BIOSIMILARI
IN ONCOLOGIA

Position Paper
2018

Roma, 12 luglio 2018
Ministero della Salute
Auditorium Cosimo Piccinno
Lungotevere Ripa,1

Esercizio di comparabilità: criteri metodologici alla base della validazione strutturale, biologica e farmacologica del biosimilare

Romano Danesi
Universita' di Pisa

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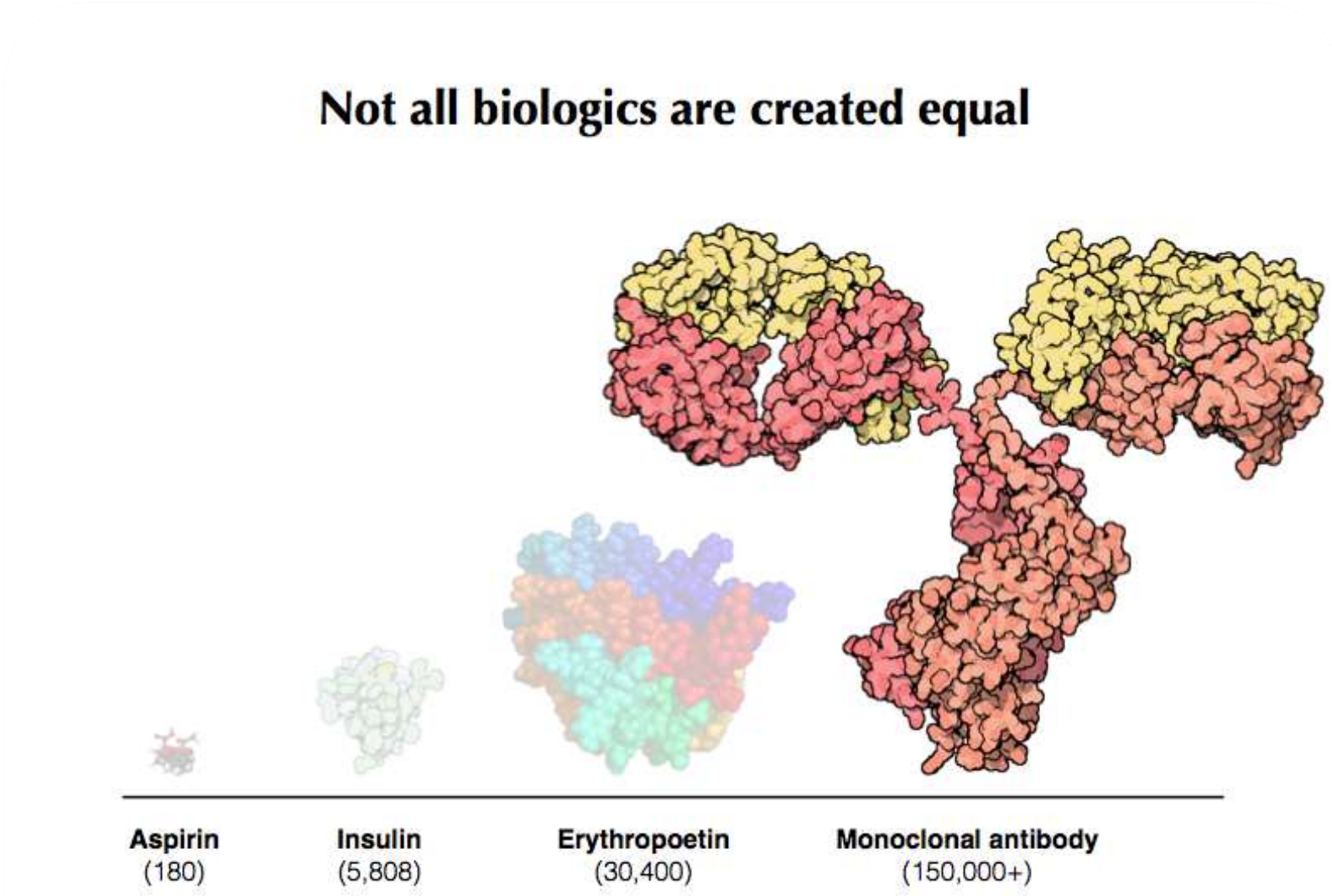
Generics, biosimilars and biosimilar antibodies: differences in size and complexity



Revers, L. & Furczon, E. (2010) An introduction to biologics and biosimilars. Part I: Biologics: What are they and where do they come from? *Can. Pharm. J.* **143**:134.

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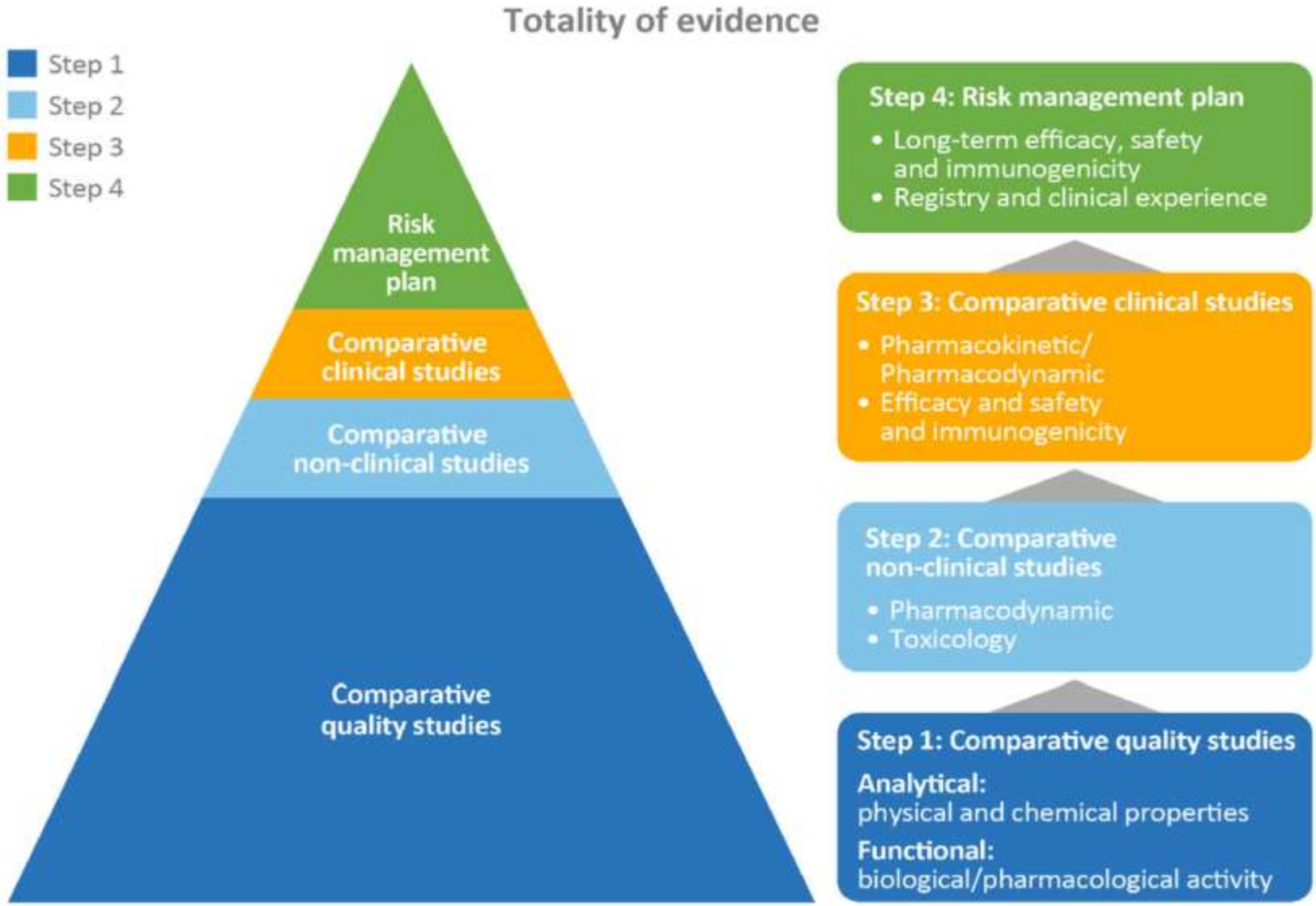
Data requirements for approval of a biosimilar



Rezk MF, Pieper B. Rheumatol Ther (2017) 4:209–218

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EMA requirements to earn marketing authorization for a biosimilar monoclonal antibody

Preclinical comparability

Analytical studies

- Same amino acid sequence and folding.
- Highly similar analytical profiles based on highly sensitive methods.
- Same set of glycans, comparable levels of functionally relevant glycans.
- Comparable or lower levels of nonglycan variants (N- and C-terminal variants, aggregates, deamidation, oxidation…), all minor differences clinically not relevant.
- Comparable stability profiles.
- High purity (extremely low levels of contaminants from cell line and process).

From Pivot X et al., Anti-Cancer Drugs, 2015 modified

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EMA requirements to earn marketing authorization for a biosimilar monoclonal antibody

Preclinical comparability

In-vitro studies

Binding to target antigen(s)

Functional cellular assays:

- **Fab-associated functions (e.g. neutralization of a soluble ligand, receptor activation or blockade)**
- **Fc-associated functions (e.g. antibody-dependent cell-mediated cytotoxicity, ADCC; complement-dependent cytotoxicity, CDC; complement activation)**

In-vivo (animal) studies, if appropriate

PK/PD studies

Activity studies

Safety studies

From Pivot X et al., Anti-Cancer Drugs, 2015 modified

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EMA requirements to earn marketing authorization for a biosimilar monoclonal antibody

Clinical comparability
Clinical pharmacology studies in a sufficiently sensitive and homogeneous population
PK & PD studies **Immunogenicity** **Dose–concentration–response curve**
Comparative clinical studies
Efficacy (e.g., neoadjuvant treatment of HER2-positive breast cancer) **Safety (including immunogenicity)**

From Pivot X et al., Anti-Cancer Drugs, 2015 modified

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State-of-the-art technologies to characterize the biosimilar molecule

Primary structure e.g.,:
- LC-MS intact mass
- LC-MS subunits
- Peptide mapping

Impurities e.g.,:
- CEX, cIEF acidic/basic variants
- LC glycation
- Peptide mapping deamidation
- Oxidation, mutation, glycation
- SEC/FFF/AUC aggregation

Biological activity e.g.,:
- Binding assay
- ADCC assay
- CDC assay

Higher order structure e.g.,:
- NMR
- CD spectroscopy
- FT-IR

Post translat. modif. e.g.,:
- NP-HPLC-(MS) N-glycans
- AEX N-glycans
- MALDI-TOF N-glycans
- HPAEC-PAD N-glycans
- MALDI-TOF O-glycans
- HPAEC-PAD sialic acids
- RP-HPLC sialic acids

Combination of attributes e.g.,:
- MVDA, mathematical algorithms

Windisch J. Int. J. Clin. Rheumatol 2015;10(6)

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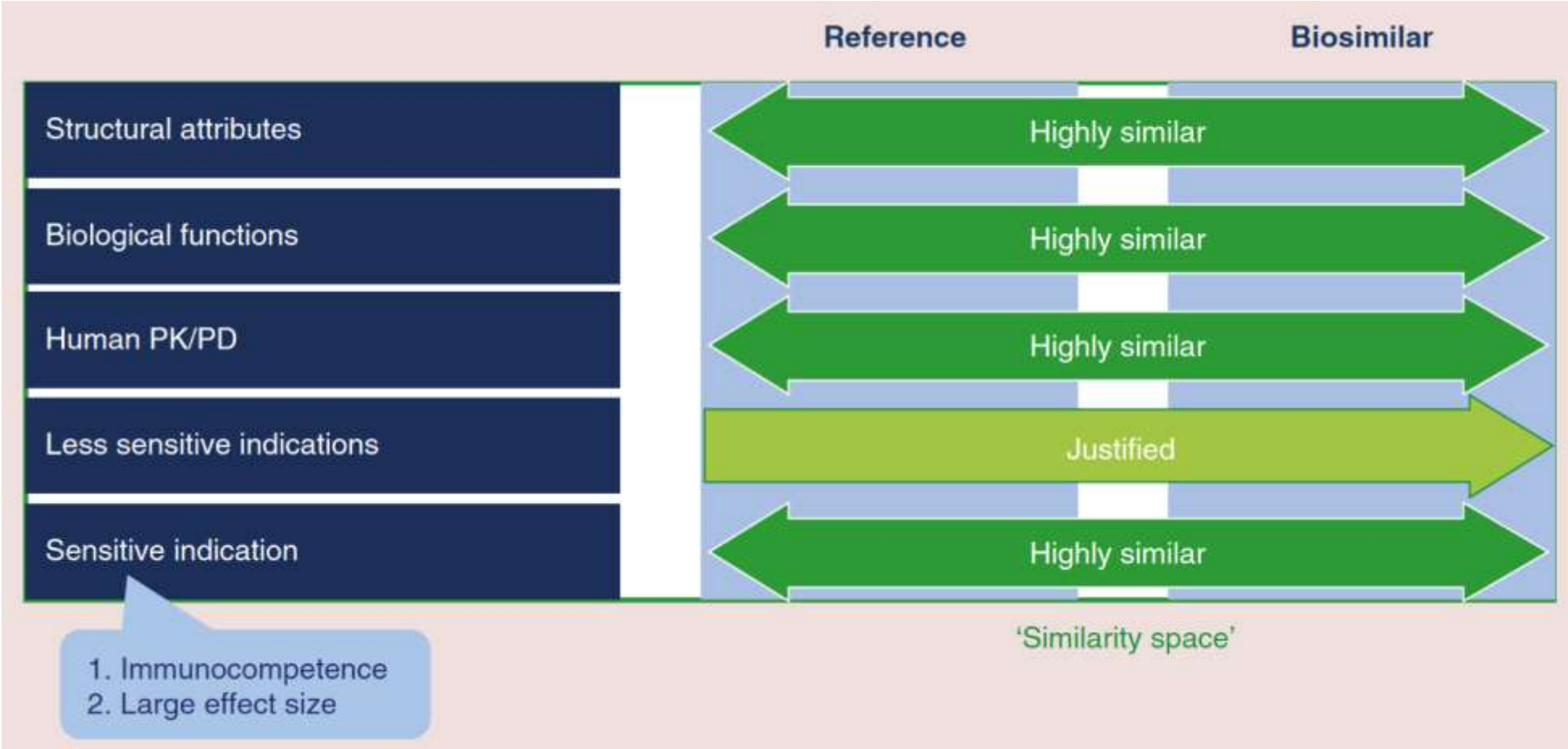
The “similarity space”



Windisch J. Int. J. Clin. Rheumatol 2015;10(6)

Variability in the Biopharmaceutical Manufacturing Process

Innovator Biologic Product

DNA-Cloning/ Vector Creation	Cell Expression	Cell Expansion	Protein Production	Protein Harvest	Protein Purification	Characterization/ Stability
Viral vectors Non-viral vectors	Cell selection	Selection of media, temperature, cell density	Selection of media, temperature, cell density	Recovery through filtration and centrifugation	Chromatography Highly selective resin and process conditions	Primary/ higher-order structure, post-translational modifications, biological activity, impurities, immunochemical properties

Sources of Biosimilar Variability from the Innovator Biologic

Use of a different Vector	Different cell line expression system	Different cell line growth media, pH, temperature, and method of expansion	Different cell line growth media, pH, temperature, and method of expansion	Different operating conditions and methods	Different binding and elution conditions	Different methods, reagents, reference standards

Adapted from Camacho et al., 2014; Amgen, 2014

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Manufacturing changes for biotechnology products

Vezer B et al. Curr Med Res Opin 2016; 32, 829

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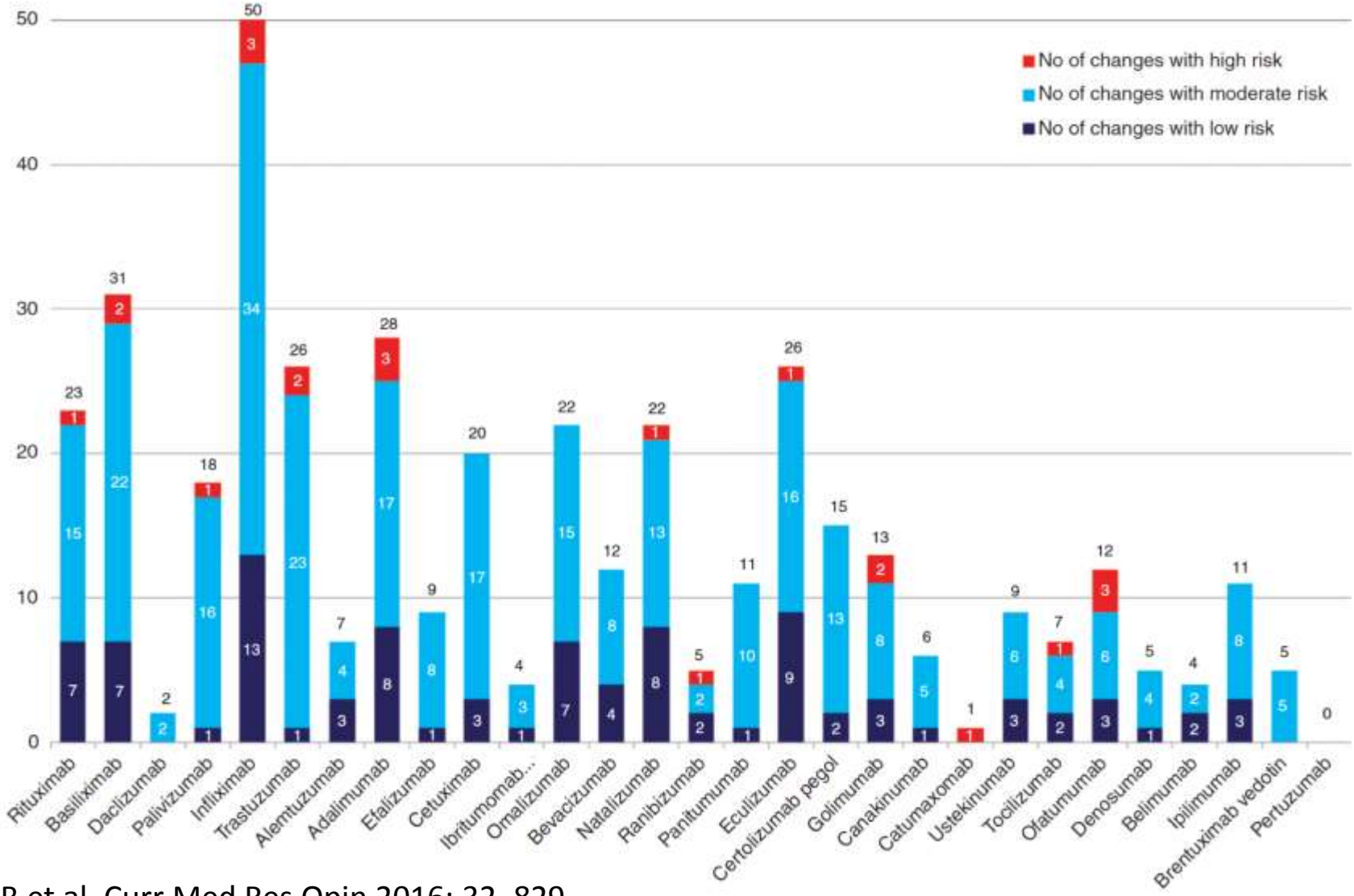
Changes in manufacturing process during originator biologic's life



Vezer B et al. Curr Med Res Opin 2016; 32, 829

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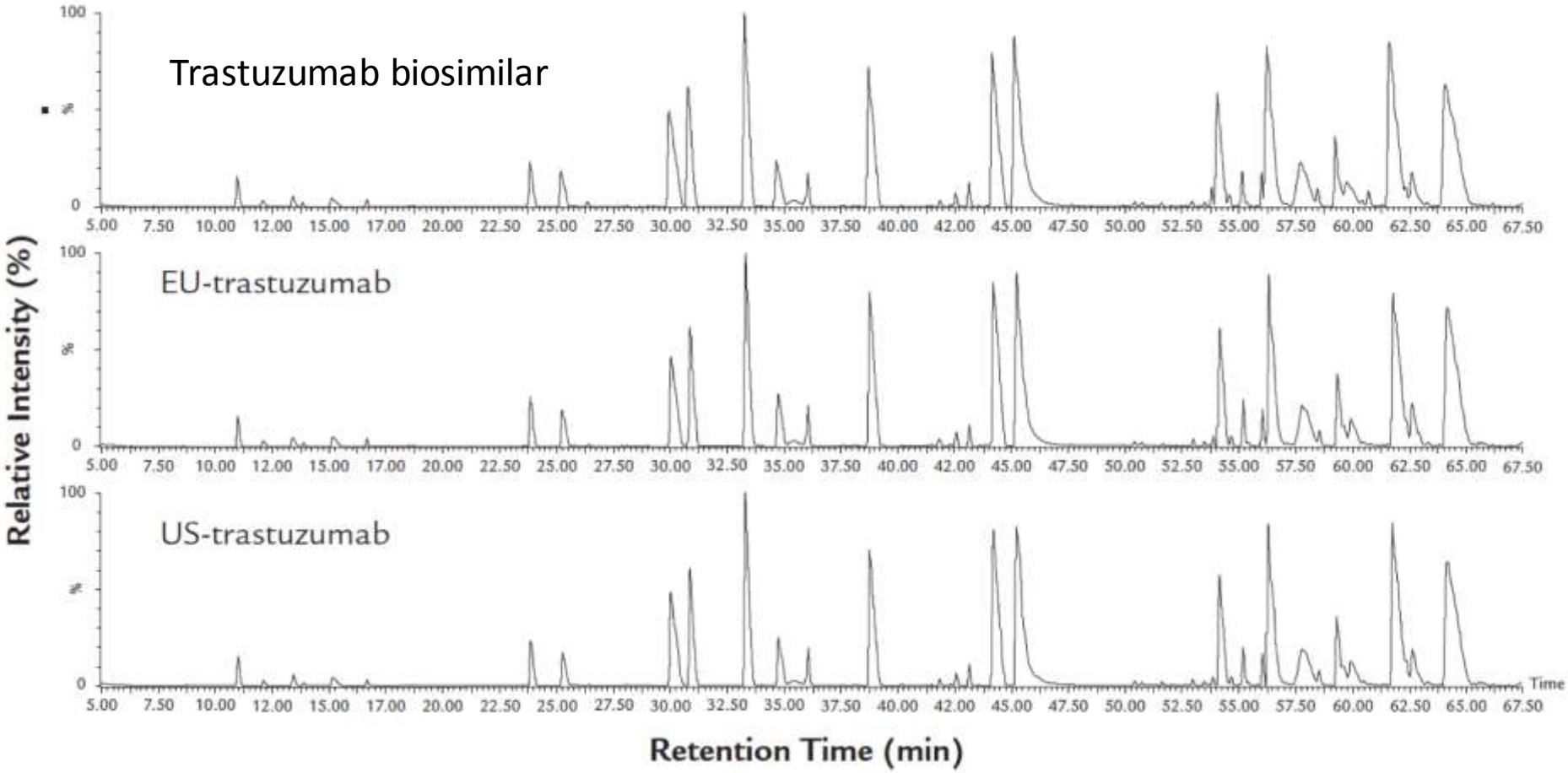
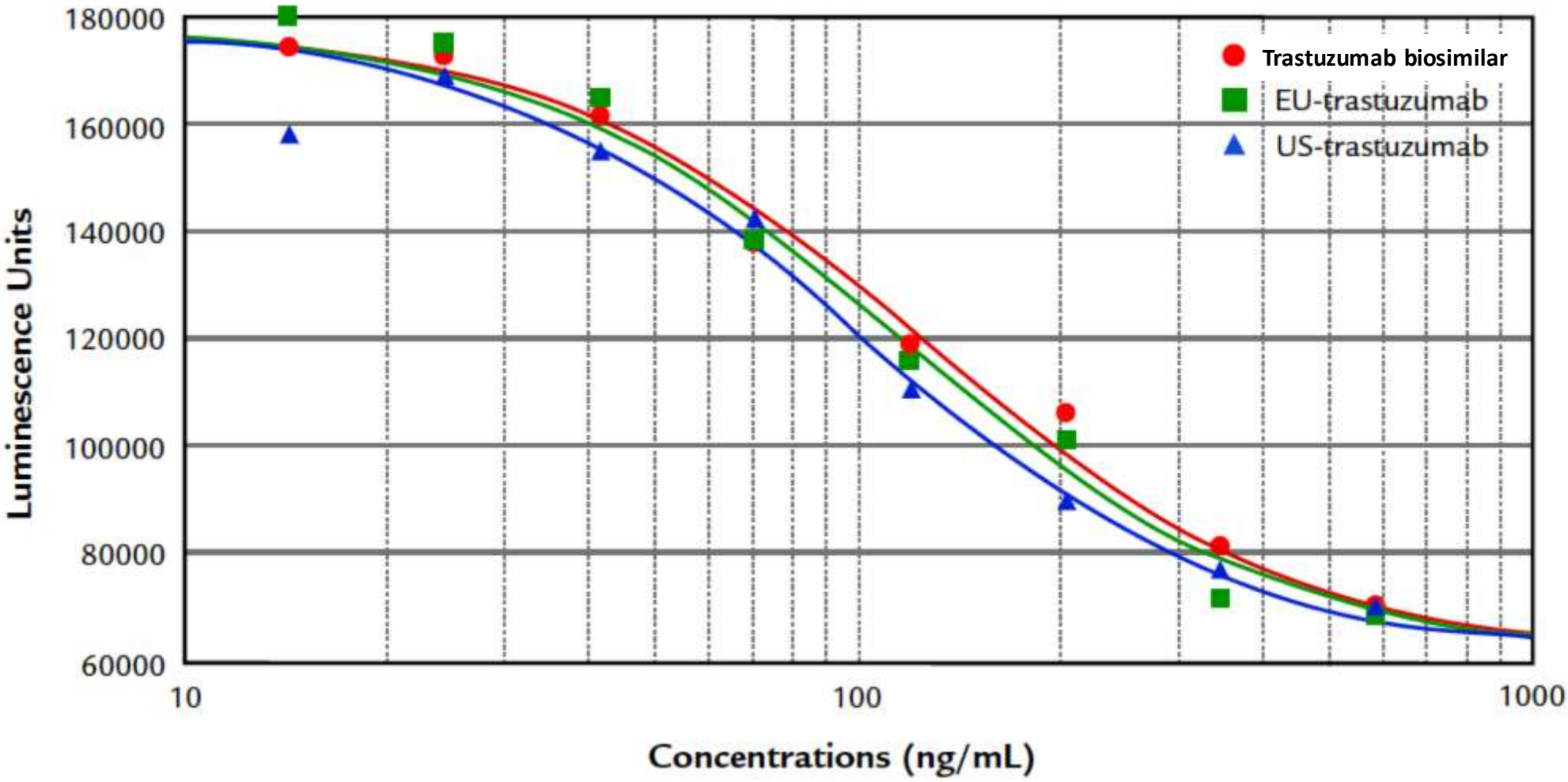
Lys-C maps of trastuzumab biosimilar, EU-trastuzumab and US-trastuzumab



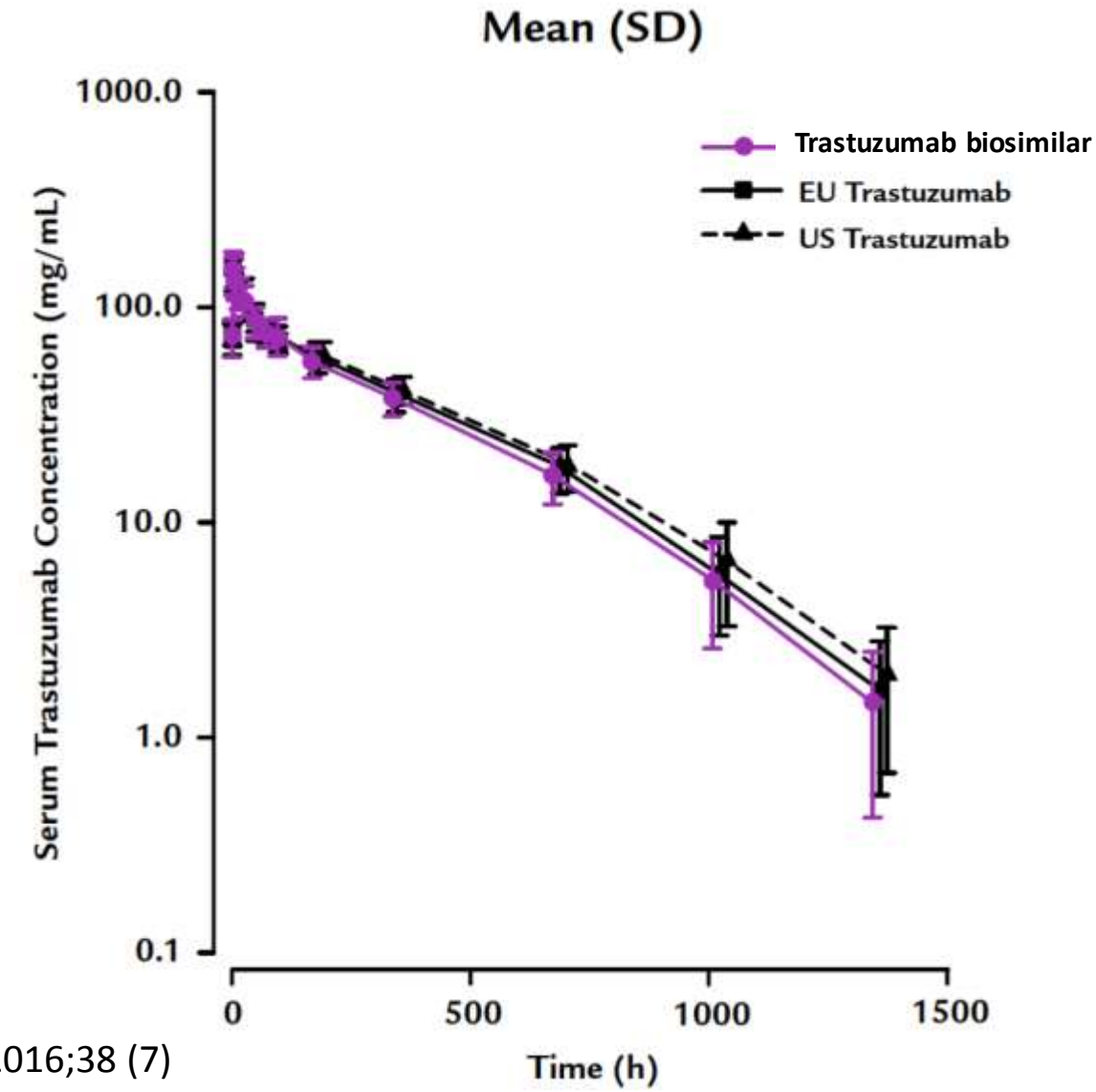
Pivot X et al. Clin Ther 2016;38 (7)

In vitro antiproliferative effect of trastuzumab biosimilar, EU-trastuzumab and US-trastuzumab



Pivot X et al. Clin Ther 2016;38 (7)

PK after a single dose of 6 mg/kg in healthy male subjects of trastuzumab biosimilar, EU-trastuzumab and US-trastuzumab



Pivot X et al. Clin Ther 2016;38 (7)

Conclusions

- Stringent regulatory requirements set by the EMA guarantee high quality, matching that of the originator.
- Proof of similarity is demonstrated using state-of-the-art analytical and functional methods.
- Biosimilar, or Interchangeable Biologic Drug?