Teva BioForum 2011

KEEPING YOU IN TOUCH WITH TEVA'S PROGRESS IN BIOPHARMA

Biosimilars: Making Biological Medicine Accessable

Udo Mueller, MD, PhD

Medical Director

Teva Global Oncology and Biosimilars

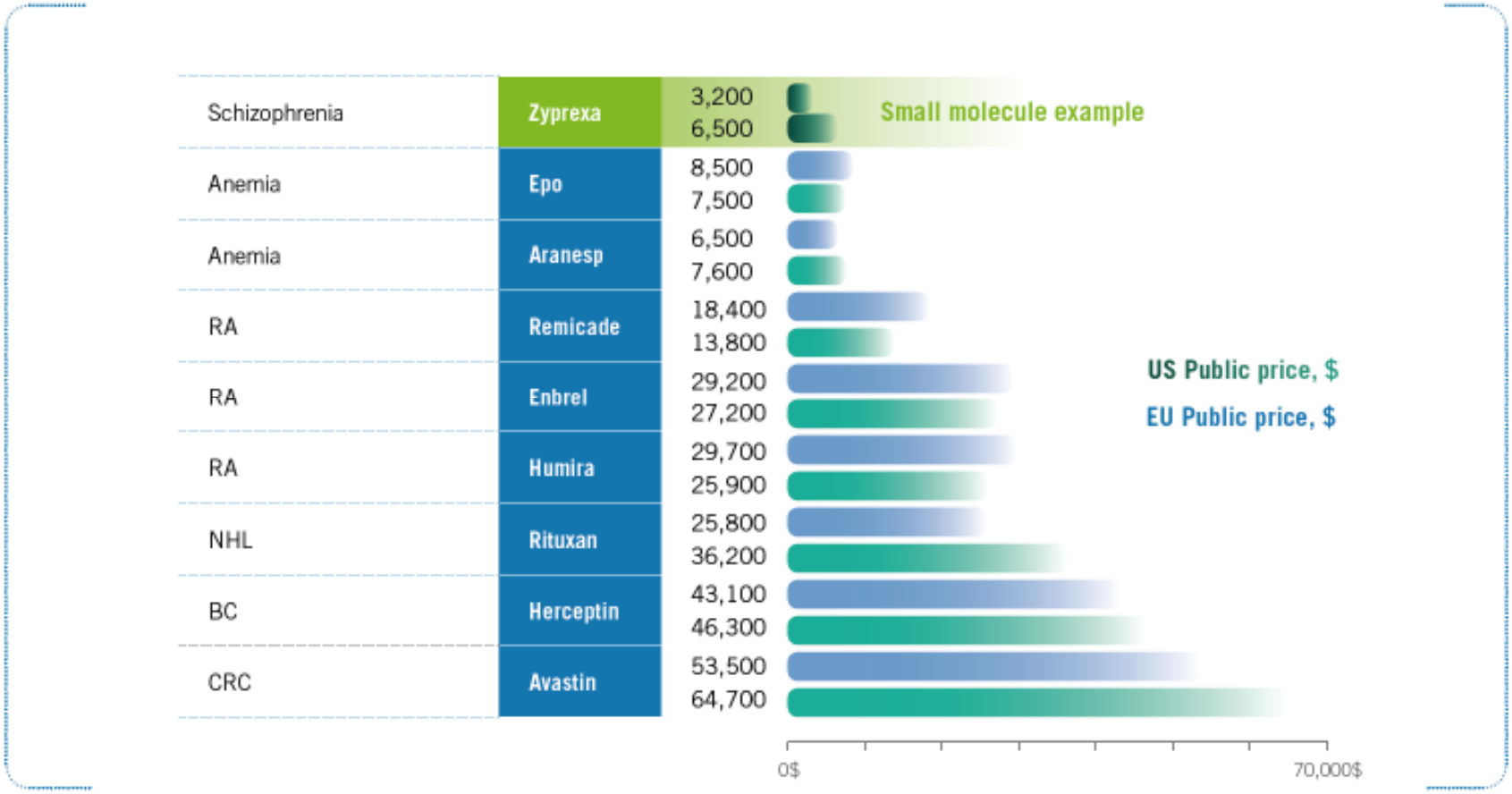
Biotech drugs treat serious diseases

The top 10 biotech drugs today**

	Indication	Molecule type	$bn Sales (2011)
Humira	Autoimmune	MAb (anti-TNF)	7,3
Enbrel	Autoimmune (RA, Psoriasis, Crohn's)	Fusion-protein (anti-TNF)	6,9
Remicade	Autoimmune	MAb (anti-TNF)	6,9
Rituxan	Cancer (hematological)	MAb (anti-CD-20)	5,8
Avastin	Cancer (solid tumors)	MAb (anti-VEGF)	5,3
Lantus	Diabetes	Long-acting insulin	5,3
Herceptin	Cancer (solid tumors)	MAb (anti-HER2)	4,7
Novorapid/Novomix	Diabetes	Short Acting Insulin	4,4
Neulasta	Cancer (supportive)	Long-acting GCSF	4,3
Lucentis	Wet Age Related Macular Degeneration	MAb (VEGF-A inhibitor)	3,9

** Source : IMS padds 2011

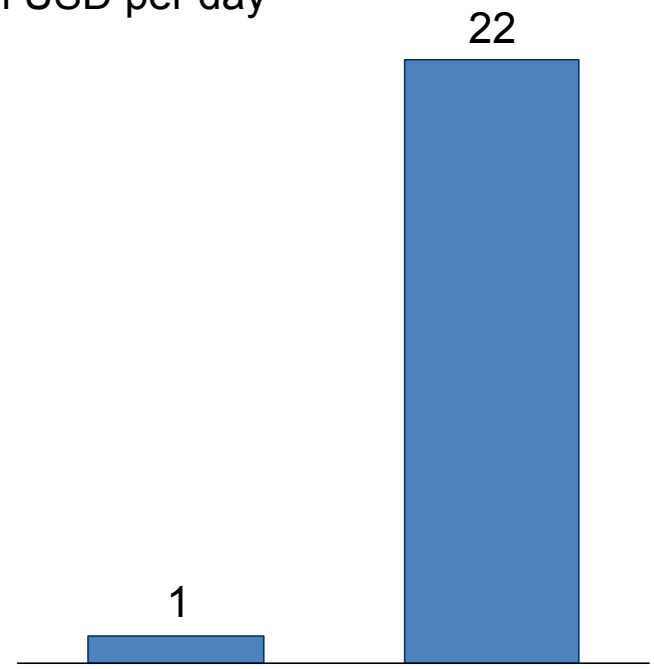
Today the average cost of treatment is high



Source : IMS Padds Q4 2010 EU : average EU5

Growing demand drives costs… and threatens to limit patient access (US example)

Estimated daily treatment costs[1]
in USD per day



The "Biologics Boondoggle"

"A breast cancer patient's annual cost for Herceptin is $37,000…

People with rheumatoid arthritis or Crohn's disease spend $50,000 a year on Humira…

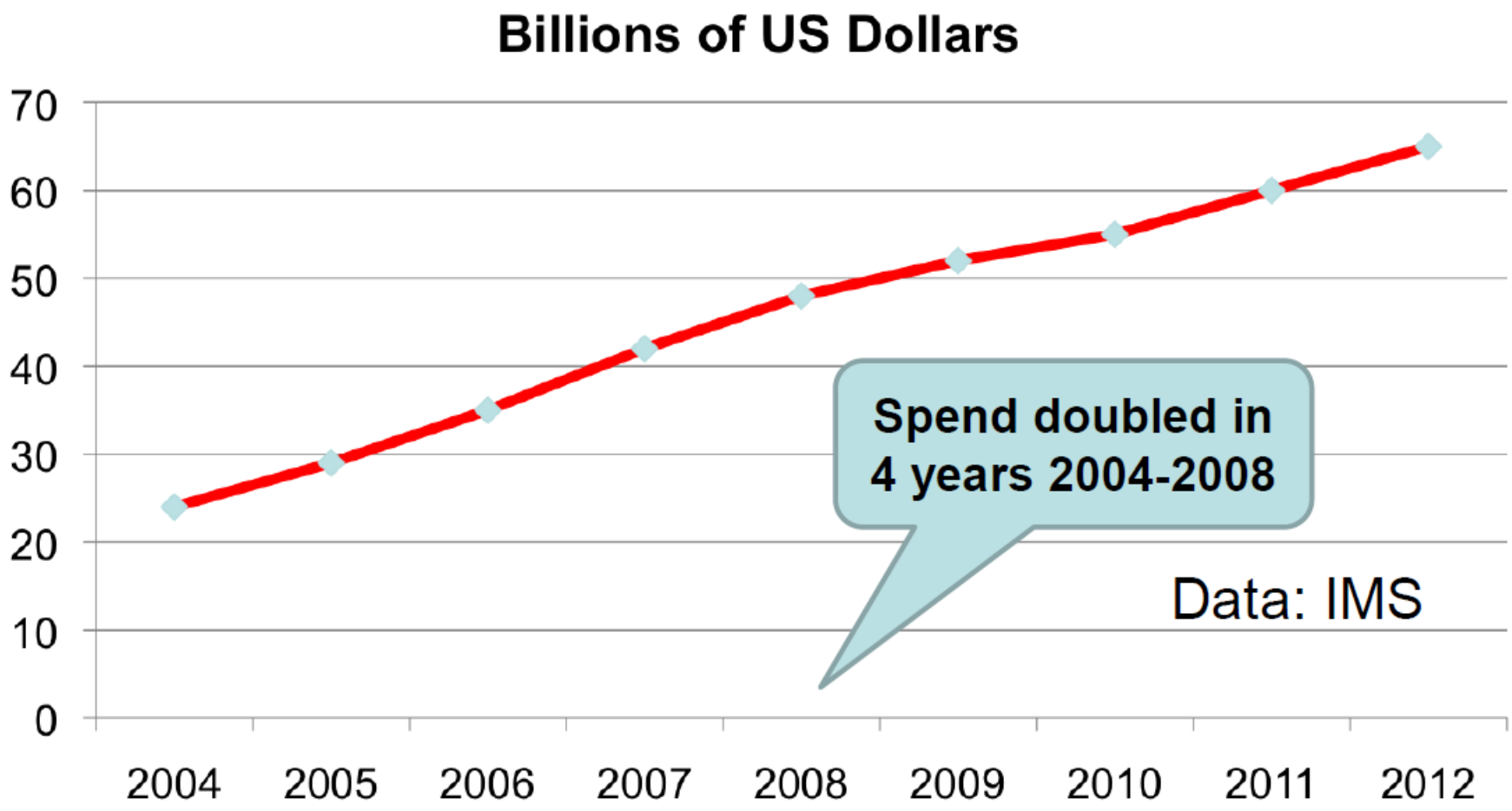
…and those who take Cerezyme to treat Gaucher disease….spend a staggering $200,000 a year…

"…the top six biologics already consume 43% of the drug budget for Medicare Part B" The New York Times Expect the World®

[1] Source: NY Times, March 2010

The world spends more each year for cancer treatment

Global spend on oncology drugs: projected for 2010-12



High impact of Biosimilars are expected on healthcare cost savings

Biosimilars will have more impact on biologic brands and markets over the next ten years than

any other single factor

It may look easy to develop a biosimilar

…

BUT …..

BIOSIMILARS DEFINITION

What is a BioSimilar

A BioSimilar is a biopharmaceutical that is physically, chemically, biologically, and clinically similar to an approved biological reference product

Why “similar” and not “identical” ?

Biologic drugs are complex / large molecules

As a Result

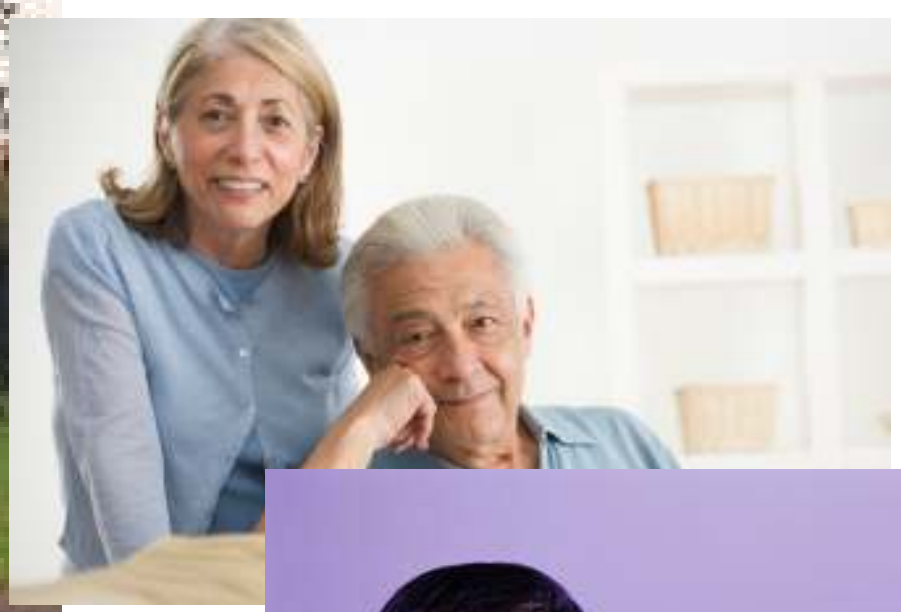
Manufactured drugs **may vary slightly*** from the drug that was originally approved

Slight variations, within well-defined product specifications, do not affect efficacy and safety as long as the manufacturing process is well controlled

For example:
batch to batch variation is often observed for any innovator’s drug

* In drug structure and physico-chemical profile

How similar is too similar?



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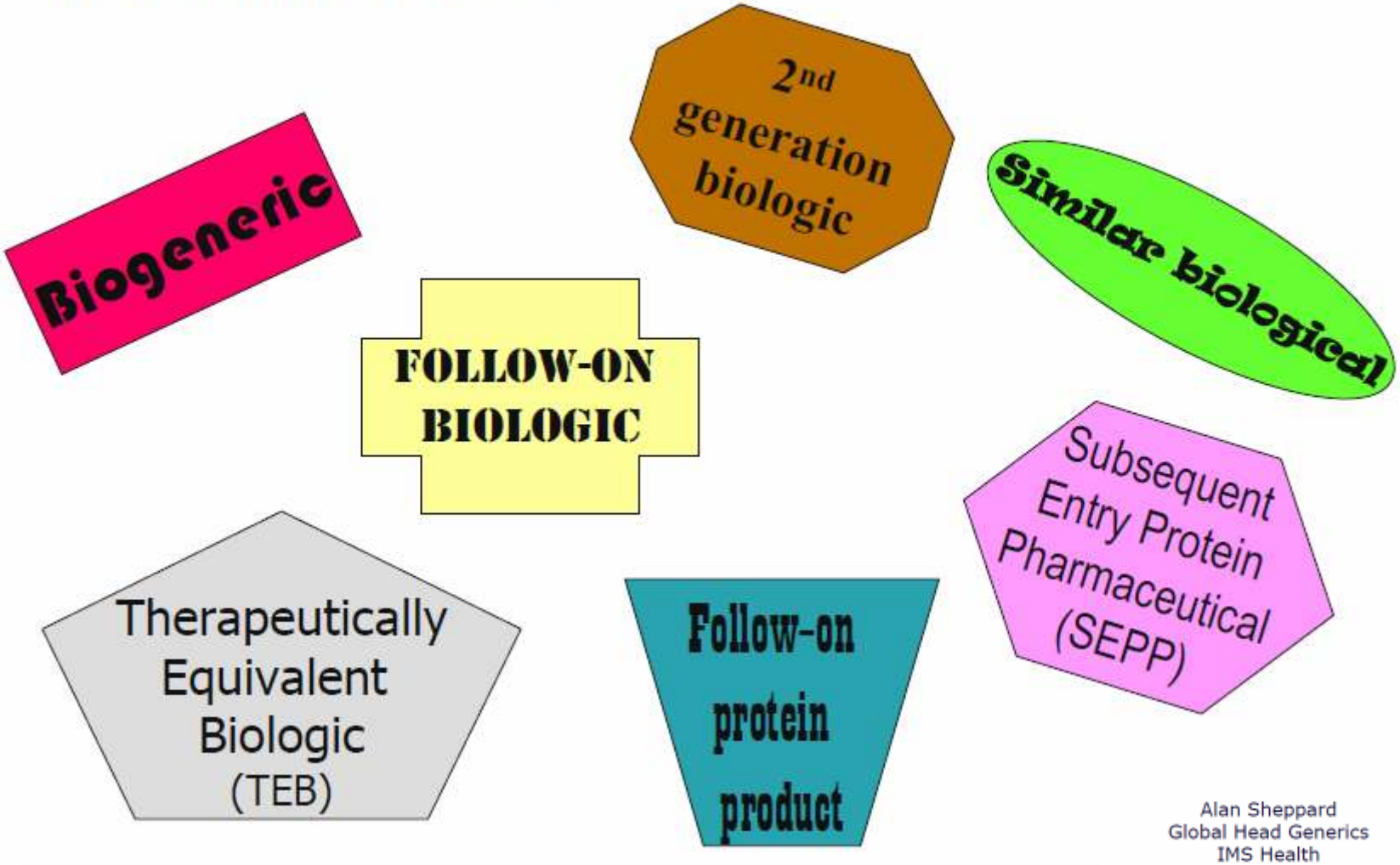
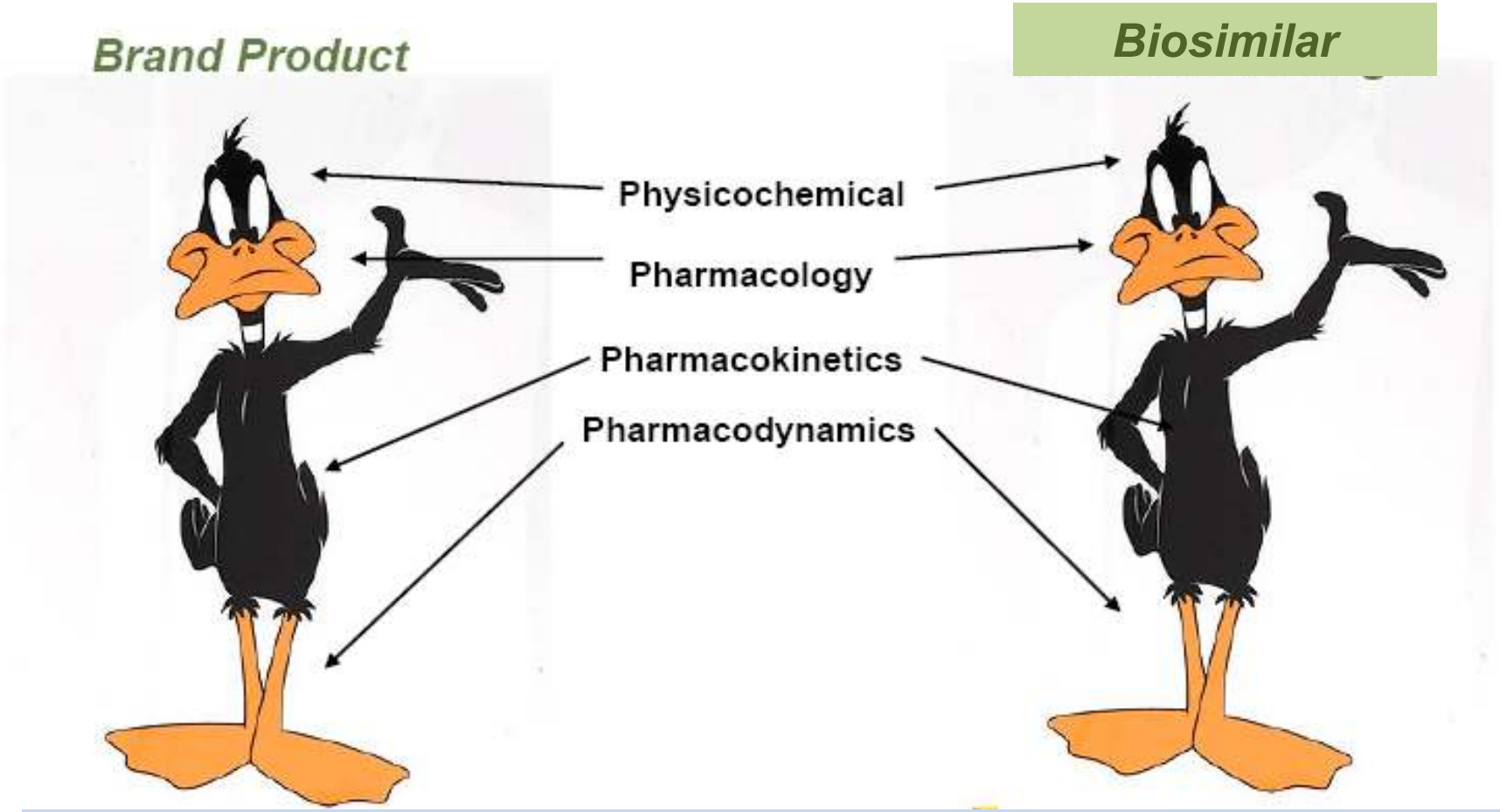
Biosimilars or....



Alan Sheppard
Global Head Generics
IMS Health
ASheppard@uk.imshealth.com

It's a Duck



Such copies (biosimilars) are normally not fully identical to the innovator compound, but resemble it to a certain degree only.

Challenges to make a biosimilar

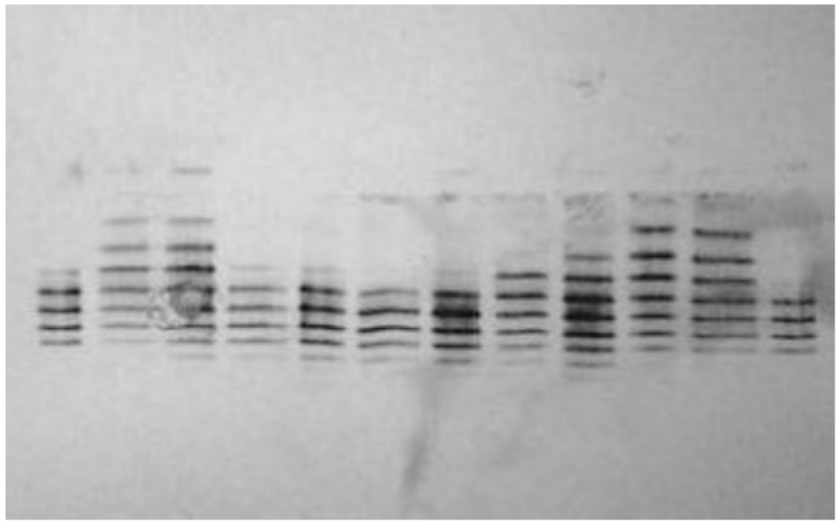
- Comparability has to be demonstrated to an EU approved product - reference product
- All studies have to be planned and conducted to find differences to the reference product, if there are any
- Comparability to the reference product has to be demonstrated, not “the response *per se*”
- Demonstration of comparability is a step-wise approach

Non-comparable “copy biologics” – not approved in highly regulated markets – are NOT biosimilars

Isoelectric focusing gels

Non-comparable “copy biologic” ≠ biosimilar

NOT similar to Reference E

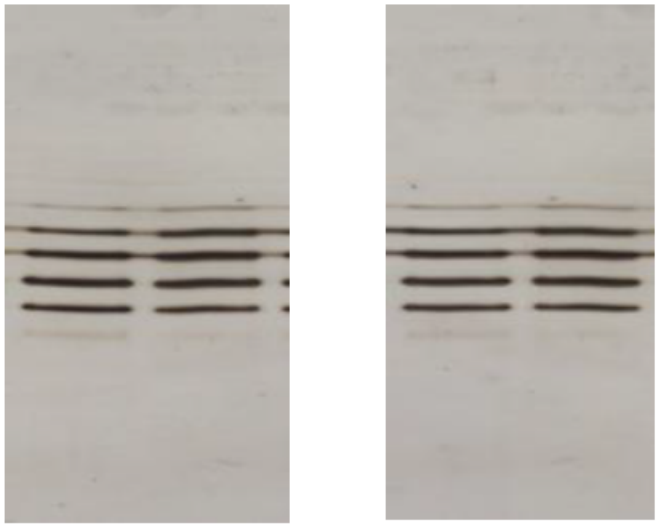


Sample E IA IB IIA IIB IIIA IIIB IV V VII VIII E

Schellekens H *et al. Eur J Hosp Pharm Pract* 2004;3:43–7

Approved biosimilar in EU

NO difference to originator



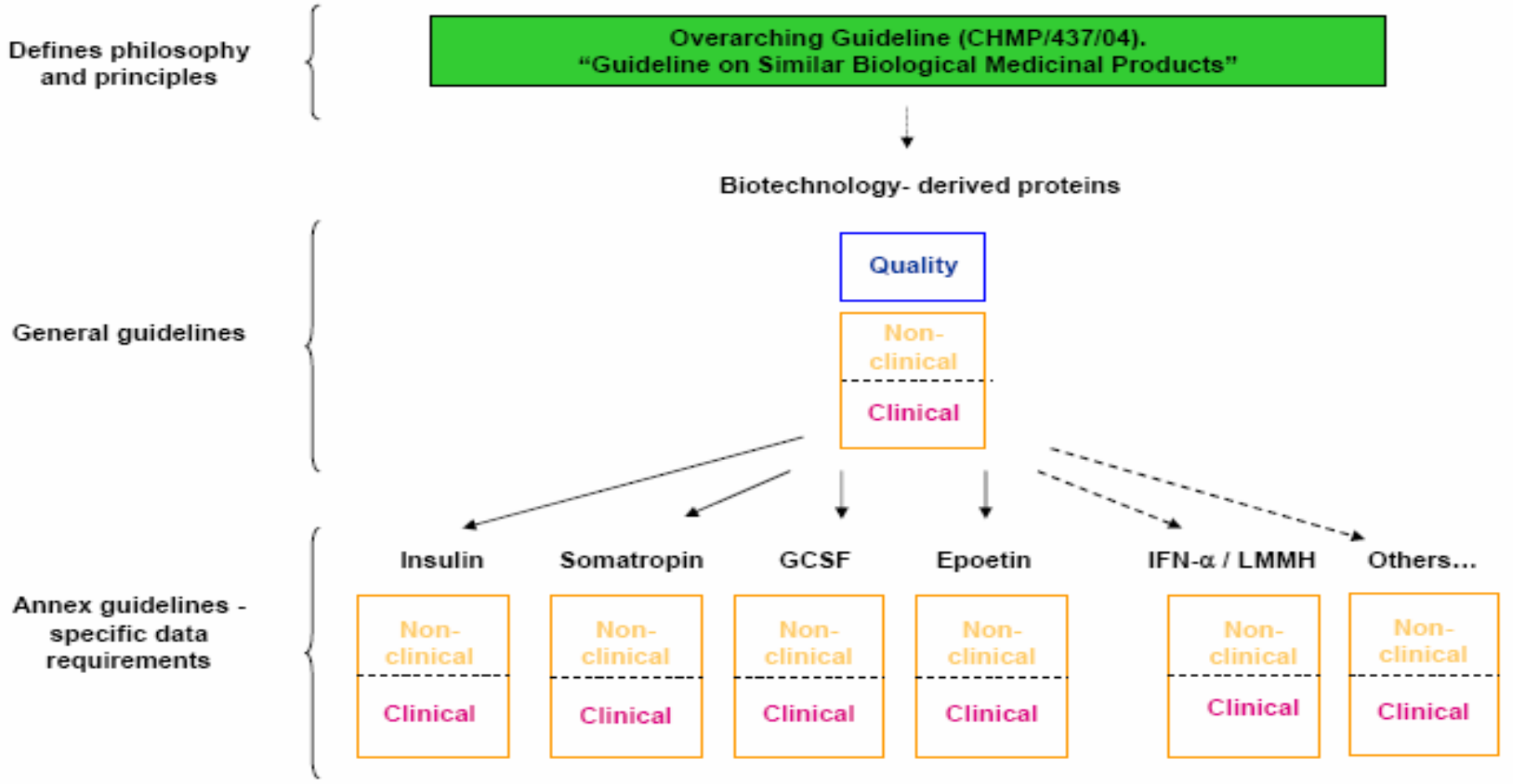
Sample 1 2 3 4

Brockmeyer C & Seidl A *et al. Eur J Hosp Pharm Pract* 2009;15:34–40

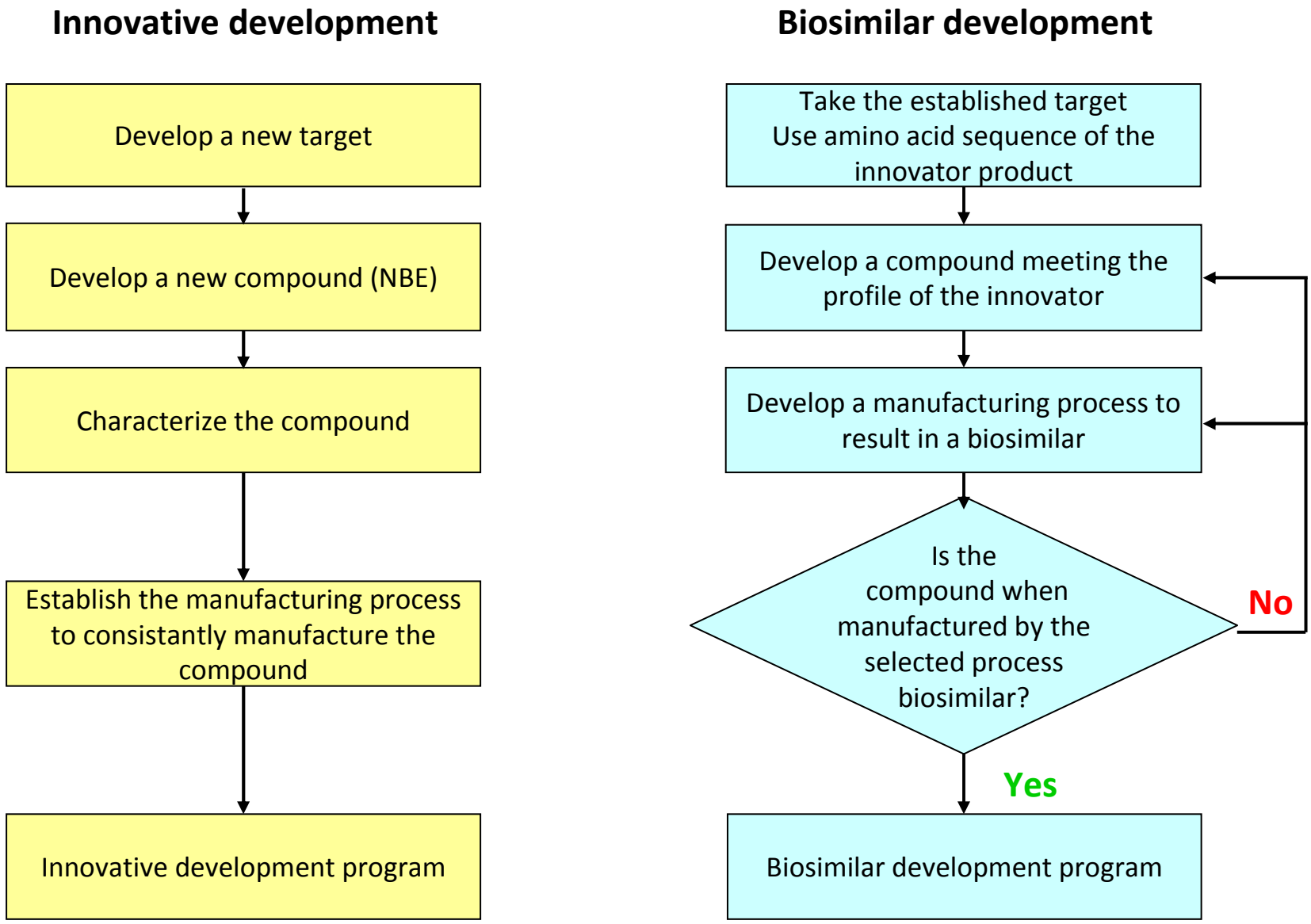
REGULATORY PROCESS FOR BIOSIMILARS

Biosimilars - It‘s all about comparability

Current Biosimilar Guidelines – Summary

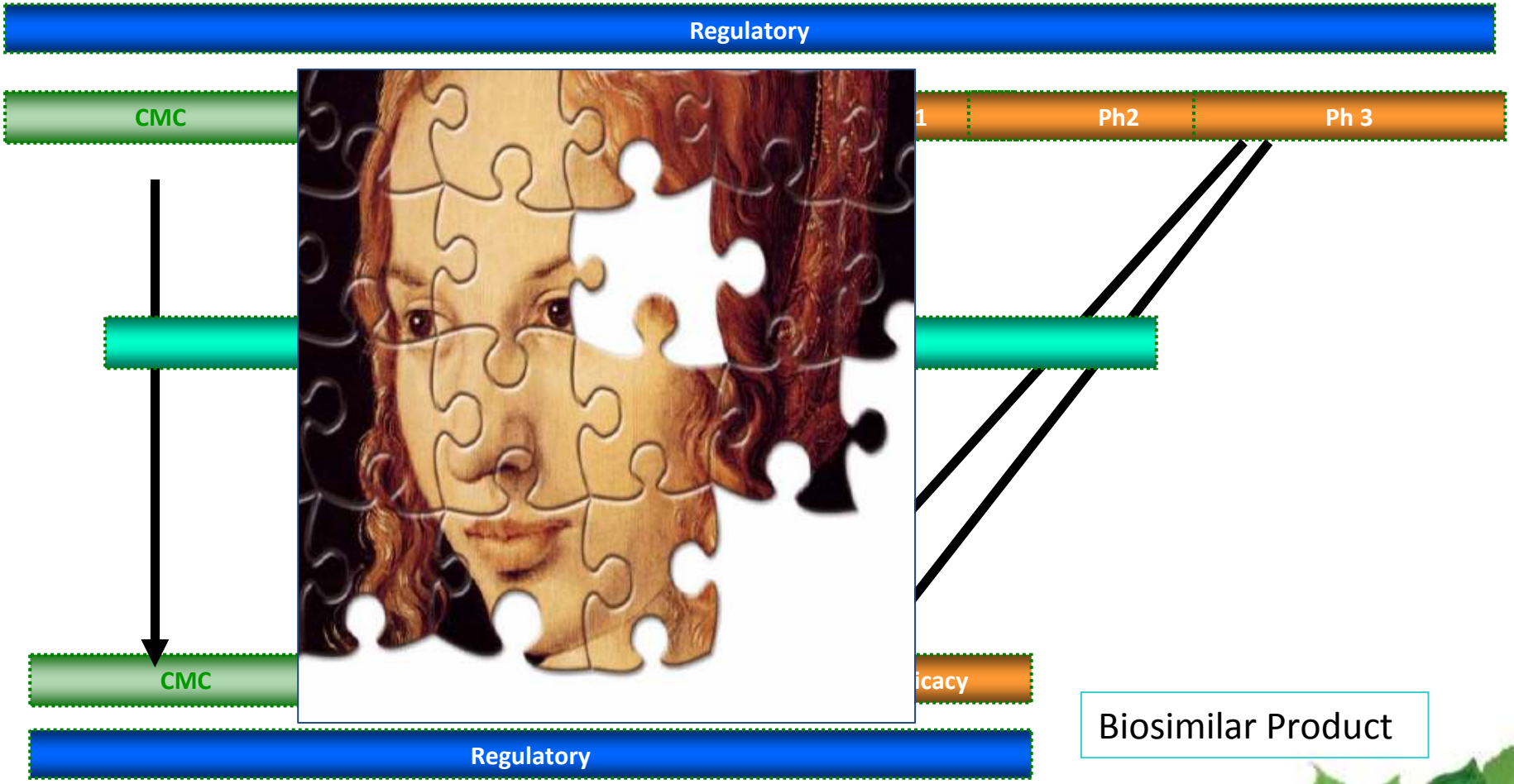


Challenges - Finding of the right Candidate



Challenges – “The comparability exercise”

Originator Product



Biosimilar Product

Challenges – “The comparability exercise”

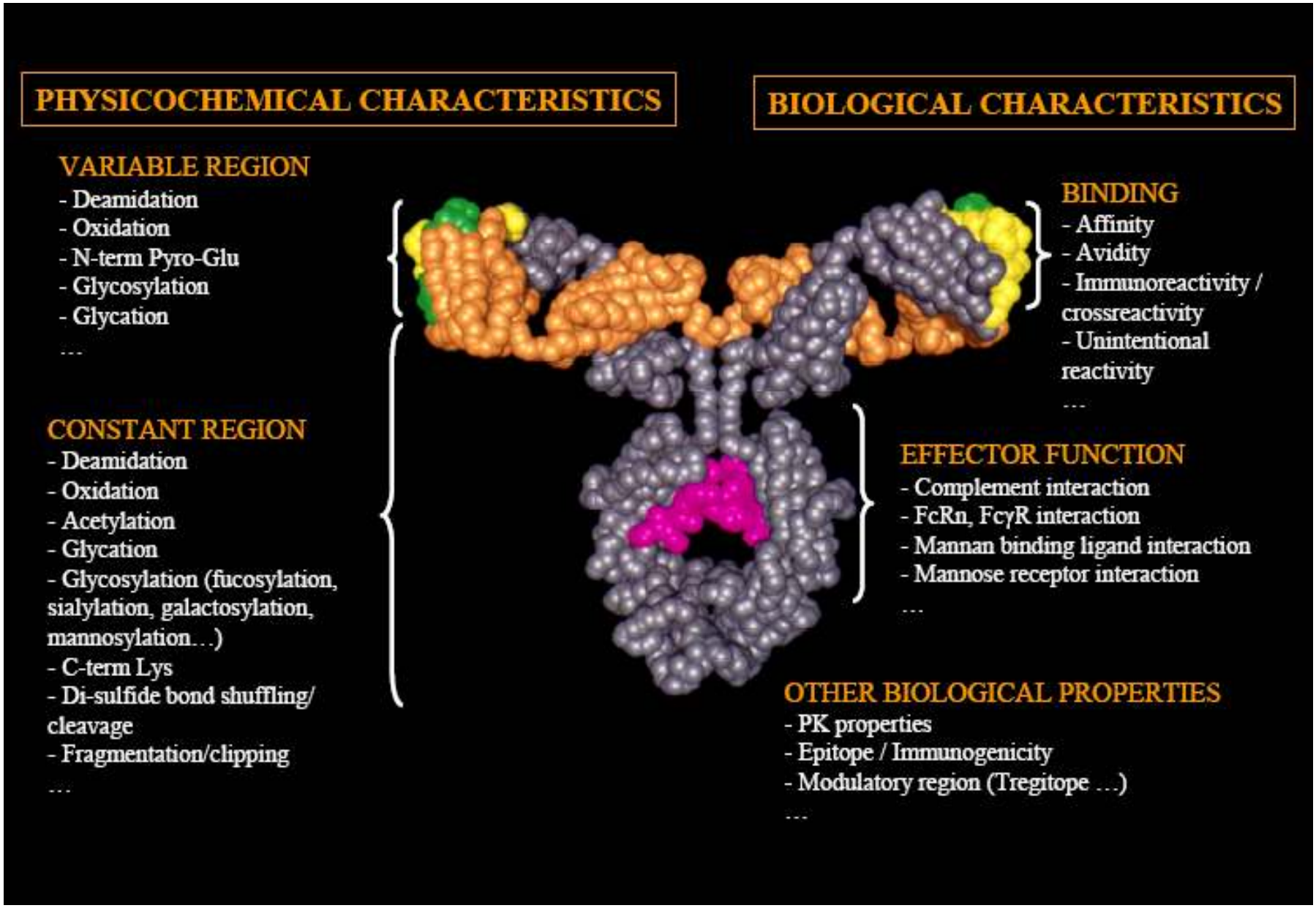
John Purves
EMEA

Overview on the regulatory environment

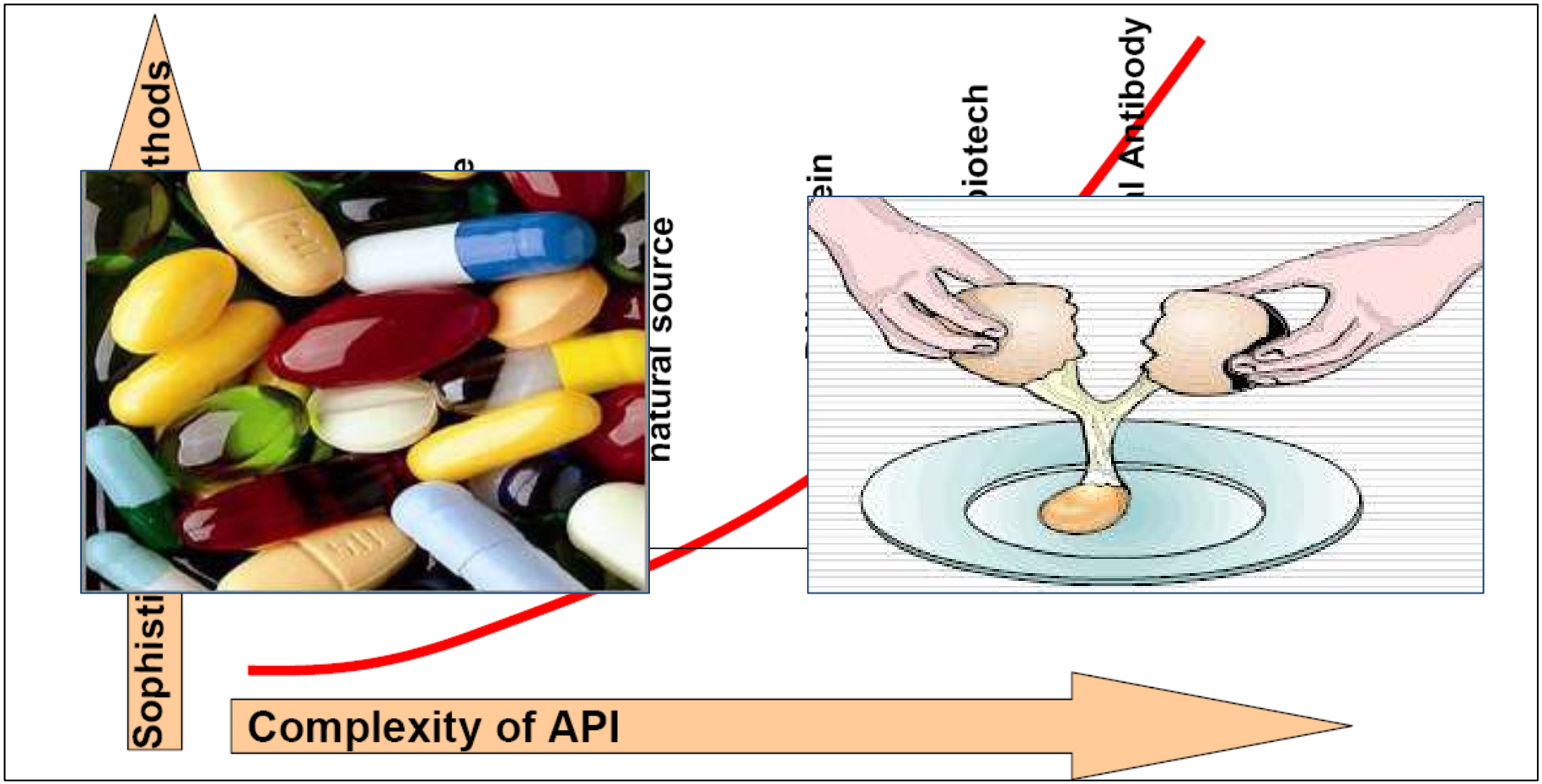
- EU has established a comprehensive regulatory system for biosimilars, comprising an overarching guideline, a guideline on quality issues, a guideline on non-clinical and clinical issues, product specific guideline and class specific guideline
- The US regulatory system is currently under being established. Most likely the US will differentiate between “simple biosimilars” and “interchangeable biosimilars”
- Several countries have established national pathways, partially very close to the EU pathways, partially essentially different to the EU pathway.
- Key issue: Each national / regional system requires that the reference product is a national / regional approved product. This term is currently interpreted as the reference product needs to be sourced from the country / region. Consequently a global development is rather challenging.

MONOCLONAL ANTIBODY BIOSIMILARS

Very complex biologicals



Challenges - Complexity of the Compounds



Dr. Helmut Vigenschow, ratiopharm, 2010

To assess the effects of complex molecules in clinical use additional investigations are necessary.

New challenges ahead (1)

- **Example anti-TNFα antibodies*): How to design a biosimilar development programme?**

- **Licensed indications:**
  - » Rheumatoid arthritis
  - » Adult Crohn's disease
  - » Paediatric Crohn's disease
  - » Ulcerative colitis
  - » Ankylosing spondylitis
  - » Psoriatic arthritis
  - » Psoriasis

Therapeutic equivalence?
Non-inferiority?

All indications?
Extrapolation of efficacy?
Extrapolation of safety??

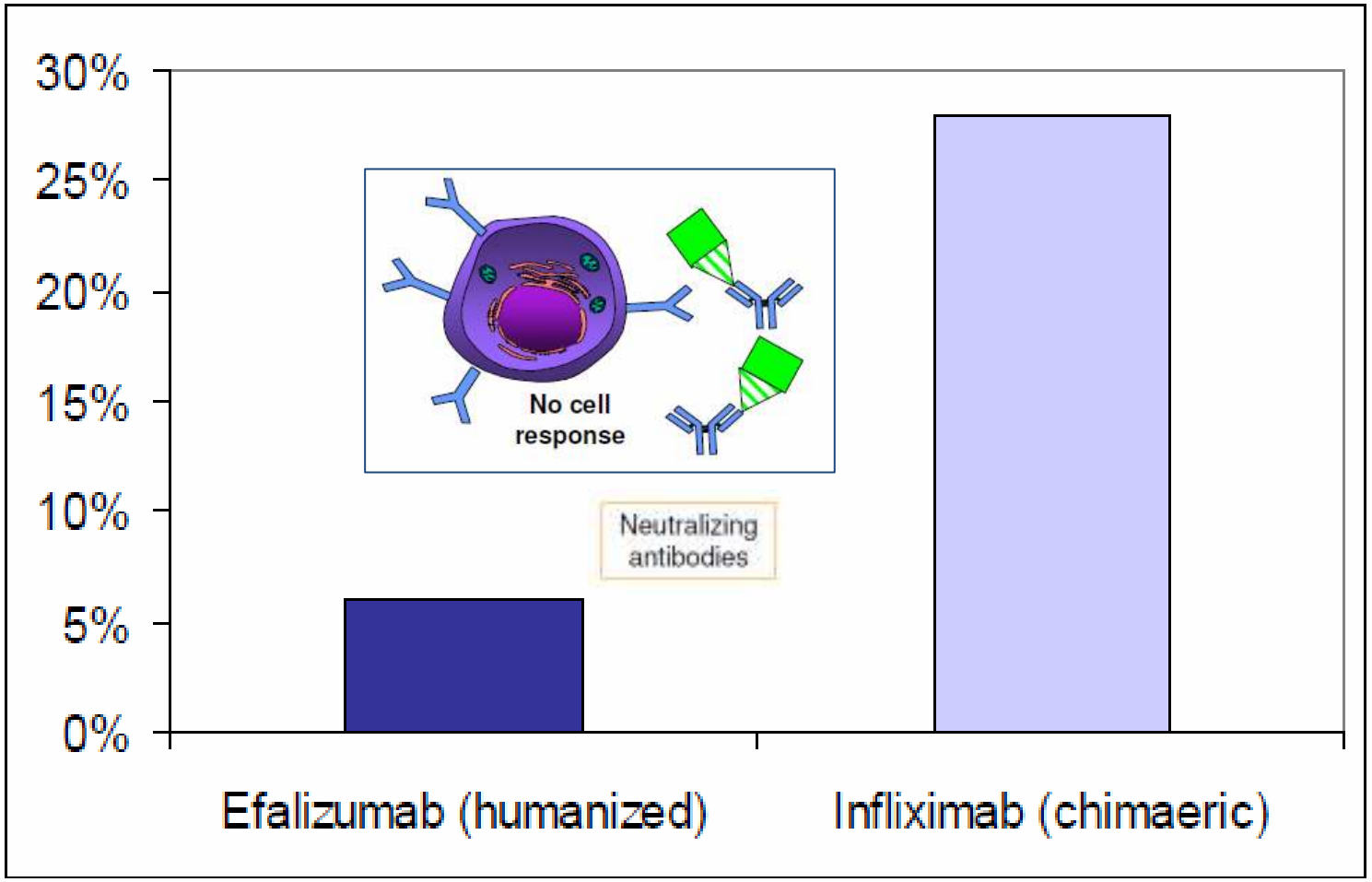
What endpoints?
(Activity or Benefit?)
(Phase II or Phase III endpoints?)

*) example chosen since well suitable to explain regulatory issues

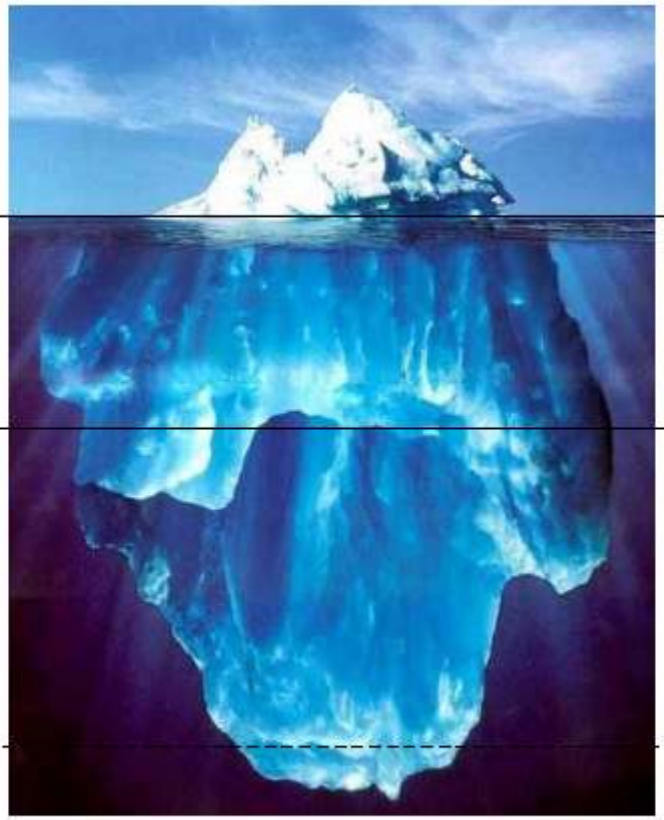
New challenges ahead (2)

Monoclonal antibodies as a paradigm

Immunogenicity related to structure



Biotech Company Know-how mandatory



Release Tests (Specifications)

Extended Characterization
(Process & Product)

Process Control
- Procedures
- Materials
- In-process testing
- Monitoring
- Validation

Unknown
Learned over time – update control strategy

Consistency

Similarity

Comparability

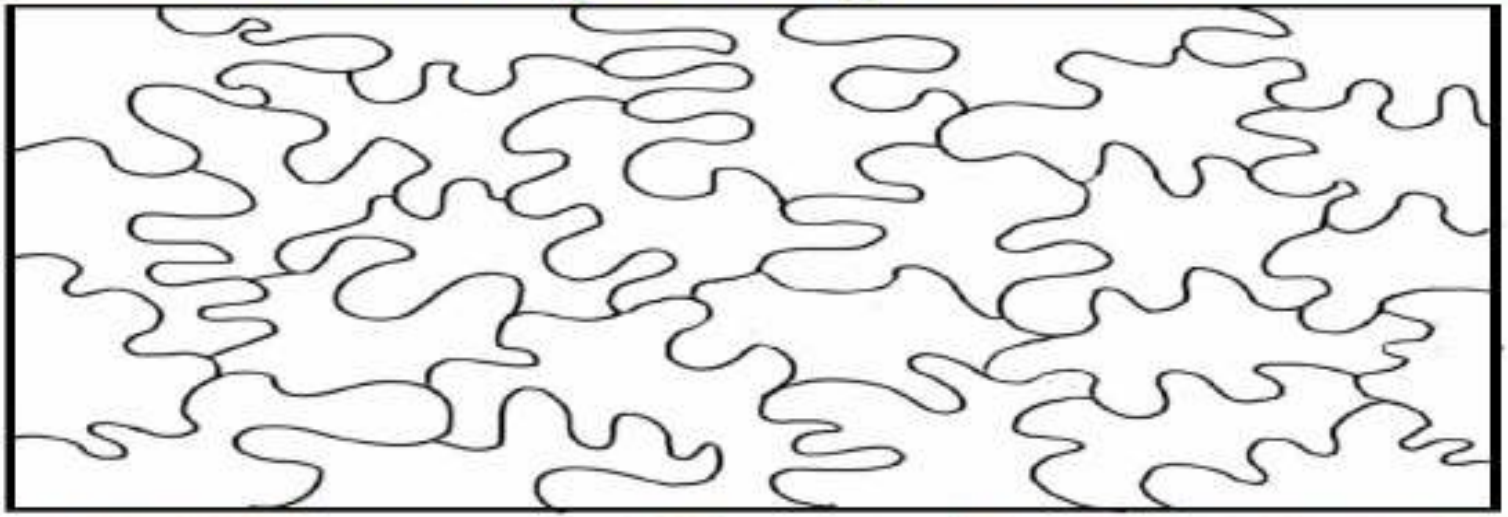
End-Product only

In-Process Controls

Modified from: Koszlowski, S. & Swann, P. (2006) Adv. Drug Delivery Revs. **58**, 707-722

GENERAL ISSUES FOR BIOPHARMACEUTICALS & BIOSIMILARS

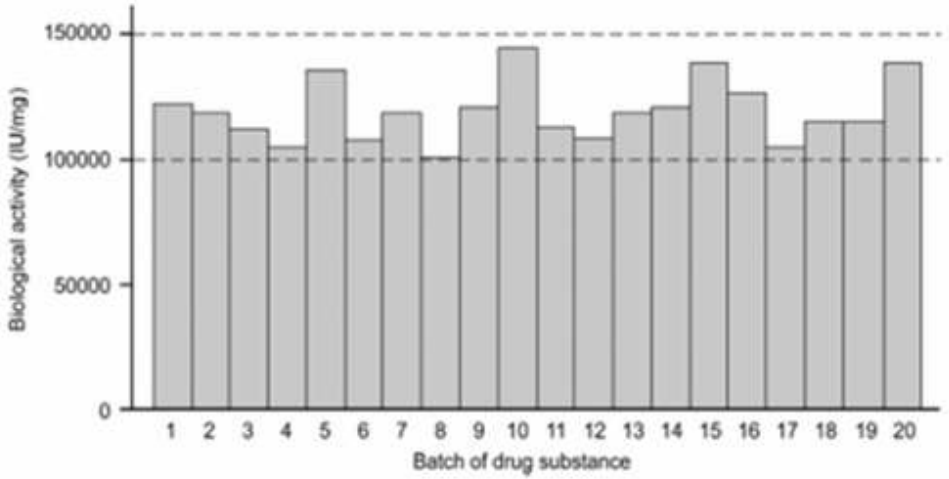
Biosimilar & Reference Biotherapeutic products



Two pieces to the same puzzle

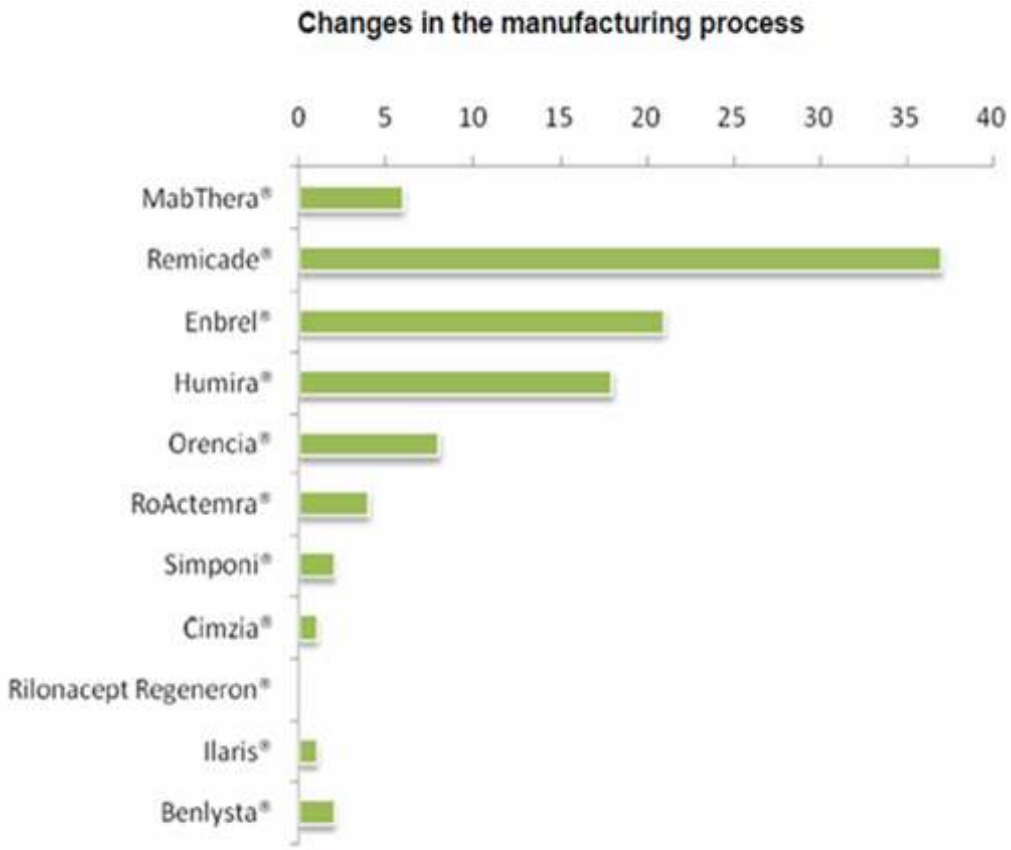
“Similar but not identical”

- „Non-identicality“ is a normal principle in biotechnology.
- No batch of any biological is „identical“ to the others



- The „art“ is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, within current technical and scientific limitations (inherent variability)

Changes of originator biologicals



Schneider CK: Biosimilars in rheumatology: the wind of change. Ann Rheum Dis (in press)
(Data source: EPARs on EMA website)

Highly similar originator products – “similar but nevertheless different”*

“Thus, the **interchangeability of biologics has been routine in the US for almost 15 years**, as every FDA comparability determination results in a "new" postmanufacturing-change version of a **product being treated (by the FDA, the innovator, and physicians) as fully substitutable** with the premanufacturing-change product. Furthermore, the FDA, EMA, and physicians have felt it appropriate to substitute certain non-comparable products that have never even been compared in clinical studies. Thus, as the US enters the world of biosimilars, **we should keep in mind the full extent of interchangeability that has been going on in this space for years.**”

Laura Bush, Editor, BioPharm International, *Biosimilars, Part 3, Interchangeability* (Sept. 2010), digital edition online *at* www.biopharminternational.com

* 9th EGA International Symposium on Biosimilar Medicines
London – April 14-15, 2011

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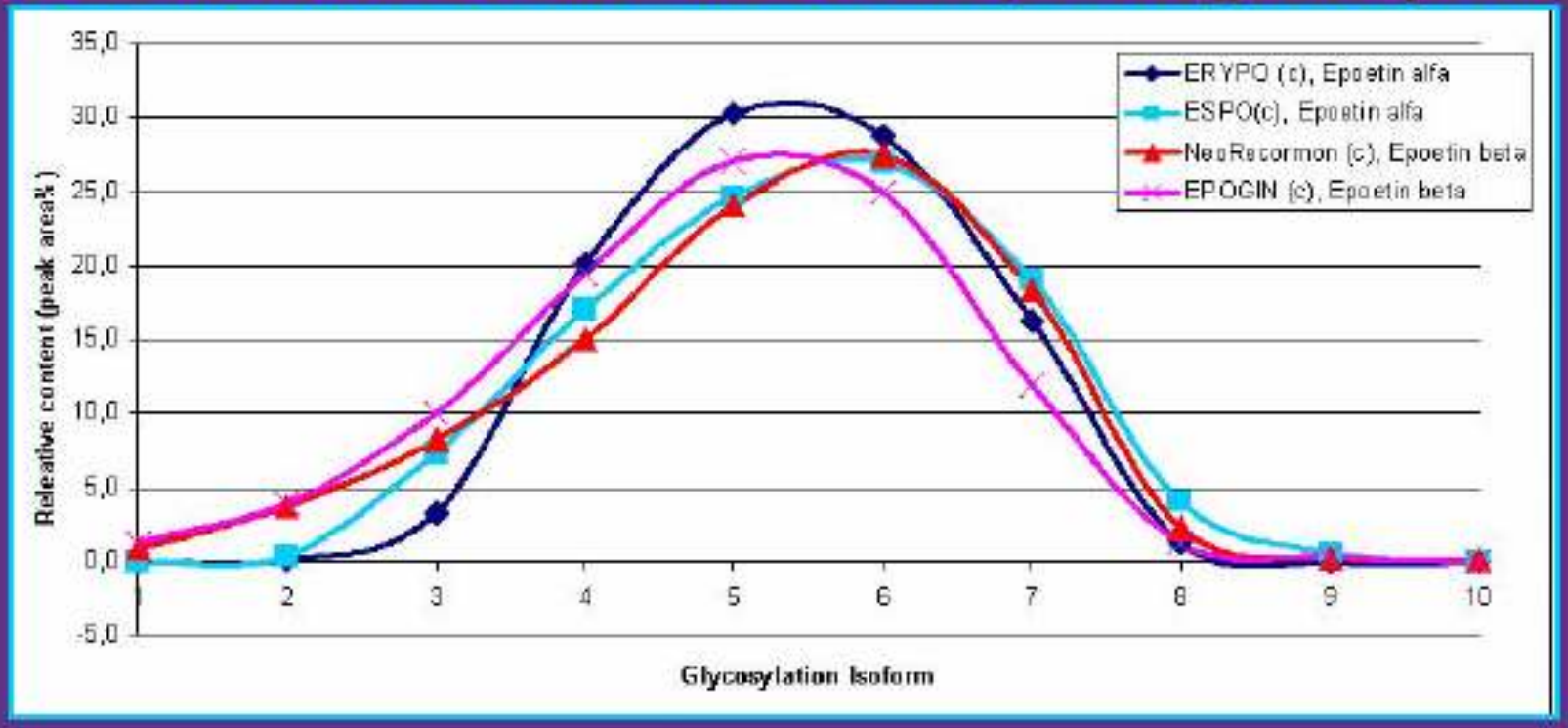
ENGEL & NOVITT, LLP
THE LAW FIRM THAT KNOWS ITS SCIENCE

Epo alfa ≠ Epo alfa

Difference between EPO alfa and EPO alfa (both originator products)



Glycosylation Isoform: potential isoforms in a specific biologic product

Relative content: percent of total biologic product represented by one isoform

Source: Biosimilars Workshop, Suzette Kox , EGA, 2007

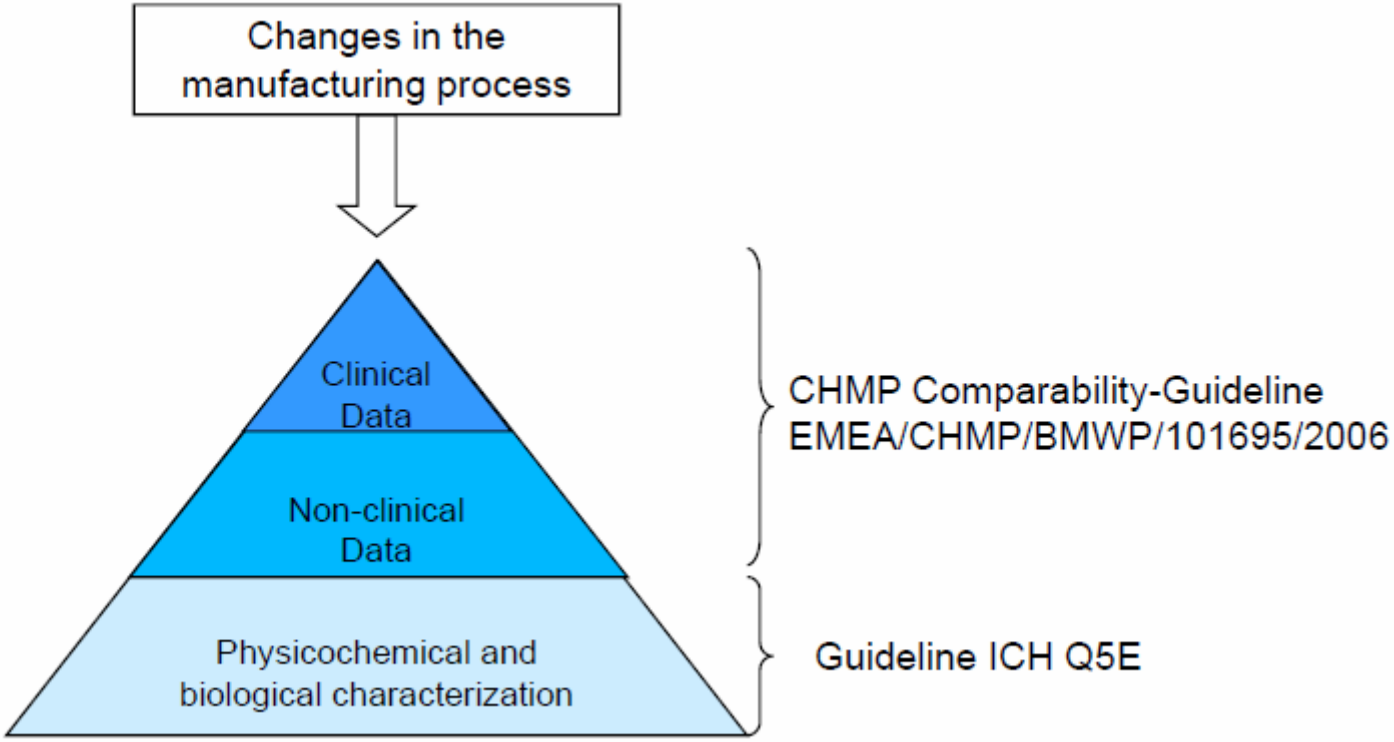
Challenges - Quality of the Reference Product

- Development of a biosimilar is to establish comparability of the follow-on compound and product to a well characterized innovator product.
- Therefore, it is important to fully understand the characteristics and the quality of the reference product.
- Shifts in quality of the reference product heavily influence the development of the biosimilar.

HERCEPTIN® produced at South San Francisco and Vacaville manufacturing facilities on the market simultaneously and fully interchangeable after being shown to be highly similar based upon comparability assessments

ENBREL® produced at all manufacturing facilities on the market simultaneously and fully interchangeable after being shown to be highly similar based upon comparability assessments

From Press Releases of Genentech and Amgen



Example: Genentech outsourced Rituxan to prepare for Avastin approval

Acceptable changes in quality attributes of glycosylated biopharmaceuticals

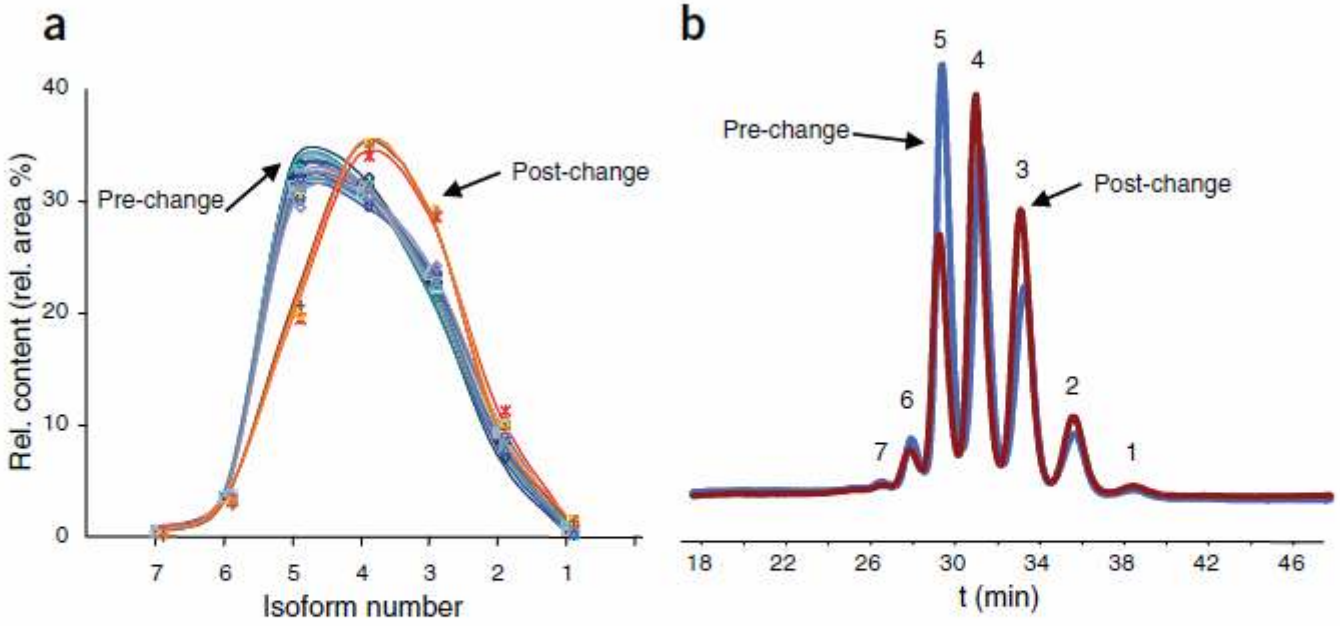
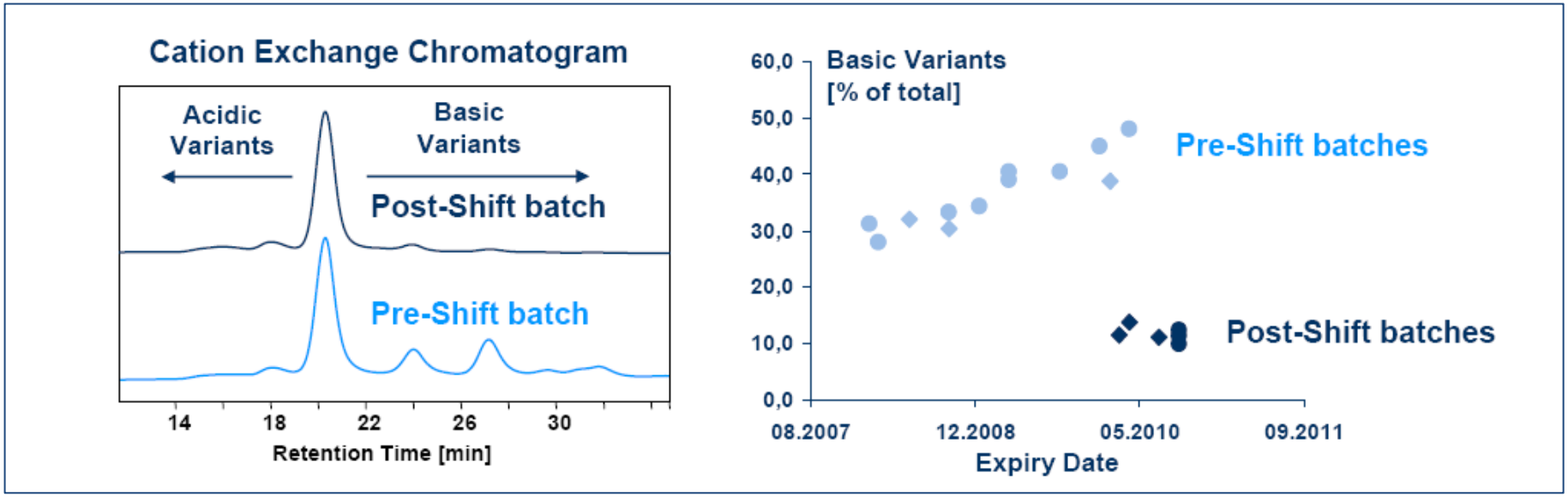


Figure 1 Comparison of the pre- and post-change Aranesp batches measured by capillary zone electrophoresis. (**a**) Relative content of the individual isoforms of the pre-change ($n = 18$) and the post-change ($n = 4$) batches. (**b**) Representative electropherograms; peaks are labeled with the isoform number.

Challenges - The reference product may exhibit changes in quality attributes (1)

- Monitoring batches of MabThera®/Rituxan® (rituximab)

  - Shift in the identity profile measured by cation exchange chromatography



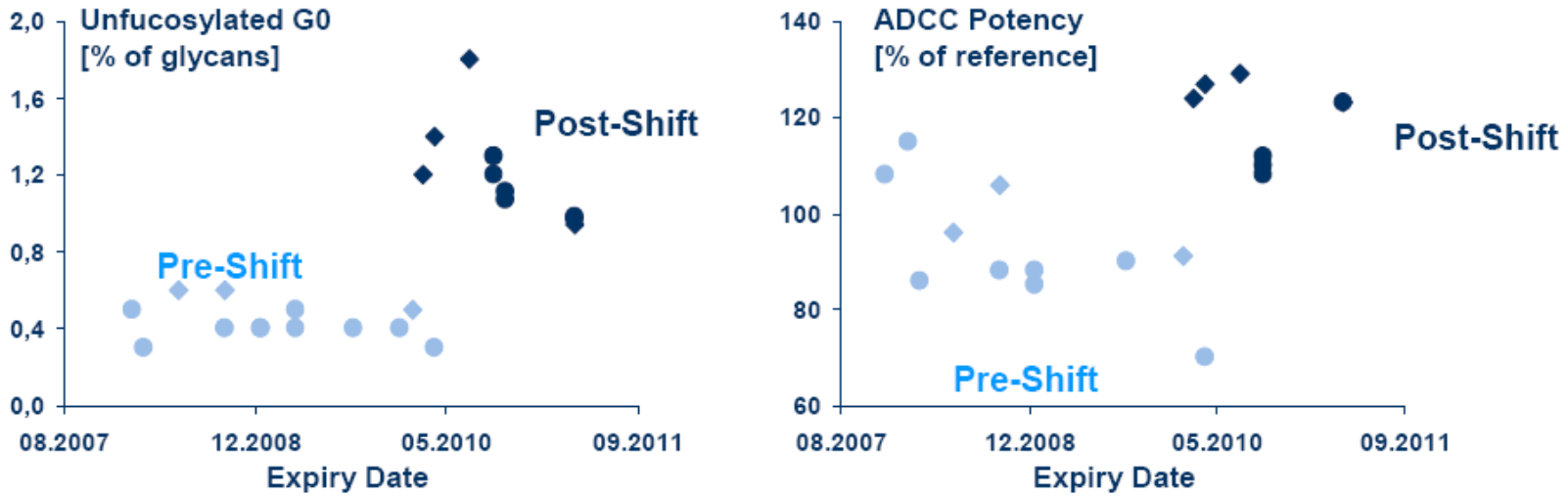
  - Separation of differently charged variants, e.g. basic N-terminal glutamine and C-terminal lysine variants.

Dr. Martin Schiestl, Sandoz, 2010

Challenges - The reference product may exhibit changes in quality attributes (2)

- Monitoring batches of MabThera®/Rituxan® (rituximab)

  - Shift in glycosylation profile and ADCC potency



  - Differences/shift in glycosylation pattern results in different potency in cell-based assays.

Dr. Martin Schiestl, Sandoz, 2010

Worldwide experience with biosimilar development

Mark McCamish[1] and Gillian Woollett[2,*]

[1]Head Global Biopharmaceutical Development; Sandoz Biopharmaceuticals; Sandoz International GmbH; Holzkirchen, Germany; [2]Engel & Novitt, LLP; Washington, DC USA

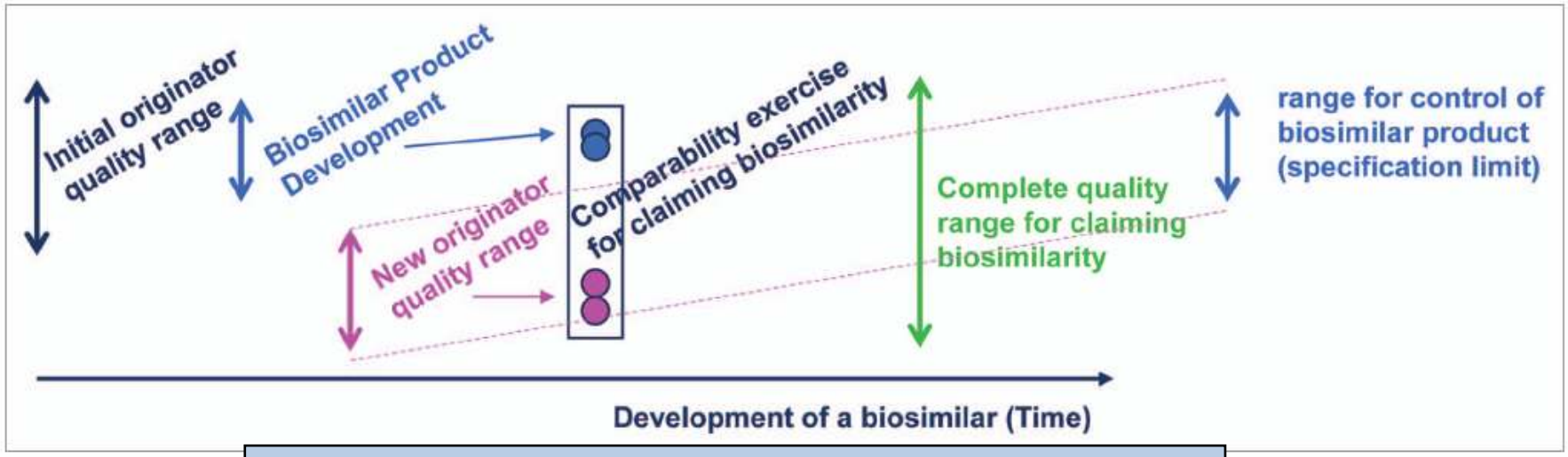


Figure 4. Biosimilarity
product attributes pre
biosimilar candidate. W
a tighter range of cont
alysis of the distribution of
t the design space for their
e biosimilar sponsor will select

A biosimilar can sometimes be more similar to its reference product than a post-change version to a pre-change version of a single product

BIOSIMILARS
CONCERN ABOUT PATIENT SAFETY

Biotherapeutics in the Era of Biosimilars

What Really Matters is Patient Safety

Declerck P.J.; Drug Safety
2007; 30 (12): 1087-1092

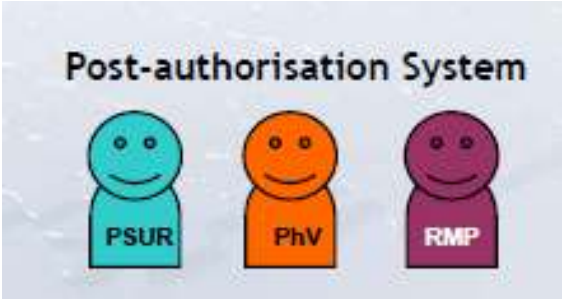
Almost same patient numbers as for Neulasta® in clinical development programs

	Neulasta®		Ratiograstim® TevaGrastim®	
Clinical phase	Indication	Subjects/patients	Indication	Subjects/patients
Phase I	---	32	---	56
	---	41	---	144
Phase I/II	NSCLC/other thoracic tumours	94		
Phase II	Breast cancer	154		
	HL/NHL	66		
	NHL	50		
Phase III	Breast cancer	157	Breast cancer	348
	Breast cancer	310	Lung cancer	240
			NHL	92
	Total	904	Total	880

[1]EMEA European Medicines Agency. European Public Assessment Report (EPAR) Neulasta®
[2]EMEA European Medicines Agency. European Public Assessment Report (EPAR) Ratiograstim®

Patient safety

- **PhV plan**
  - Required for all new drug applications including biosimilars!
  - To be submitted at time of MA application
  - RMP of the reference product usually „inherited“
- **PhV system:** must be functioning at time of approval
- **Competent authorities**: to assess PhV plan, PhV system and compliance of the MAH and ensure traceability



PSURs (**P**eriodic **S**afety **U**pdate **R**eports)

(see *ICH guideline on pharmacovigilance planning (E2E, 2004)* and *EU PhV guidelines, www.emea.europa.eu/htms/human/phv/phvwp.htm*)

DO BIOSIMILARS INCREASE ACCESS TO BIOLOGICAL DRUGS?

THE FUTURE OF BIOSIMILARS

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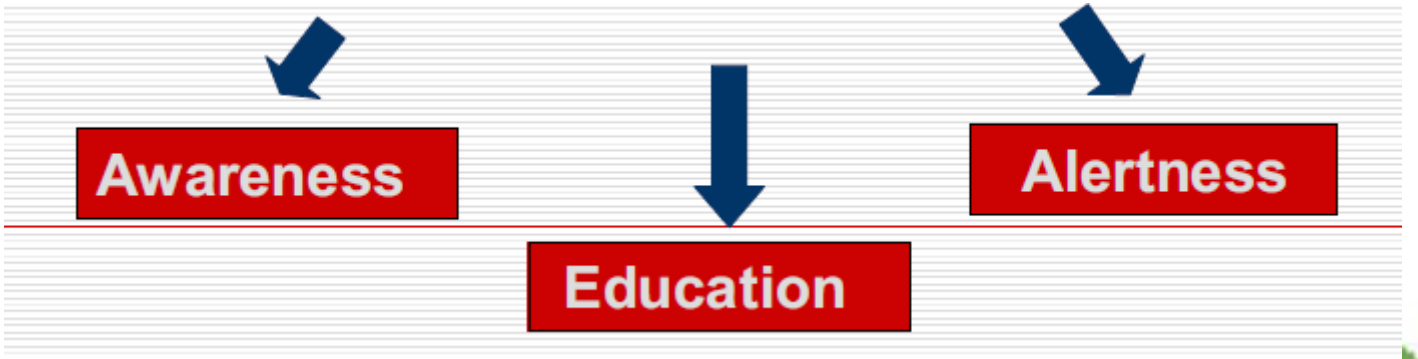
- Biological market relatively small but rapidly growing
- Pharmemerging markets leading growth
- Biosimilar market continues to double and now approaches $200m worldwide
- Success of Biosimilars variable
  - Regional impact: Germany greater than France
  - Product Impact: Epoetin greater than Growth Hormone
- Plenty of opportunity ahead

Biological/Biotechnological and Biosimilars' Market: the Global Outlook *Douglas M. Long, IMS Health, USA*

Challenges – Convince users that biosimilars are with no compromise on quality, efficacy and safety



The concept of biosimilarity is evolving with science and experience…



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Thank you for your attention