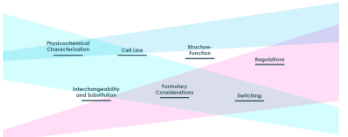


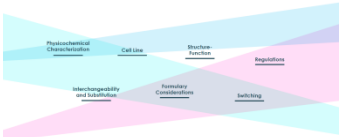
Assistant Professor Gianluca Trifirò MD, PhD, Italy

- Clinical Pharmacologist and Assistant Professor of Pharmacology, Department of Clinical and Experimental Medicine, University of Messina, Italy
- Honorary Assistant Professor of Pharmacoepidemiology, Department of Medical Informatics, Erasmus University Medical Center Rotterdam, The Netherlands
- External Consultant of the Scientific Secretariat, Pharamcovigilance Office, Italian Medicines Agency (*AgenziaItaliana del Farmaco, AIFA*)

GaBI Scientific Meetings

First GCC Stakeholder Meeting on **Approval Process, Interchangeability/Substitution and Safety of Biosimilars**

20 November 2017, Holiday Inn Izdihar Riyadh, Saudi Arabia



The false myths of biosimilars

Assistant Professor Gianluca Trifirò, MD, PhD

20 November 2017

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

SPS Saudi Pharmaceutical Society الجمعية الصيدلية السعودية
PPCI Pro Pharma Communications International

First GCC Stakeholder Meeting on Approval Process, Interchangeability/Substitution and Safety of Biosimilars

20 November 2017, Riyadh, Saudi Arabia

The false myths about biosimilars

Prof. Gianluca Trifirò

Dpt. Scienze Biomediche, Odontoiatriche e Immagini Morfologiche e Funzionali, Università di Messina (Italy)

Dpt. Medical Informatics, Erasmus Medical Center, Rotterdam (Netherlands)

Disclaimer

- I have been part of advisory boards on biosmilars organized by Sandoz and Hospira
- As scientific coordiniator of an academic pharmacoepi team I have been coordinating observational studies on biological drugs which have been funded by several pharmaceutical companies, e.g. Amgen, Novartis, Daiichi Sankyo

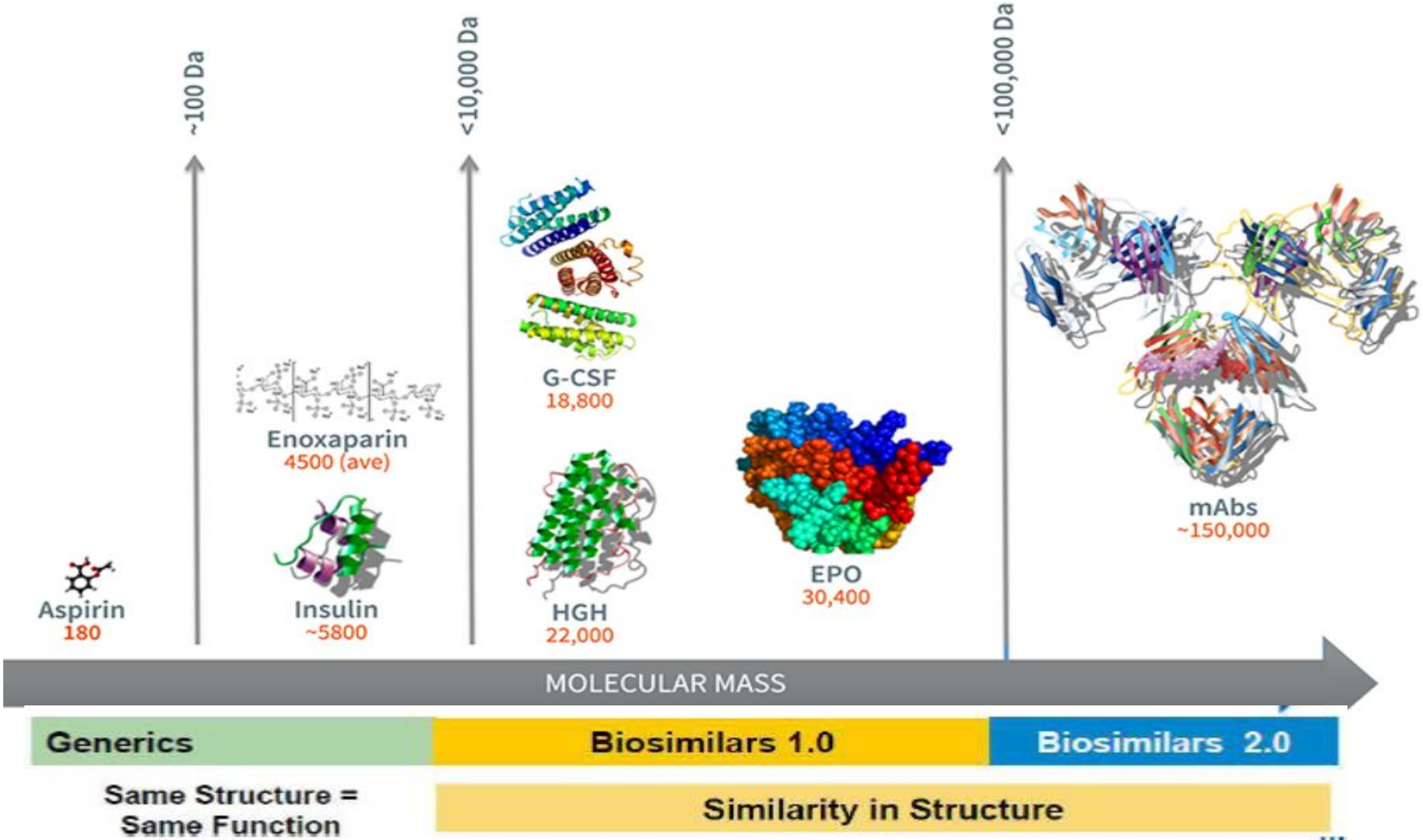
Myths

- Bio-identicality versus similarity
- Pre-marketing evidence on benefit-risk profile of biosimilars
- Post-marketing safety of biosimilars
- Interchangeability of biosimilar and reference product

Biologic drugs

Biologic drug: substance made from living organism or its products, e.g. vaccines, blood components, gene therapies, antibodies, interleukins, and living cells used in cell therapy

Biotechnology: use of living systems and organisms to develop therapeutic proteins



EMA definition of biosimilars

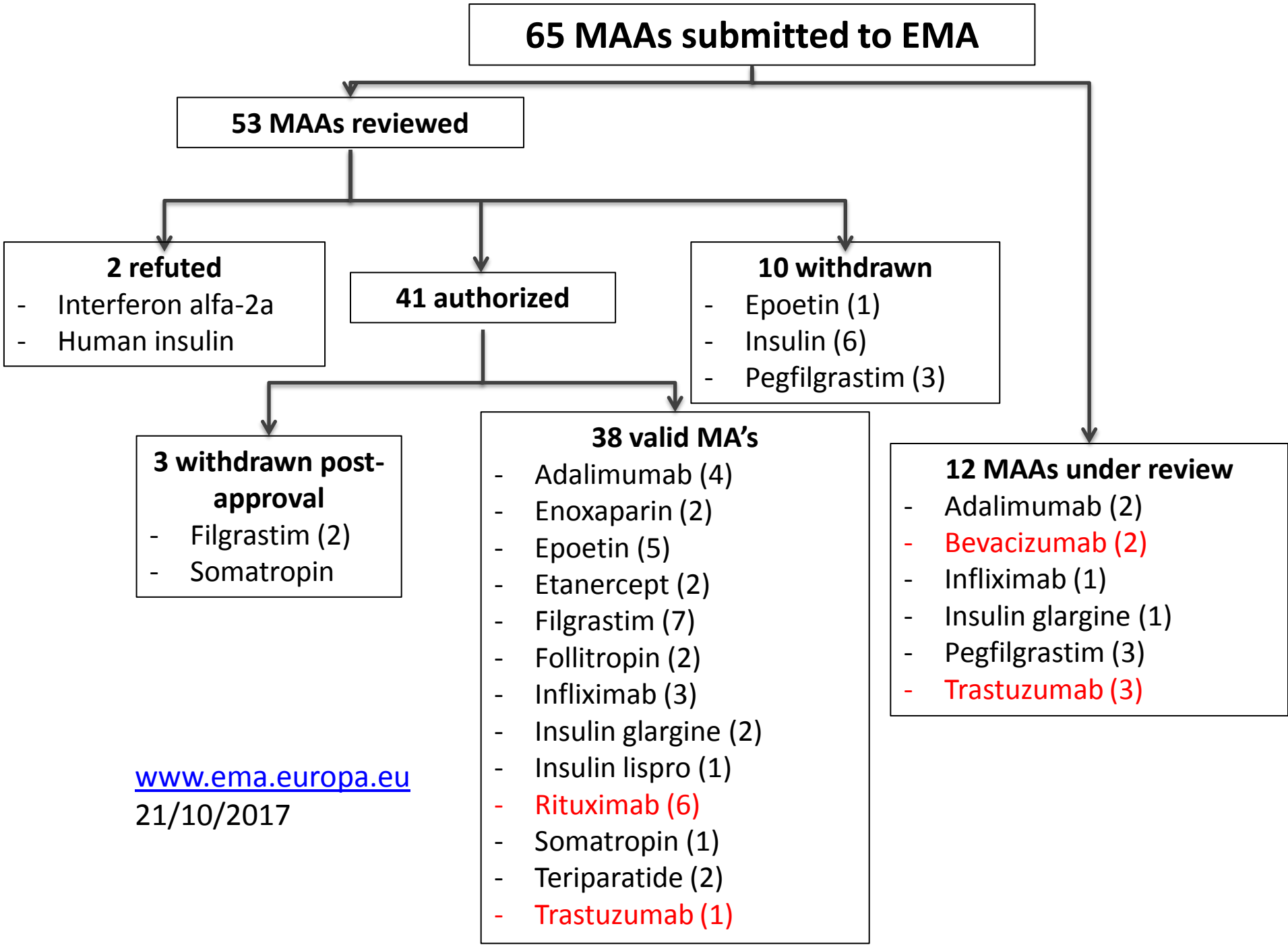
*"A biosimilar is a **biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product** (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established"*

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

FDA: follow-on biologics

Abbreviation: EEA: European economic area

1. EMA. http://www.ema.europa.eu/../WC500176768.pdf [Accessed May 2015].

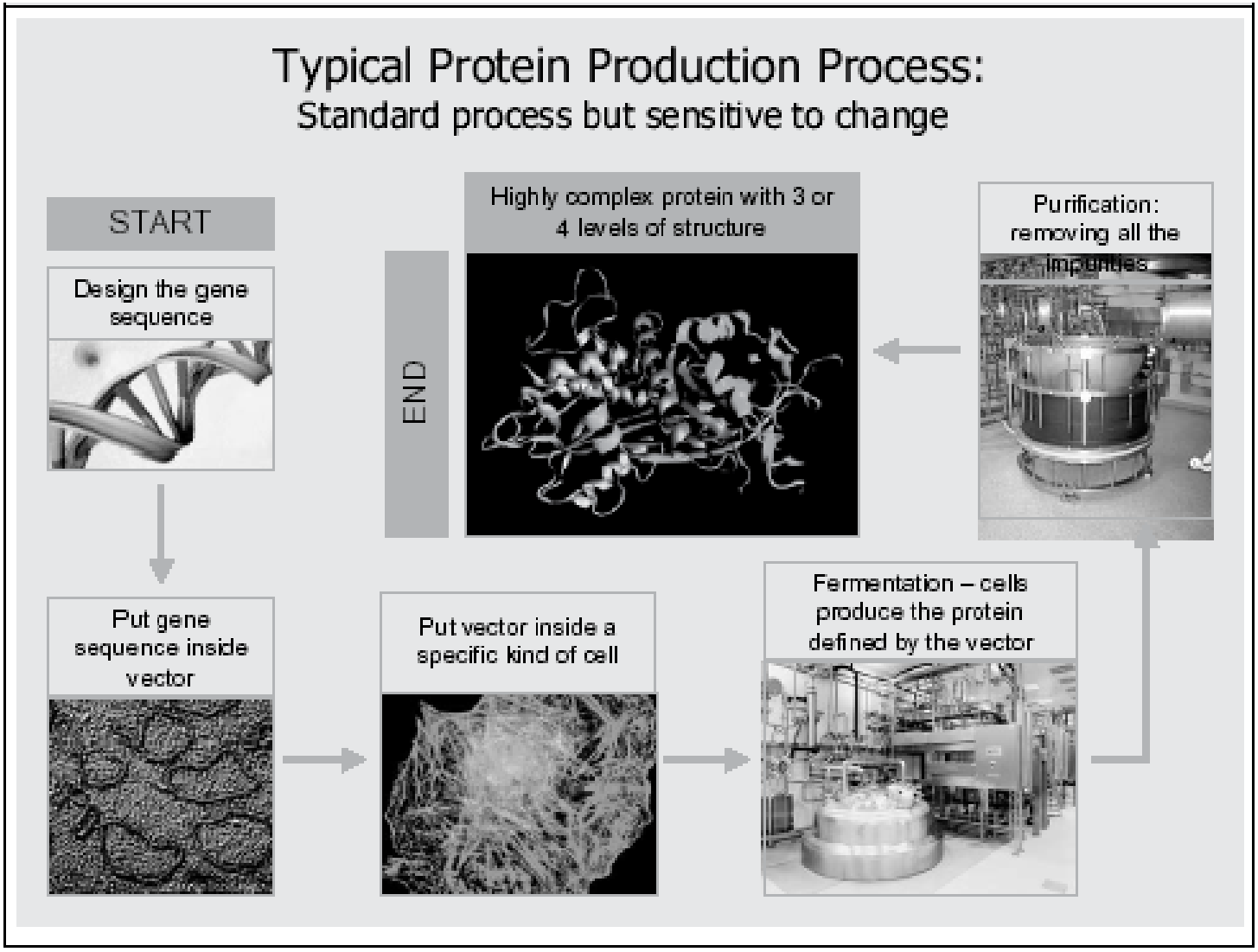

65 MAAs submitted to EMA
53 MAAs reviewed
2 refuted
- Interferon alfa-2a
- Human insulin
41 authorized
10 withdrawn
- Epoetin (1)
- Insulin (6)
- Pegfilgrastim (3)
3 withdrawn post-approval
- Filgrastim (2)
- Somatropin
38 valid MA's
- Adalimumab (4)
- Enoxaparin (2)
- Epoetin (5)
- Etanercept (2)
- Filgrastim (7)
- Follitropin (2)
- Infliximab (3)
- Insulin glargine (2)
- Insulin lispro (1)
- Rituximab (6)
- Somatropin (1)
- Teriparatide (2)
- Trastuzumab (1)
12 MAAs under review
- Adalimumab (2)
- Bevacizumab (2)
- Infliximab (1)
- Insulin glargine (1)
- Pegfilgrastim (3)
- Trastuzumab (3)
www.ema.europa.eu
21/10/2017

The false myths about biosimilars – 1

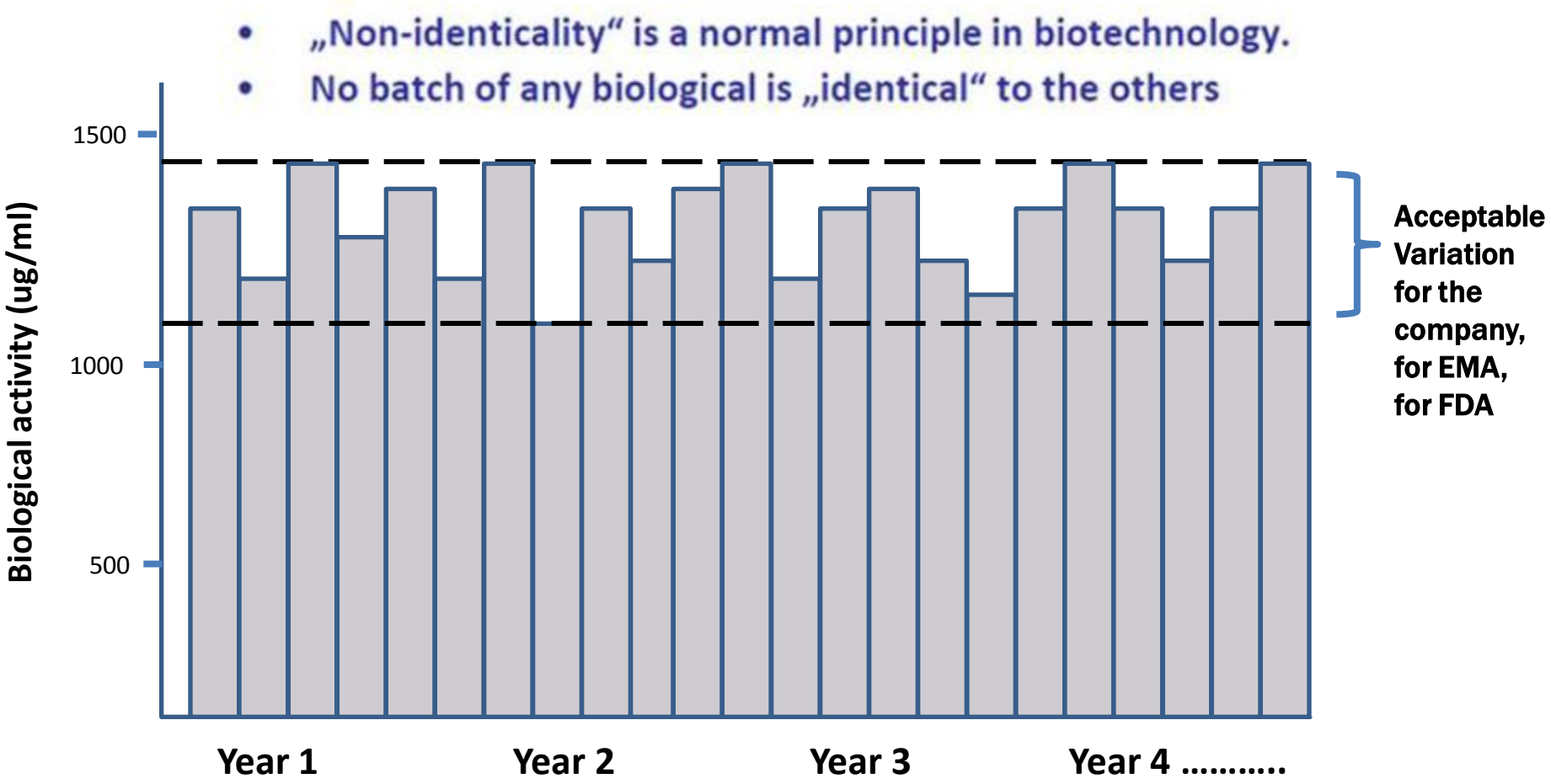
Bio-identicality vs. similarity

«Biosimilars are not identifical but only similar to reference product, thus they are to be considered as different drugs»

“One process, one product”

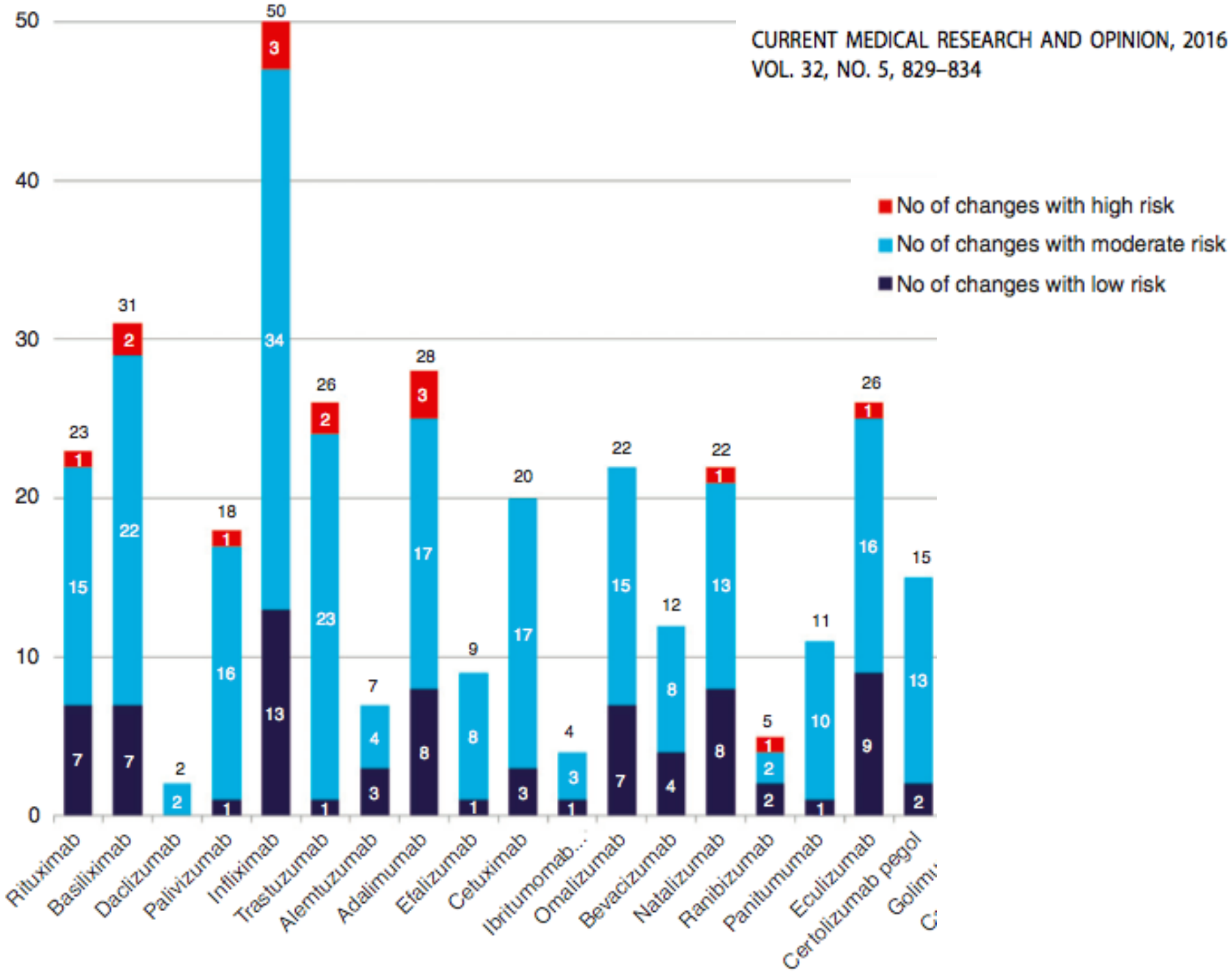


Biologicals are similar but not identical



Disclaimer: Hypothetic mAb production

CURRENT MEDICAL RESEARCH AND OPINION, 2016
VOL. 32, NO. 5, 829–834

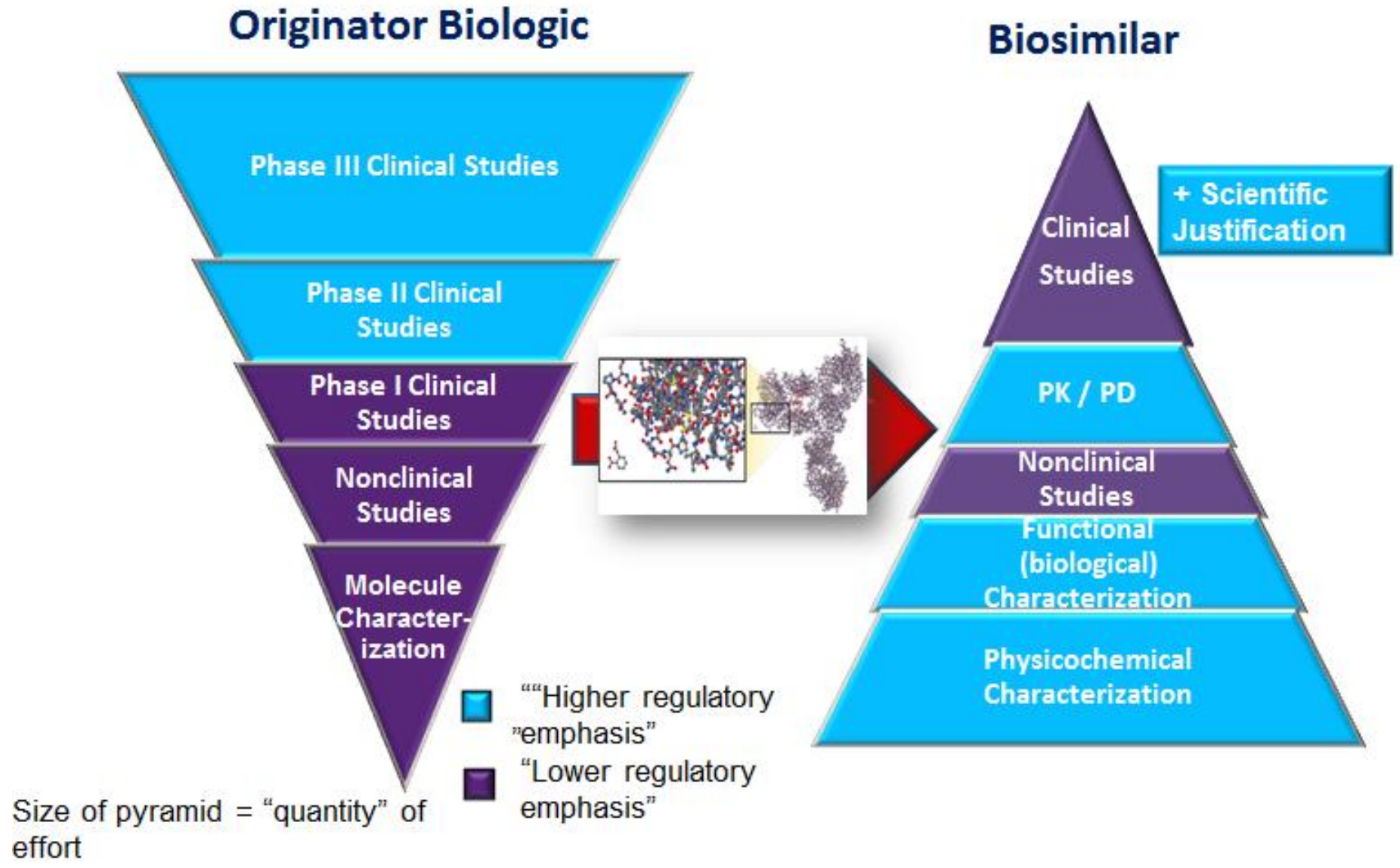


The false myths about biosimilars – 2

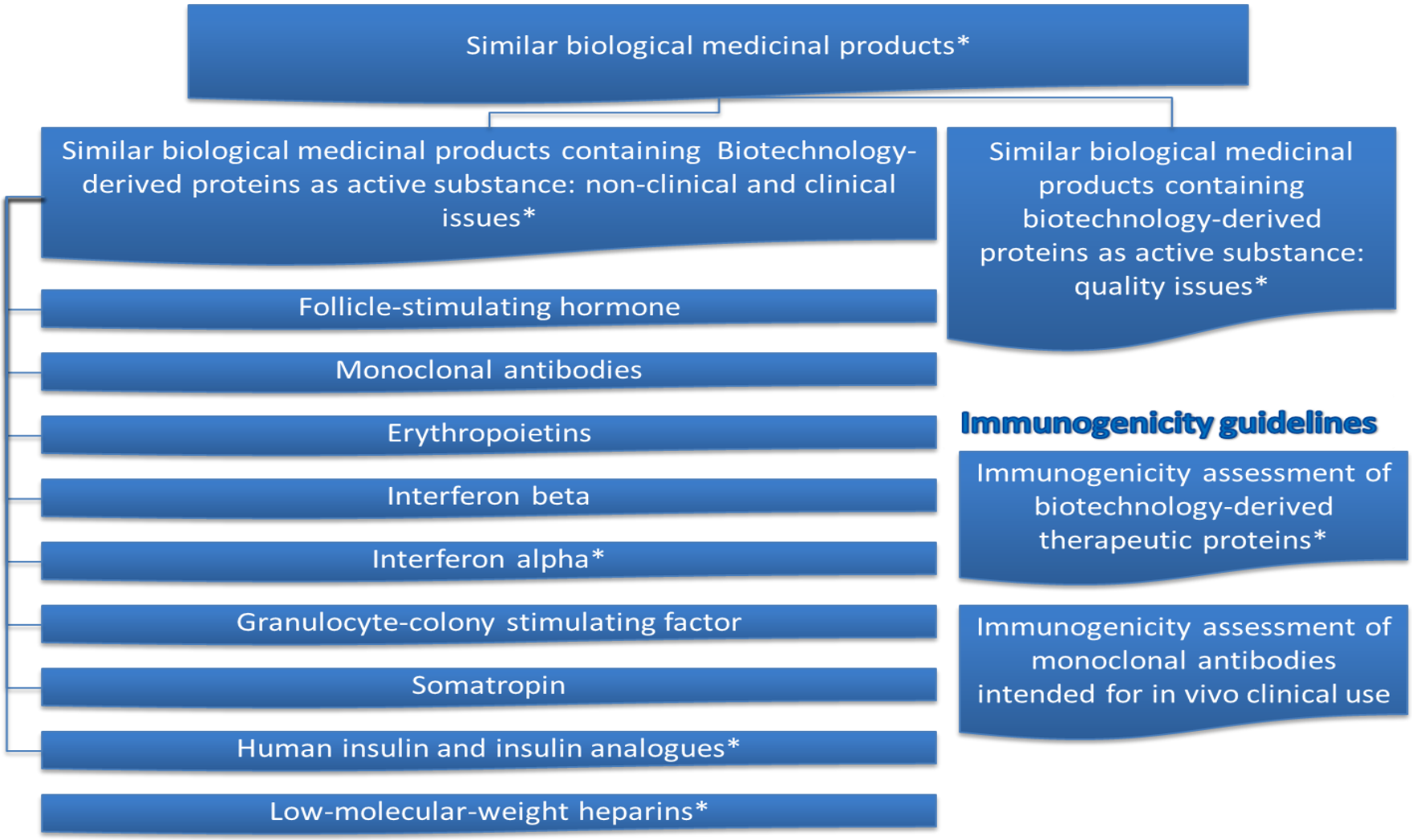
Pre-marketing evidence on benefit-risk profile of biosimilars

«The pre-marketing evidence on biosimilars are much more limited than what is available for reference product at the time the drug is marketed»

Biosimilars “inverted pyramid”



EMA Biosimilar WP Guidelines



EMA website

The false myths about biosimilars – 3

Postmarketing safety of biosimilars

«As a result of the limited pre-marketing evidence, biosimilars are less safe than reference product in routine care»

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pure Red-Cell Aplasia and Epoetin Therapy

Charles L. Bennett, M.D., Ph.D., M.P.P., Stefano Luminari, M.D., Allen R. Nissenson, M.D., Martin S. Tallman, M.D., Stephen A. Klinge, B.A., Norene McWilliams, J.D., M.P.H., June M. McKoy, M.D., J.D., M.P.H., Benjamin Kim, M.D., E. Allison Lyons, B.A., Steve M. Trifilio, R.P.H., Dennis W. Raisch, Ph.D., Andrew M. Evens, D.O., Timothy M. Kuzel, M.D., Glen T. Schumock, Pharm.D., M.B.A., Steven M. Belknap, M.D., Francesco Locatelli, M.D., Jerôme Rossert, M.D., Ph.D.,

A confluence of factors related to the production, handling, and route of administration of epoetin may account for the increased incidence of Eprex-associated pure red-cell aplasia beginning in 1998. Processes (such as freeze-drying) and formulations that facilitate the oxidation or aggregation of protein can enhance immunogenicity. In the mid-1990s, a shift from intravenous administration of epoetin to subcutaneous administration for patients with chronic kidney disease occurred in many countries, because subcutaneous administration was thought to be more cost-effective and because it avoided the need for intravenous access.[23,24] As has been noted with other proteins, subcutaneous administration of epoetin, particularly self-administration, with the attendant problems in the storage and handling of the product, has the potential to induce antibody formation.[25]

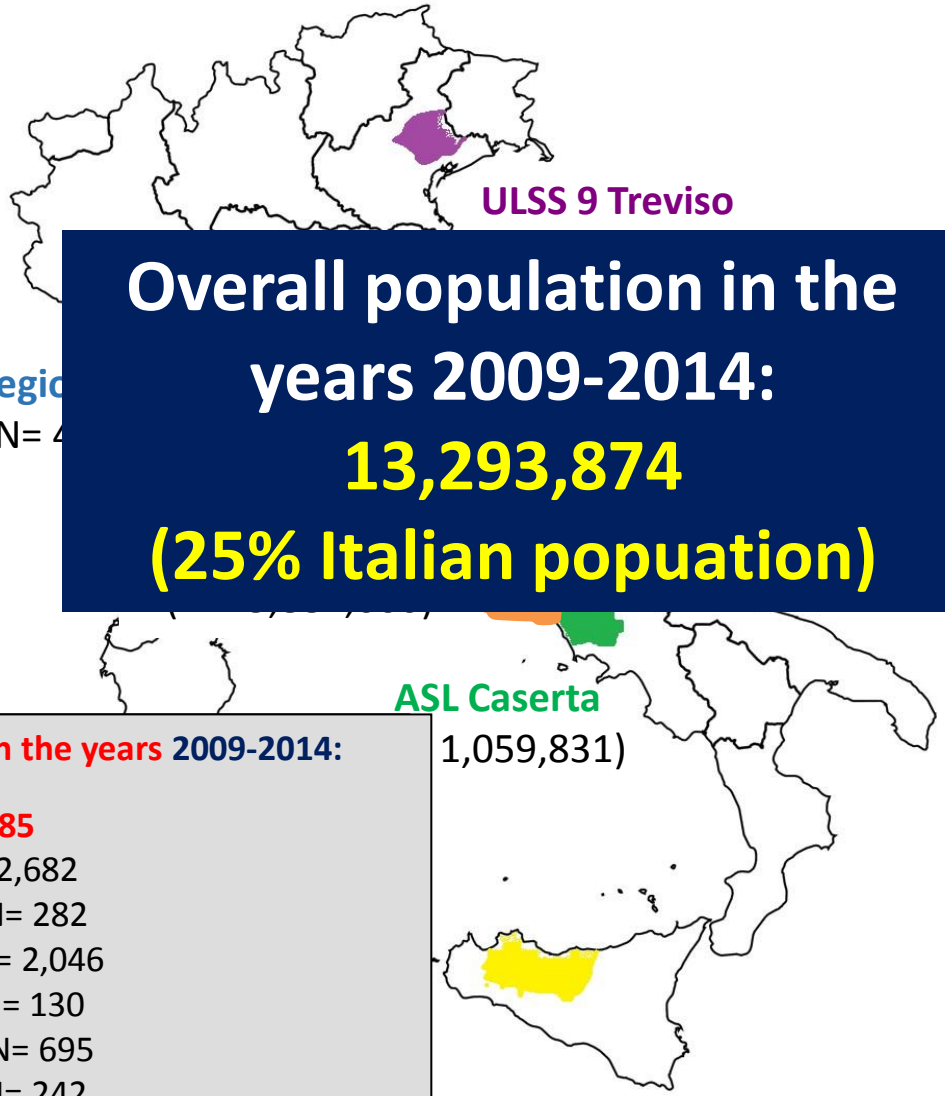
epoetin alfa and Neorecormon (a formulation of epoetin beta), both products that are marketed outside the United States.[1]

"**Tungsten-mediated** unfolding and aggregation of epoetin alfa in pre-filled syringes as a potential root cause for increased immunogenicity"
Pharm Res 2012 Jun; 29(6): 1454–1467.

Assessment of short and long term risk-benefit profile of biologics/biosimilars through healthcare database network in Italy

Azienda Ospedaliera Universitaria
Policlinico G. Martino

Ministero della Salute



Overall population in the years 2009-2014:
13,293,874
(25% Italian popuation)

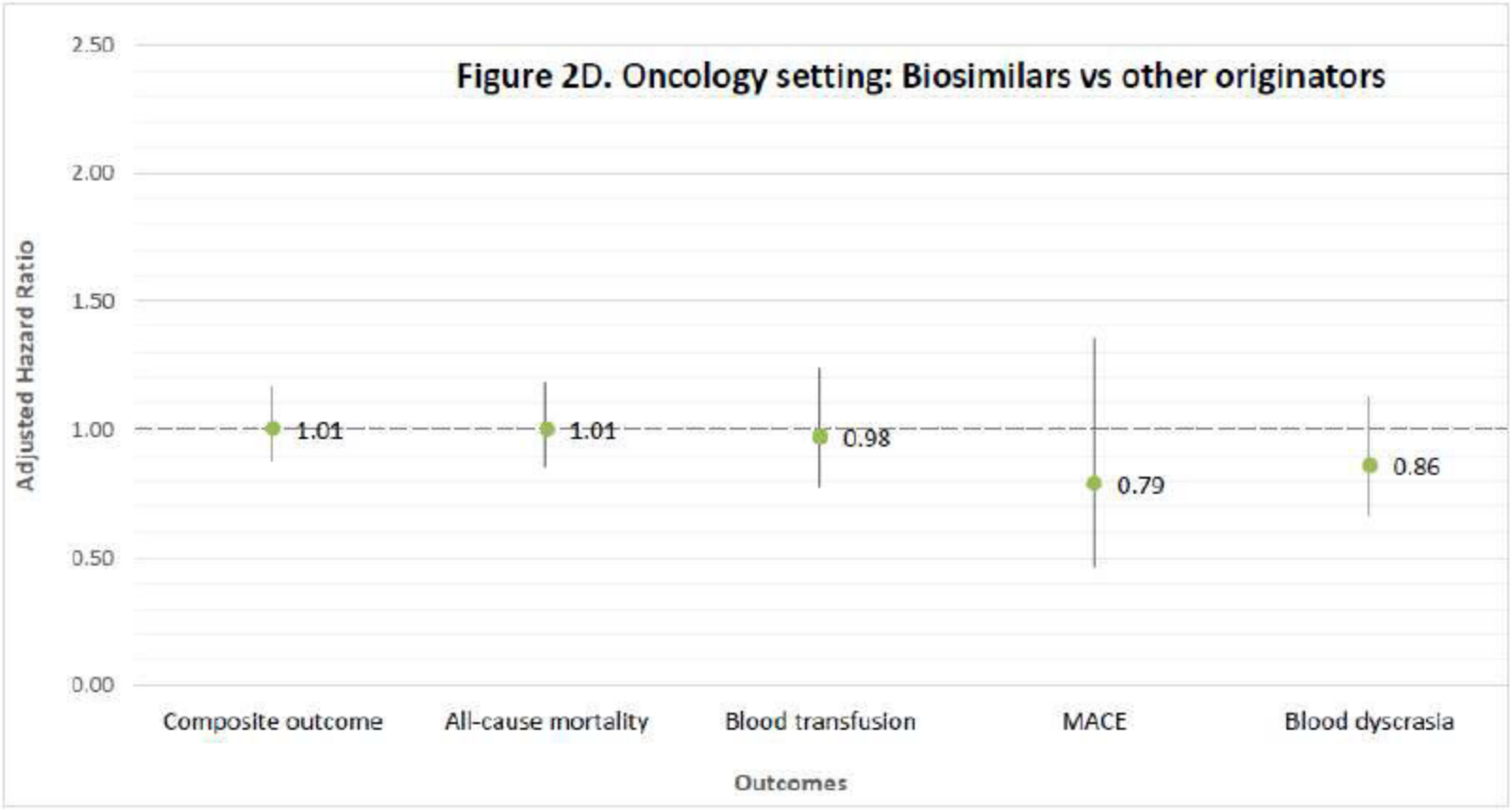
Regio
(N= 4

ASL Caserta
1,059,831)

N. users of somatotropin in the years 2009-2014:

N= 6,785
Lazio: N=2,682
Caserta: N= 282
Toscana: N= 2,046
Treviso: N= 130
Palermo: N= 695
Umbria: N= 242

Post-marketing comparative safety of different ESA types



Trotta F, et al. BMJ Open. In press

Italian society of pharmacology position paper

- All **published studies** so far on most of the indications of use of biosimilars did **not suggest any difference** of biosimilars vs. reference product with respect to **safety**;
- Biosimilars have been **increasingly prescribed in Europe** since more than 10 years and **no major safety issues** have been encountered so far;
- Several mandatory **Post Authorization Safety Studies (PASS)** have been carried out and occasionally published which did not lead tto changes in the marketing authorization of biosimilars;
- EMA examined a large number of **Periodic Safety Update Reports and did not identify any critical issue** regarding similarity of benefict-risk profile of biosimilars and reference products.

Società Italiana di Farmacologia. Revisione della posizione sui farmaci biosimilari da parte della Società Italiana di Farmacologia: Working Paper 2014. 2014. Availableonline: http://www.sifweb.org/docs/sif_position_paper_revisione_biosimilari_lug14.pdf.

The false myths about biosimilars – 4

Interchangeability of biosimilar and reference product

«Interchangeability of biosimilars and reference product is an issue to be never considered due to serious immunogenicity risks potentially associated with switching of therapeutic proteins»

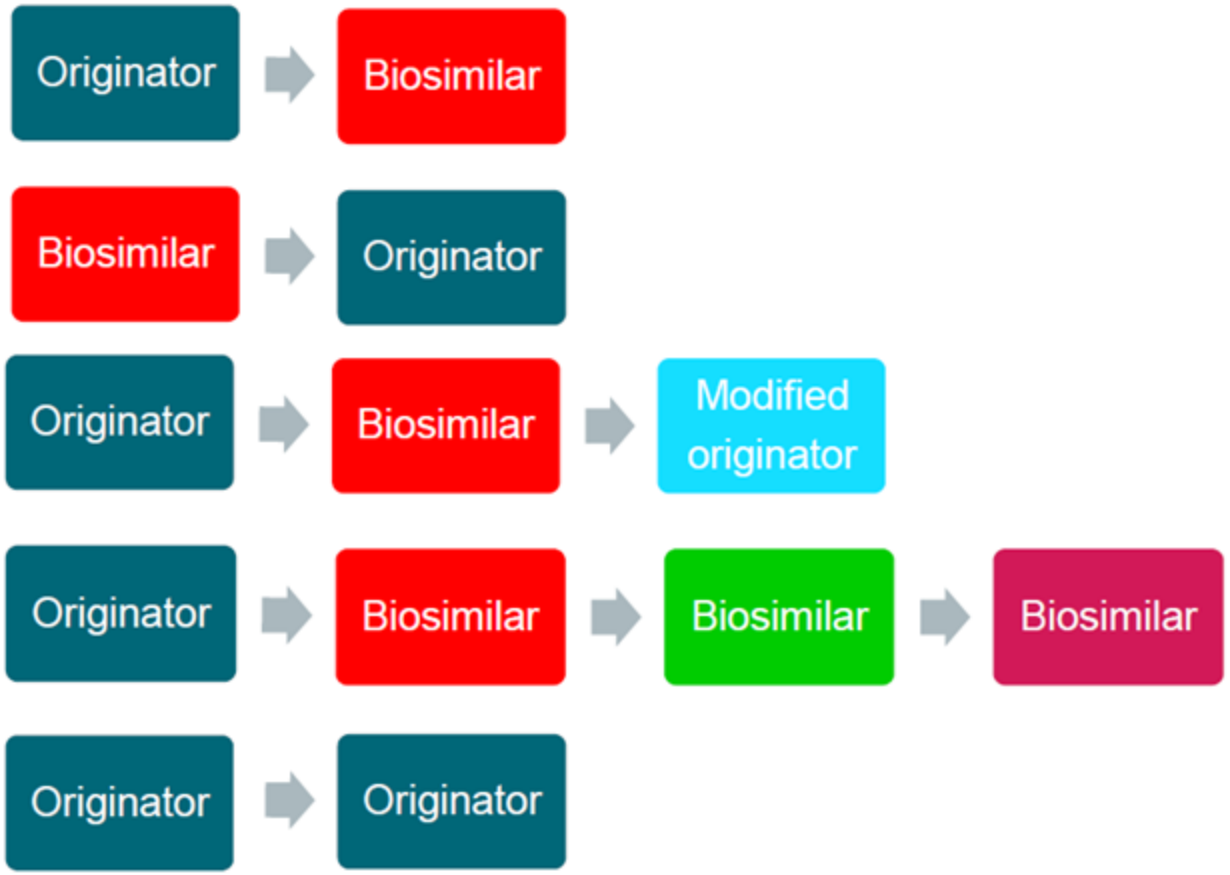
Definitions

- **Interchangeability:** possibility of exchanging one medicine for **another medicine** that is expected to have the **same clinical effect**. This could mean replacing a reference product with a biosimilar (or vice versa) or replacing one biosimilar with another;

- **Switching:** it is when the **prescriber** decides to exchange one medicine for another medicine with the **same therapeutic intent**;

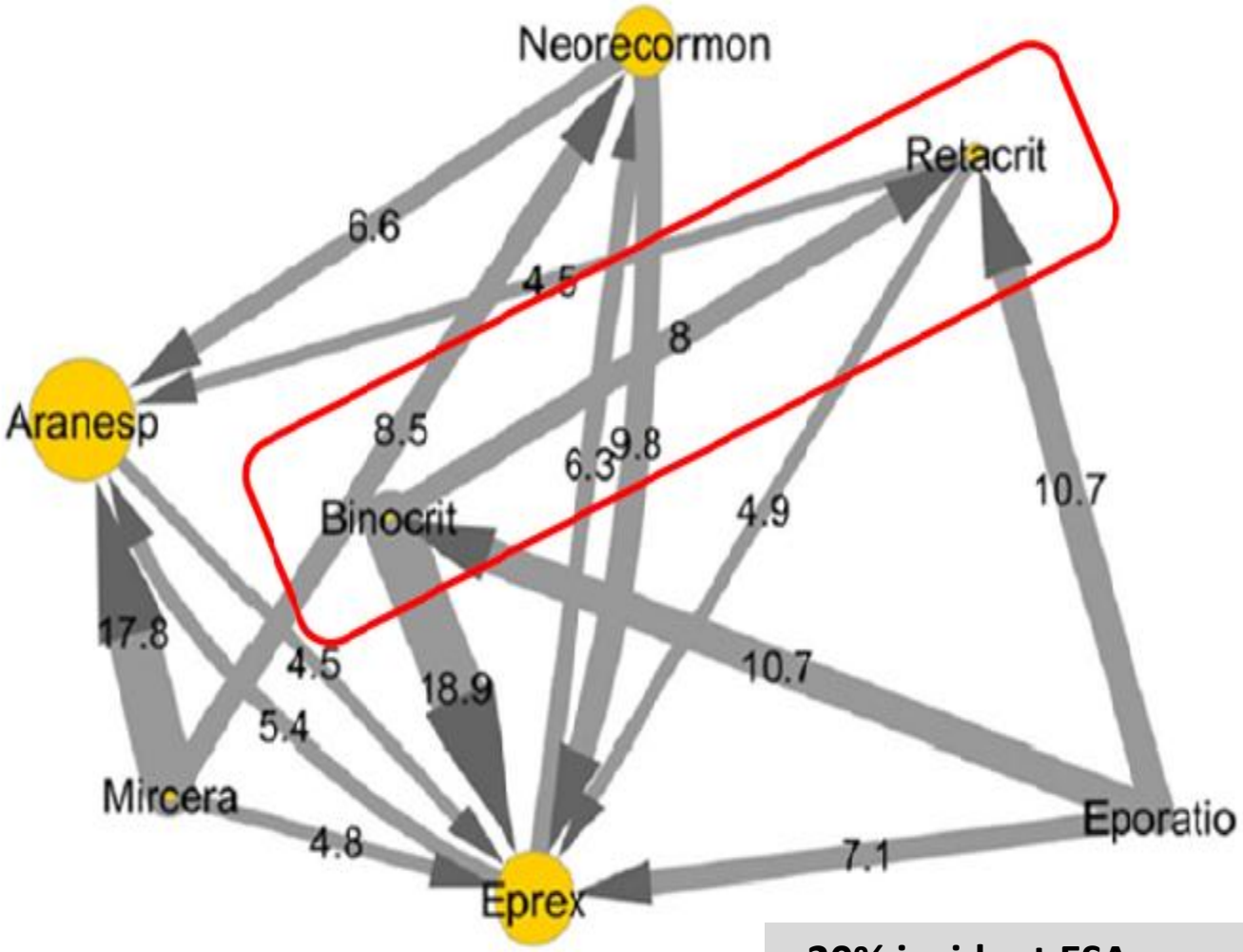
- **Substitution (automatic)**: the practice of **dispensing** one medicine instead of another equivalent and **interchangeable** medicine at pharmacy level **without consulting the prescriber.**

Switching will be an increasingly complex issue



Adapted by presentation from S. Madsen (Norway Drug Agency) – 15th Medicines for Europe conference on Biosimilars - London 23-24/3/2017

Switch between various ESAs during first year of therapy in 5 Italian Regions, years 2009-2014



Ingrasciotta Y *et al. How Much Are Biosimilars Used in Clinical Practice? A Retrospective Italian Population-Based Study of Erythropoiesis-Stimulating Agents in the Years 2009-2013. BioDrugs. 2015;29(4):275-84.*

20% incident ESA users switched to other ESAs during first year therapy

U.S. FOOD & DRUG ADMINISTRATION

- In addition to the studies demonstrating biosimilarity, it is requested to conduct pre-marketing studies on multiple and reverse switching of biosimilar and reference products to grant the biosimilar with interchangeable status;

- FDA draft guidance for industries contains detailed requests for the demonstration of interchangeability between biosimilars and reference products. This draft requires the evaluation of at least three switches between reference product and biosimilar (back and forward).

FDA. Considerations in Demonstrating Interchangeability With Reference Product Guidance for Industry. 2017

ECCO Position Statement on the Use of Biosimilars for IBD

Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.

***Danese S** et al. ECCO Position Statement on Use of Biosimilars for Inflammatory Bowel Disease-An Update. J Crohns Colitis 2017:26-34.*

"Our conclusion is that a state-of-the-art demonstration of biosimilarity, together with intensified post-marketing surveillance, is a sufficient and realistic way of ensuring interchangeability of EU-approved biosimilars under supervision of the prescriber."

Pekka Kurki[1] · Leon van Aerts[2] · Elena Wolff-Holz[3] · Thijs Giezen[4] · Venke Skibeli[5] · Martina Weise[6]

Kurki et al. 2017. BioDrugs 2017. ePub

Future challenges

- Growing number of **II generation biosimilars** will be shortly marketed, which requires post-marketing **short- and long-term monitoring**;
- To evaluate **benefit and risks of switching** between **originators and biosimilars** (and viceversa) in **post-marketing setting** to integrate pre-marketing evidence on **interchangeability**;
- To consider secondary use of **healthcare databases** for rapid and cost-saving surveillance of biosimilars in **routine care;**
- **Payers, healthcare professionals and patients** have to be all involved in the **RWE generation** about biologics and biosimilars to be **integrated with premarketing RCT** evidence.

Thanks for the attention

"The human mind is like a parachute. It works better when it is open". Paul Jansen

Gianluca Trifirò

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