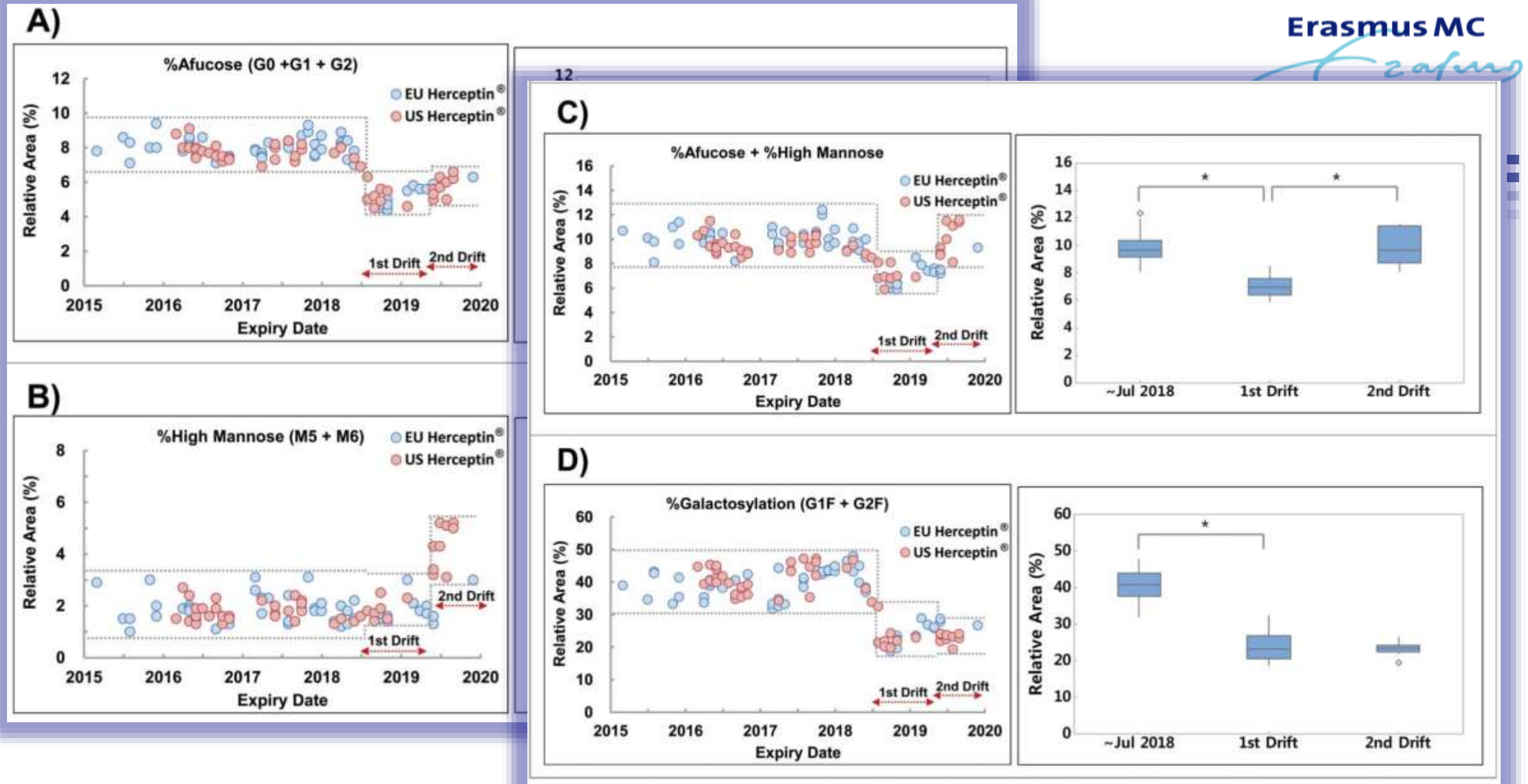


Figure 1. Trends of N-glycan attributes that are related to biologic activities by expiry date. Dotted line shows the min-max range of expiry date before August 2018, 1st drift and 2nd drift periods. Boxplot shows the interquartile range, median and outlier (◊). Statistical significance was assessed with one-way ANOVA ($^{*}P \leq 0.05$). (A) %Afucose, (B) %High-mannose, (C) %Afucose + %High-mannose and (D) %Galactosylation.

Erasmus MC

Batch-to-batch N-glycosylation study of infliximab, trastuzumab and bevacizumab, and stability study of bevacizumab

Ana Planinc,[1,2] Bieke Dejaegher,[2,3,4] Yvan Vander Heyden,[2,4] Johan Viaene,[2,4] Serge Van Praet,[5] Florence Rappez,[5] Pierre Van Antwerpen,[1,2] Cédric Delporte[1,2]

ABSTRACT

Objectives Infliximab, trastuzumab and bevacizumab are among the most frequently prescribed therapeutic proteins, and like most other therapeutic proteins, are glycosylated. As differences in glycosylation may significantly change the safety and efficacy of therapeutic glycoproteins, it is extremely important to control N-glycosylation consistency. In the first part of this study, the batch-to-batch consistency of the N-glycosylation of infliximab, trastuzumab and bevacizumab was analysed. In the second part, the consistency of the N-glycosylation of bevacizumab stored in polycarbonate syringes (for off-label drug use) for 3 months was examined.

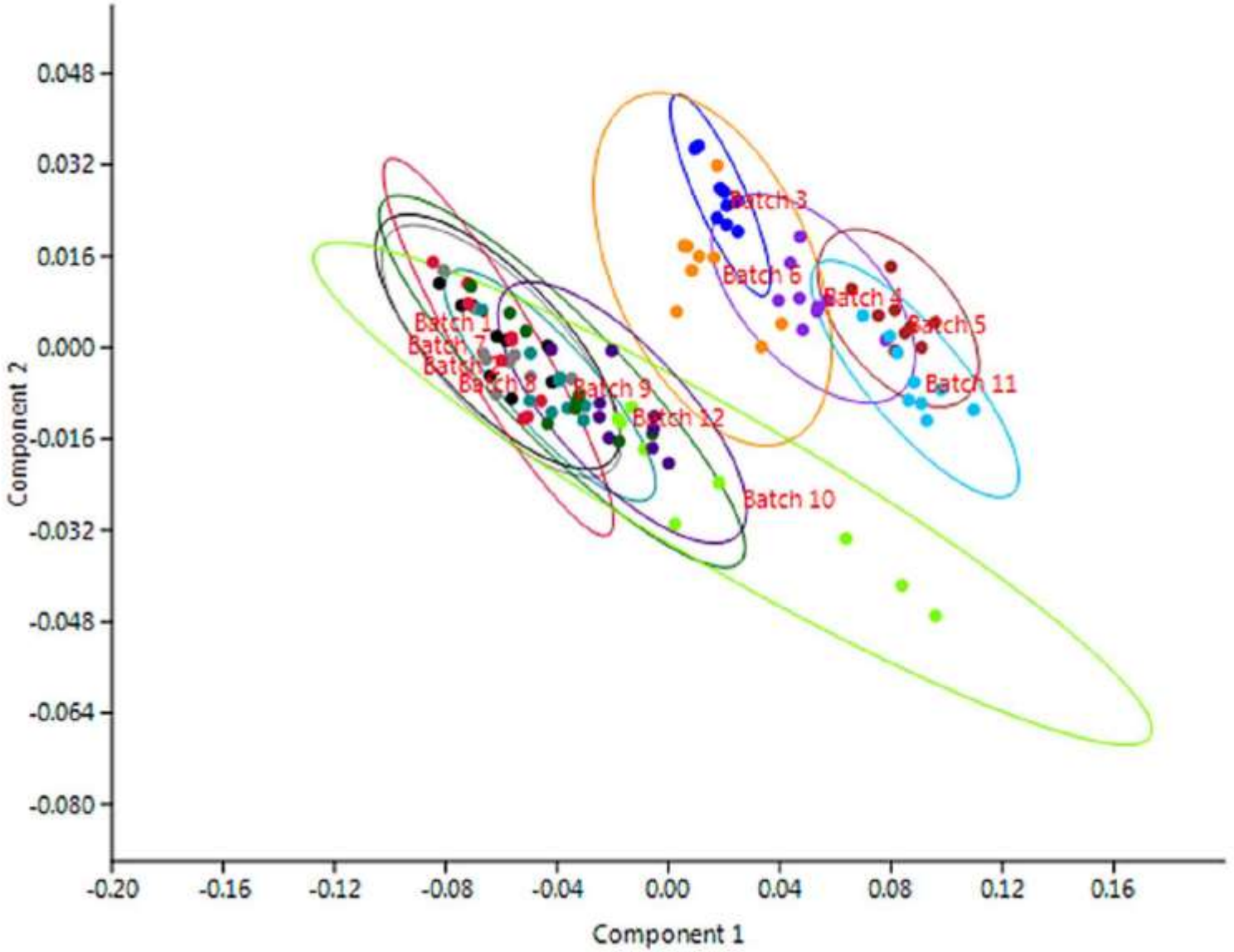
used in the treatment of autoimmune diseases, such as Crohn's disease, rheumatoid arthritis and psoriasis.[6] Infliximab is the most extensively studied therapeutic glycoprotein in the context of biosimilar products.[7] Trastuzumab is a recombinant humanised monoclonal antibody binding the HER2/neu receptor and is used in the treatment of certain breast cancers.[8] Finally, bevacizumab is a recombinant humanised monoclonal antibody against vascular endothelial growth factor, and is used in the treatment of metastatic colorectal cancer as well as ovary, breast, lung and kidney cancer. Bevacizumab is also used off-label to treat neovascular

Eur J Hosp Pharm 2017

Erasmus MC

Batch-to-batch N-glycosylation study of infliximab,

Figure 2 PC1–PC2 score plot of 12 batches of infliximab: data profile of 10 N-glycans from 108 observations of infliximab (12 batches×3 replicates×3 injections). The differences between the 12 batches of infliximab are indicated. No pre-processing was performed. The 95% confidence ellipses are marked for each class.



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Batch-to-batch N-glycosylation study of infliximab, trastuzumab and bevacizumab, and stability study of bevacizumab

Ana Plani
Serge Var

Results The results of both studies make important contributions to the field of hospital pharmacy. All batches (infliximab, trastuzumab and bevacizumab) considered N-glycosylation during 3

Conclusions Threshold values for batch-to-batch N-glycosylation variations should be established and batch-to-batch glycosylation consistency should be regularly tested. In our study, samples with significantly different N-glycosylation profiles showed no significant variations in biological activity, suggesting that the differences are probably not therapeutically significant.

ABSTRACT
Objectives
are among th
proteins, and
glycosylated.
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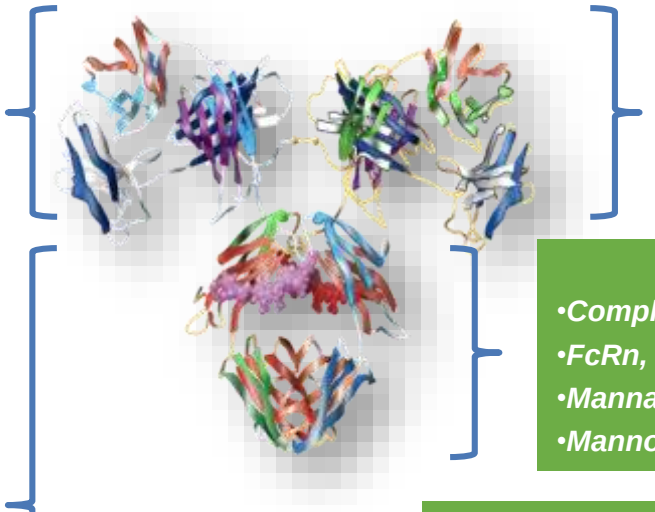
treatment of metastatic colorectal cancer as well as ovary, breast, lung and kidney cancer. Bevacizumab is also used off-label to treat neovascular

The real challenge for regulators is knowing which differences matter: critical quality attributes

Physicochemical characteristics

Variable region
- Deamination
- Oxidation
- N-terminal pyroglutamate
- Glycosylation
- Glycation

Constant region
- Deamination
- Oxidation
- Acetylation
- Glycosylation
- C-terminal lysis
- Di-sulfate bond shuffling
- Fragmentation/clipping



Biological characteristics

Binding
- Affinity
- Activity
- Cross-reactivity
- Unintentional reactivity

Effector function
- Complement interaction
- FcRn, FcγR interaction
- Mannan binding ligand interaction
- Mannose receptor interaction

Other biologic properties
- PK properties
- Epitope/immunogenicity
- Modulatory region (tregitope)

FcRn, neonatal Fc (fragment crystallizable) receptor; FcγR, Fc (gamma) receptor; PK, pharmacokinetic.

In summary

- The task of the similarity exercise is formidable
  - Both the source and the target are moving

- Biosimilar development is both a science and a military operation

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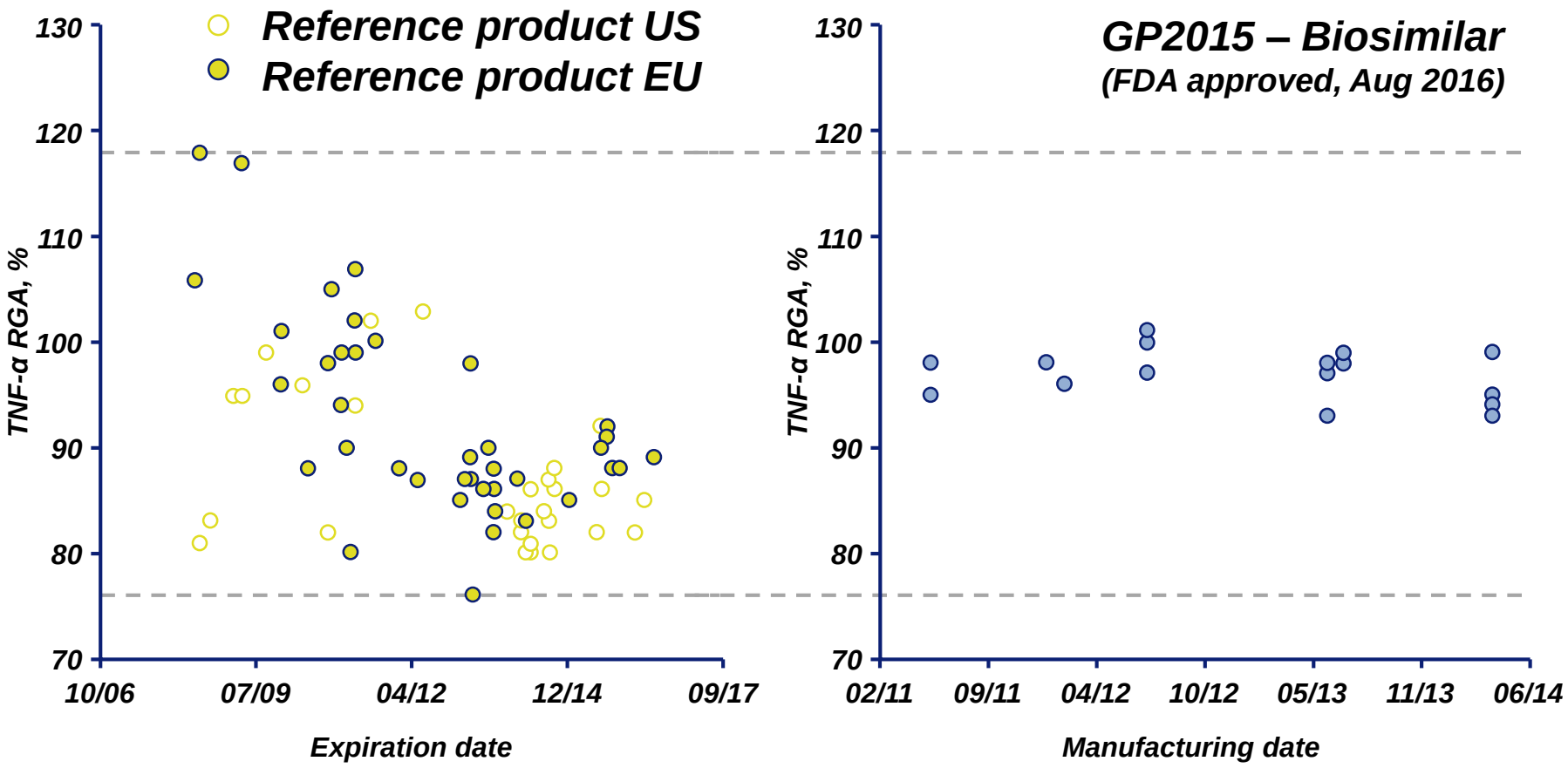
TNF-α neutralization activity of biosimilar etanercept within reference product range of variability



Reference: Sandoz presentations for the July 13, 2016 Meeting of the Arthritis Advisory Committee

Fingerprinting to ascertain no difference in critical quality attributes

REPORT

mAbs 6:5, 1163–1177; September/October 2014; Published with license by Taylor & Francis Group, LLC

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®.

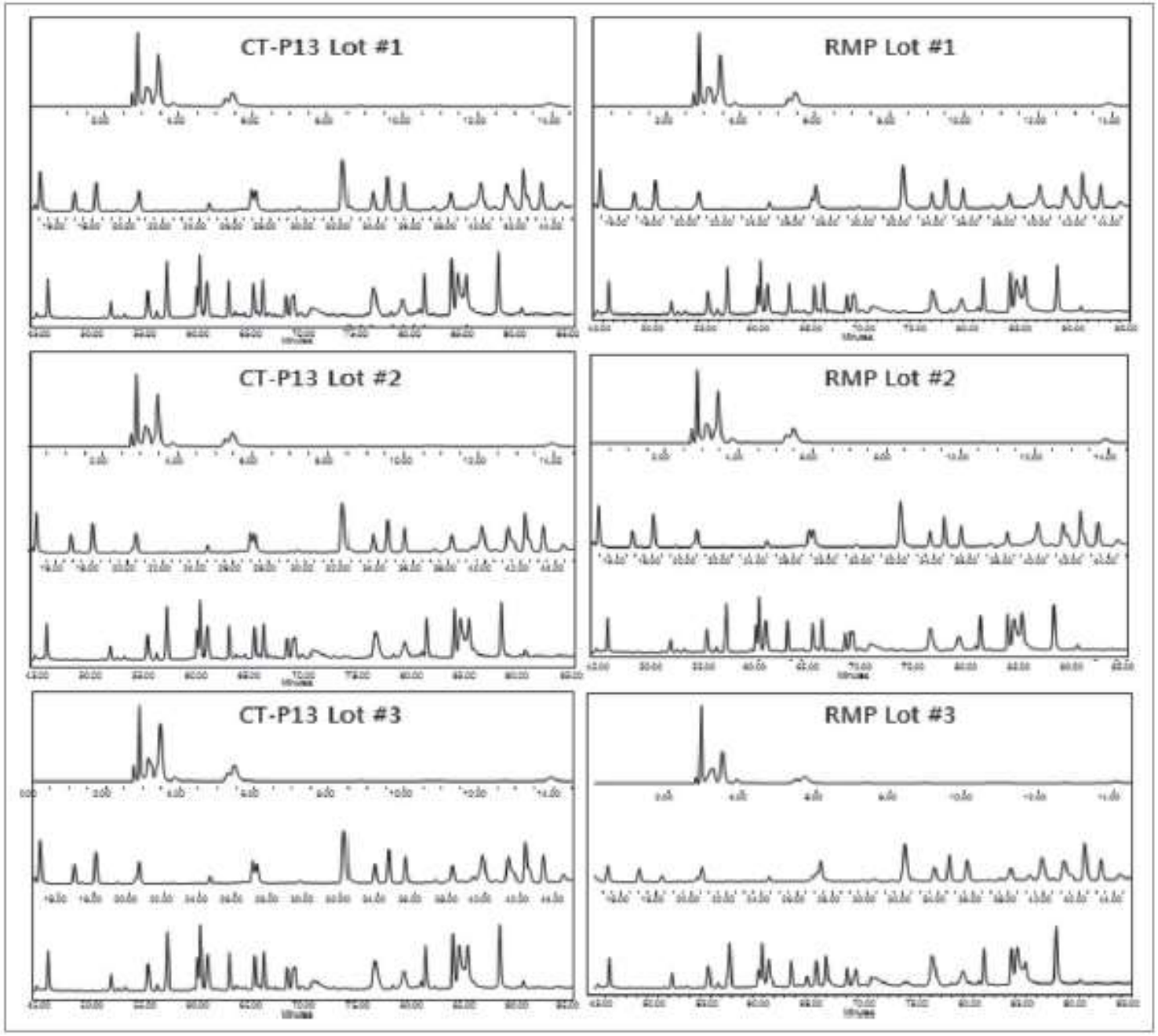


Figure 1. Expanded chromatogram of peptide mapping.

Peptide mapping (HPLC)

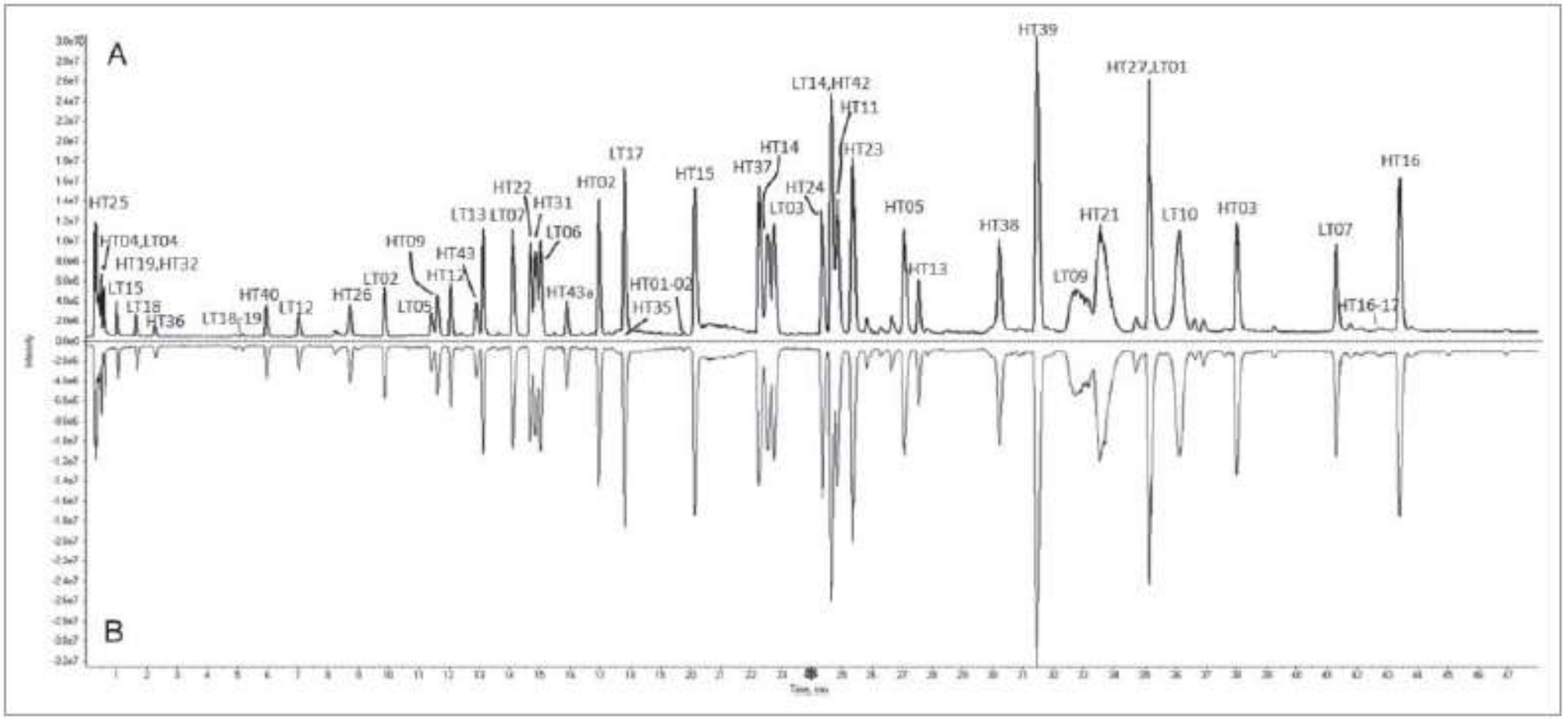


Figure 2. Comparison of Total Ion Chromatogram of LC-ESI-MS peptide mapping between (**A**) CT-P13 and (**B**) RMP, and peptide peak assignment.

Higher order structure analysis

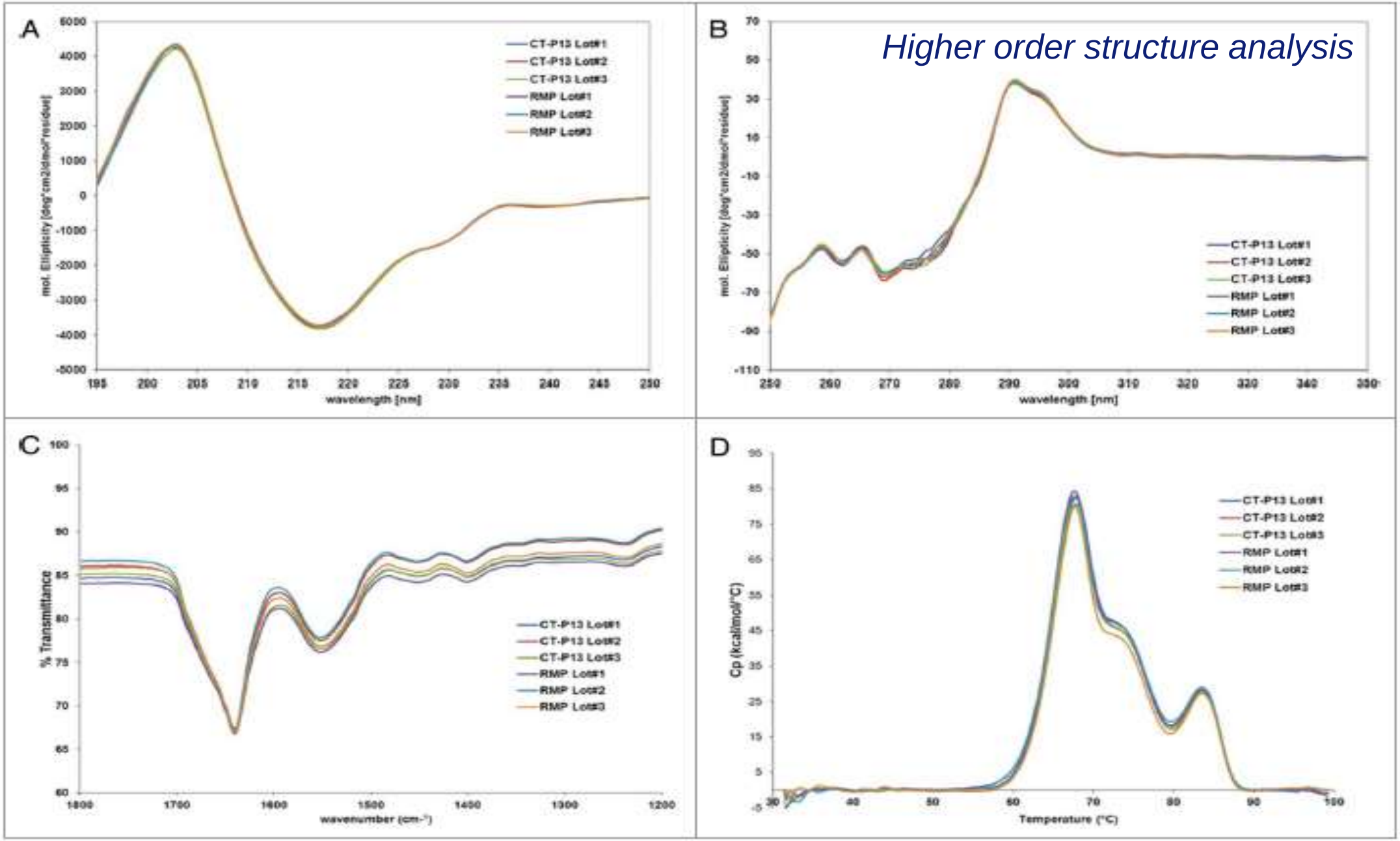


Figure 3. Higher order structure analysis: (**A**) Far-UV CD; (**B**) Near-UV CD; (**C**) FT-IR; (**D**) DSC.

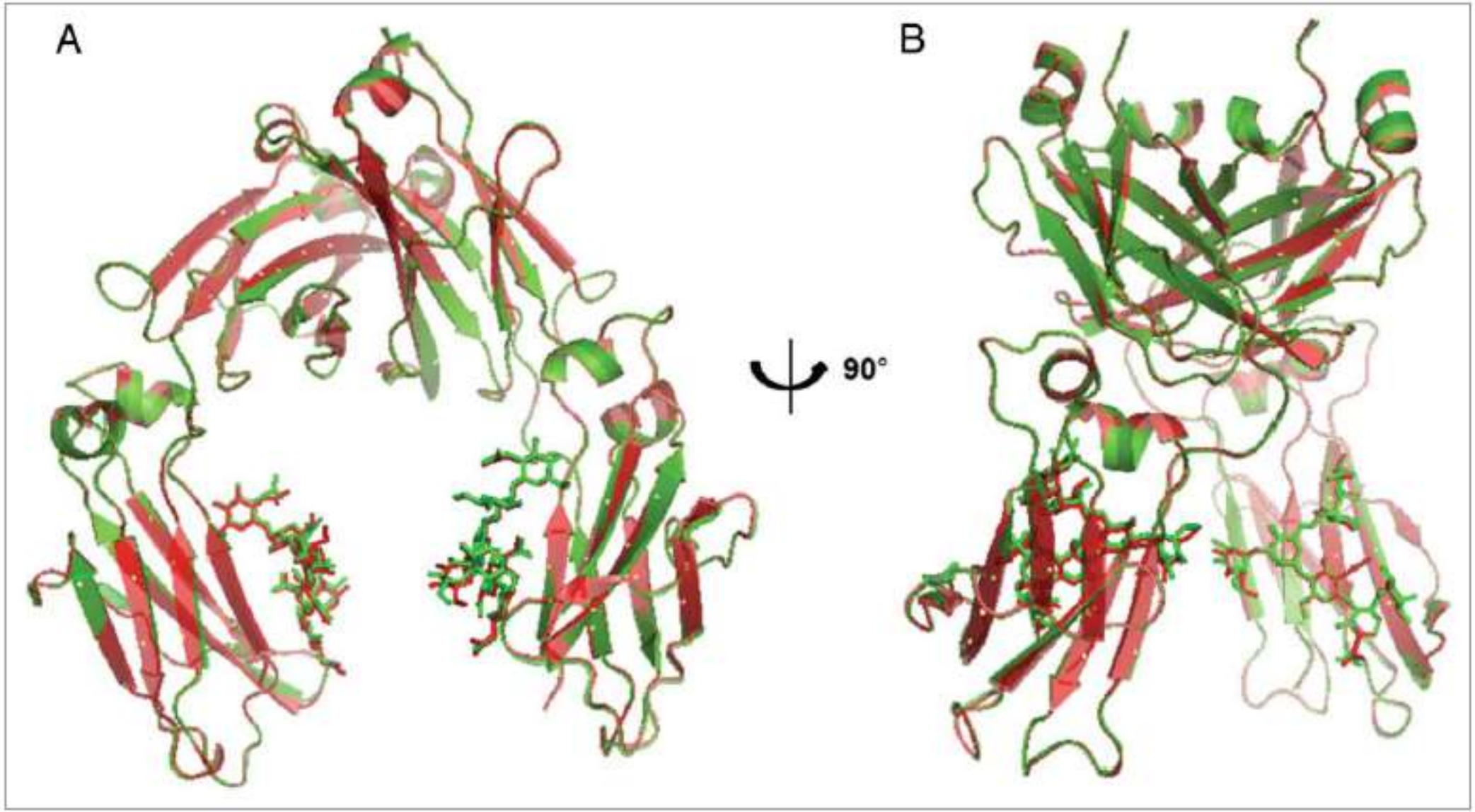


Figure 5. Superimposition of CT-P13 Fc (green) and RMP Fc (red) crystal structures: (**A**) front view; (**B**) side view.

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REPORT

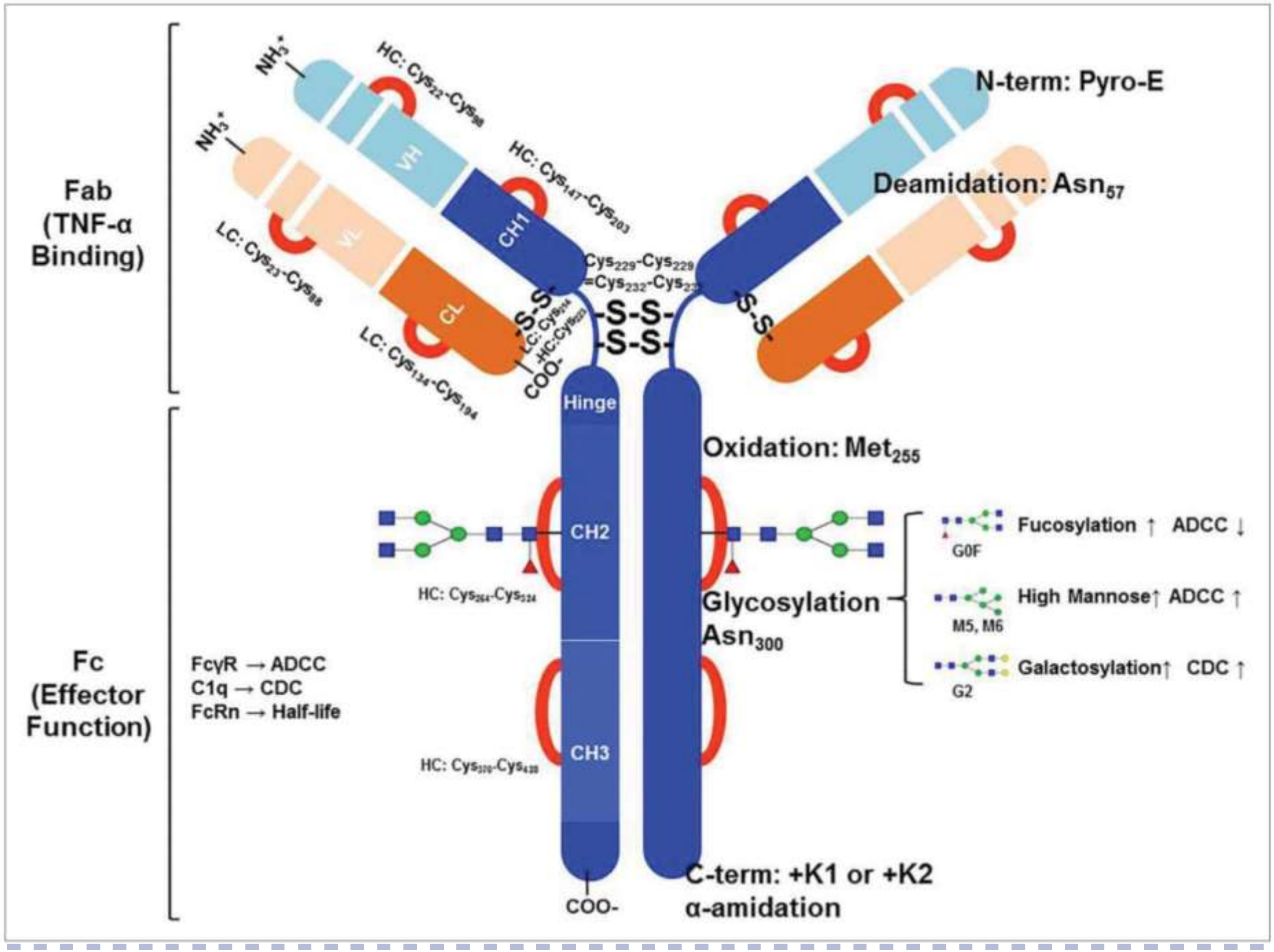
OPEN ACCESS

Physicochemical and biological characterization of SB2, a biosimilar of Remicade® (infliximab)

Juyong Hong[a], Yuhwa Lee[a], Changsoo Lee[a], Suhyeon Eo[a], Soyeon Kim[a], Nayoung Lee[a], Jongmin Park[a], Seungkyu Park[a], Donghyuck Seo[a], Min Jeong[a], Youngji Lee[a], Soojeong Yeon[a], George Bou-Assaf[b], Zoran Sosic[b], Wei Zhang[b], and Orlando Jaquez[c]

[a]Quality Evaluation Team, Samsung Bioepis Co., Ltd, Incheon, South Korea; [b]Department of Analytical Development, Biogen, Inc., Cambridge, MA, USA; [c]Department of Medical Affairs, Biosimilars, Biogen, Zug, Switzerland

- SB2 different celline (Chinese Hamster Ovary instead of murine SP2/0)
- 80 lots of EU and US-sourced Remicade
- More than 60 structural, physicochemical and biological analysis



Schematic structure of infliximab with critical quality attributes

SB2 (infliximab) characterization: Physicochemical analysis

STRUCTURAL CHARACTERIZATION (11)

- Full amino acid sequencing: LC-ESI-MS/MS
- Total mass by mass spectrometry: UPLC
- N-terminal sequencing, C-terminal sequencing: LC-ESI-MS/MS
- Peptide mapping: LC-ESI-MS/MS
- N-glycosylation site: LC-ESI-MS/MS
- Disulfide bonds by LC-ESI-MS/MS
- Free sulfhidryl (SH) group by fluorescence
- Amino acid composition
- Oxidation, deamidation, Pyro-E by LC-ESI-MS/MS

ELECTROPHORESIS (3)

- Imaged capillary isoelectric focusing with and without CPB (icIEF and CEX-HPLC)
- Capillary electrophoresis-SDS
- Lab chip based purity analysis

GLYCAN PROFILE (3)

- N-glycan profile by 2-AB HILIC-UPLC and BioLC
- N-glycan identification by LC-ESI-MS/MS

USP/EP/JP/KP (5)

- Extractable volume, protein content
- Gliding force, break-loose force
- Particulate

46 tests

CHROMATOGRAPHY (4)

- SEC, CEX-HPLC
- Protein A and G-HPLC

PROCESS IMPURITIES (10)

- Product-specific HCP assay (MSD, ELISA)
- HCD, insulin, protein A leachate
- Anti-foam agent additive (NMR, LC-CAD)
- LDAO, PF-68, MPA, (LC-CAD, LC-MS/MS)
- Endotoxin, bioburden

HIGH-ORDER STRUCTURE (10)

- UV spectra: near, far
- Fluorescence (FL spectra: intrinsic, extrinsic)
- Circular dichroism: near, far
- Differential scanning calorimeter: near, far
- FTIR: near, far
- Dynamic light scattering
- SV-AUC
- SEC-MALLS
- HDX-MS
- Micro-flow imaging
- Extinction coefficient measurement

CEX-HPLC, cation exchange-high-performance liquid chromatography; CPB, carboxypeptidase B; FL, fluorescence; FTIR, Fourier transform infrared spectroscopy; HDX-MS, Hydrogen-deuterium exchange mass spectrometry; HILIC-UPLC, hydrophilic interaction ultra-performance liquid chromatography; icIEF, imaging capillary isoelectric focusing; LC-ESI-MS/MS, liquid chromatography-electrospray ionization-tandem mass spectrometry; SEC, size exclusion chromatography; SDS, sodium dodecyl sulfate; SV-AUC, sedimentation velocity analytical ultracentrifugation; SEC-MALLS, size-exclusion chromatography coupled to multi-angle laser light scattering; UPLC, ultra-performance liquid chromatography; UV, ultraviolet.

CHMP assessment report; EMA/CHMP/272283/2016;
Hong J, et al. MAbs 2017;9(2):364–382.

Physicochemical characterization: Key SB2 similarity assessments and findings (I)

Category	Attribute	Key finding in relation to reference product
Primary structure	Molecular weight	Similar
	Amino acid sequence	Similar
	N-terminal sequence	Identical
	C-terminal sequence (after Lys-C digestion)	Similar
	Peptide mapping	Similar
	Free sulfhydryl	Similar
	Methionine oxidation	Similar
	Disulphide bonds	Similar
	Asn deamidation	Similar
	Lys-C heterogeneity	Lower C-terminal Lysine in SB2, not relevant
High-order structures	Protein secondary and tertiary structures	Far- and near-UV CD Intrinsic fluorescence HDX-MS FTIR DSC — *Similar*

CD, circular dichroism; DSC, differential scanning calorimeter; FTIR, Fourier transform infrared spectroscopy; HDX-MS, hydrogen-deuterium exchange-mass spectrometry; UV, ultraviolet.

CHMP assessment report; EMA/CHMP/272283/2016;
Hong J, et al. MAbs 2017;9(2):364–382.

Physicochemical characterization: Key SB2-infliximab similarity assessments and findings (II)

Category	Attribute	Key finding in relation to reference product
Glycosylation	N-linked glycosylation site determination	LC-ESI-MS/MS: Similar
	N-glycan identification	Procainamde labeling LC-ESI-MS/MS } *Minor differences, but not clinically meaningful*
	N-glycan profile analysis	2-AB labeling HILIC-UPLC } *Similar in terms of % Afucose and % Gal % charged glycans lower with SB2, but not clinically relevant*
Aggregation	Soluble aggregates	SV-AUC SEC MALLS DLS } *Similar* SEC-UV: Slightly higher content of HMW aggregates in SB2, but both SB2 and RP below <1%, and not expected to impact ADA
Fragmentation	Purity	CE-SDS: Similar
Charge heterogeneity	Acid variants	CEX-HPLC icIEF } *Similar*
	Basic variants	CEX-HPLC icIEF } *Lower in SB2, but not clinically meaningful*

2-AB, 2-aminobenzamide; ADA, anti-drug antibody; CEX-HPLC, cation exchange-high-performance liquid chromatography; CE-SDS, capillary electrophoresis-sodium dodecyl sulfate; DLS, dynamic light scattering; Gal, galactosylated glycans; HILIC-UPLC, hydrophilic interaction ultra-performance liquid chromatography; HMW, high molecular weight; icIEF, imaging capillary isoelectric focusing; LC-ESI-MS/MS, liquid chromatography-electrospray ionization-tandem mass spectrometry; RP, reference product; SEC-MALLS, size-exclusion chromatography coupled to multi-angle laser light scattering; SEC-UV, size-exclusion chromatography coupled to UV detector; SV-AUC, sedimentation velocity analytical ultracentrifugation; UV, ultraviolet.

CHMP assessment report; EMA/CHMP/272283/2016;
Hong J, et al. MAbs 2017;9(2):364–382.

SB2-infliximab characterization: Biological activity analysis

ADDITIONAL BIOLOGIC ASSAYS (9)

- *Transmembrane TNF-α binding (Jurkat cells by FACS)*
- *TNF-β binding (LTα3 assay by FRET)*
- *FcγRIIIa binding (F/F type by FRET)*
- *FcγRIIIa binding (PBMC by FACS)*
- *FcγRIIIb binding assay (neutrophils by FACS)*
- *Regulatory macrophage (FACS/MLR)*
- *Cytokine release activity (IBD model by ELISA)*
- *Apoptosis activity (IBD model)*
- *Antibody conformational array*

FC-MEDIATED FUNCTION (11)

- *ADCC (cell-based)*
- *ADCC (healthy donor PBMC)*
- *CDC*
- *FcRn binding assay (AlphaScreen®)*
- *FcγRIa binding assay (FRET)*
- *FcγRIIa binding assay (SPR)*
- *FcγRIIb binding assay (SPR)*
- *FcγRIIIa binding assay (SPR)*
- *FcγRIIIb binding assay (SPR)*
- *C1q binding assay (ELISA)*

FAB MEDIATED FUNCTION (3)

- *TNF-α neutralization (NF-κβ reporter gene)*
- *TNF-α binding assay (FRET)*
- *Apoptosis (Jurkat cells)*

23 tests

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; ELISA, enzyme-linked immunosorbent assay; FACS, fluorescence-activated cell sorting; FRET, fluorescence resonance energy transfer; IBD, inflammatory bowel disease; MLR, mixed lymphocyte reaction; PBMC, peripheral blood mononuclear cells; SPR, surface plasmon resonance.

CHMP assessment report; EMA/CHMP/272283/2016;
Hong J, et al. MAbs 2017;9(2):364–382.

Biologic characterization: Key SB2-infliximab similarity assessments and findings

Category	Attribute	Key finding in relation to reference product
Fab-related biologic activity	TNF-α neutralization activity	Similar
	TNF-α binding activity	Similar
	Apoptosis activity	Similar
	Transmembrane TNF-α binding assay	Similar
Fc-related biological activity	FcRn binding	Similar
	FcγRIIIa (V/V type binding)	Similar
	ADCC (using healthy donor PBMC)	Similar
	CDC	Similar
	C1q binding	Similar
	FcγRIa binding	Similar
	FcγRIIa binding	Similar
	FcγRIIb binding	Similar
	FcγRIIIb binding	Similar

ADCC, antibody-dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; FcRn, neonatal Fc receptor; PBMC, peripheral blood mononuclear cells; TNF-α, tumor necrosis factor-alpha.

CHMP assessment report; EMA/CHMP/272283/2016;
Hong J, et al. MAbs 2017;9(2):364–382.

SB2 (infliximab) comparison in summary

- *Physicochemical characterization* results showed that SB2-infliximab was similar to Remicade®
  - Although a few differences in physicochemical attributes were observed, evidence from the related literature, structure-activity relationship studies and comparative biologic assays showed that these differences were unlikely to be clinically meaningful

- *Biologic characterization* results showed that:
  - SB2-infliximab was similar to Remicade® in terms of TNF-α binding and TNF-α neutralization activities as a main mode of action
  - SB2-infliximab was also similar in Fc-related biologic activities, including: ADCC, CDC, FcRn receptor binding, C1q binding and Fc gamma receptor binding activities

Original Articles

Toxicologic Pathology, 42: 1069-1081, 2014

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Comparative Nonclinical Assessments of the Proposed Biosimilar PF-05280586 and Rituximab (MabThera®)

Anne M. Ryan[1], Sharon A. Sokolowski[1], Chee-Keng Ng[2], Norimitsu Shirai[1], Mark Collinge[1], Amy C. Shen[1], Joshua Arrington[3], Zaher Radi[4], Thomas R. Cummings[1], Stephen A. Ploch[3], Sarah A. Stephenson[3], Niraj K. Tripathi[3], Susan I. Hurst[5], Gregory L. Finch[1], and Michael W. Leach[6]

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[6]*Drug Safety Research and Development, Pfizer Inc., Andover, Massachusetts, USA*

BioDrugs (2013) 27:495–507
DOI 10.1007/s40259-013-0036-3

ORIGINAL RESEARCH ARTICLE

Physicochemical and Functional Comparability Between the Proposed Biosimilar Rituximab GP2013 and Originator Rituximab

Jan Visser · Isabel Feuerstein · Thomas Stangler · Timo Schmiederer · Cornelius Fritsch · Martin Schiestl

Agenda

1. Introduction
2. A new drug development paradigm
3. Critical quality attributes of biological medicines
4. Variability is inherent to biological medicines
5. What needs to be done in biosimilar development
    1. Fingerprinting the originator (reference product)
    2. Compare with biosimilar fingerprint
6. ***Take Home Message***

Take Home message

- Modern techniques can characterise Mabs in almost every aspect and detail and more precise than can be done in a clinical trial
- Current physicochemical fingerprinting techniques provide assurance on efficacy and safety of biosimilars
- With this knowledge pharmacists can educate other healthcare professionals
- With these insights pharmacists can play a key role in the sustainability of medical care

- Korean biosimilar companies are gamechangers with their publication strategy
- I have learned more on biologicals from biosimilar companies than from originators

Thank you for your attention

Questions?

Contact: a.vulto@erasmusmc.nl

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