Laureate Biopharmaceutical Services

Scientific Advisory Board meeting

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Biosimilars and Biobetters

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Outline

- Biosimilars and biobetters
  - Opportunity
- Regulatory developments
  - US regulatory pathway
- Challenges for biosimilars
  - Alternative technologies vs. improved production efficiency
  - Analytical characterization
    - Sandoz' experience
- Conclusions

Biosimilars vs. biobetters

- Biosimilar
  - Recombinant therapeutic that resembles but is not identical to the original product. The biosimilar must closely resemble the reference product, e.g., *safety, purity and potency do not show clinically meaningful differences* from reference product.
  - Potential for improved *process*
- Biobetter
  - Enhanced version of the innovator product. For a biobetter, *safety, purity and potency <u>will</u> show clinically meaningful differences* from the reference product.
  - Potential for improved *product*

The opportunity for biosimilars

- US healthcare spending
  - Projected to be 20% ($4,000B) of US domestic GDP ($20,000B) by 2015
    - Of this, prescription pharmaceuticals will be 10% (proejcted $446B)
- Biologics
  - For 2010, 14% ($43B) of pharmaceutical spending ($307B)
  - Certain to rise in the future
    - 33% of all drugs in development

The opportunity for biosimilars (cont'd.)

IMS Health 2011 report

- By 2015, spending on biosimilars will exceed $2 billion annually, or about 1% of total global spending on biologicals.
- This growth in biosimilars will be driven mainly by patent expiries coming in the next 5 years, of which there are many. Between 2011 and 2015 a total of $17 billion worth of sales in the US alone will lose patent protection, presenting a huge opportunity for biosimilar manufacturers to gain market share.

US regulatory paths
Historical perspective

- Four pathways to drug approval
  - NDA 505(b)(1) path is for new drugs
  - ANDA path is for generics
  - NDA 505(b)(2) path covers reformulations and combinations of existing drugs
  - BLA path is for new biologics
- To date, FDA approvals for "generic" biologics have been under 505(b)(2)
  - Novo Nordisk's recombinant human glucagon GlucaGen in 1998 was first
  - Six biologics approved by FDA to date

Currently available biosimilars worldwide 2010

Company	Drug class	Biosimilar	Approval/Launch (year)	Country
Biopartners	rhGH	Valtropin	2006/07	EU/US[1]
Baxter	rhHyaluronidase	Hylenex	2005	US[1]
CT Arzneimittel	rhG-CSF	Biograstim	2008	EU
Dr. Reddy's Laboratories	rhG-CSF	Grafeek	-	India
	ch anti-CD20 mAb	Reditux	2007	India
	rhEPO	Cresp	2010	India
Hexal	rhEPO	Epotin alfa Hexal	2007	EU
	rhG-CSF	Filgrastim Hexal	2009	EU
Hospira	rhEPO	Retacrit	2007	EU
	rhG-CSF	Nivestim	2010	EU
Medice	rhEPO	Abseamed	2007	EU

[1] FDA approval via 505(b)(2)

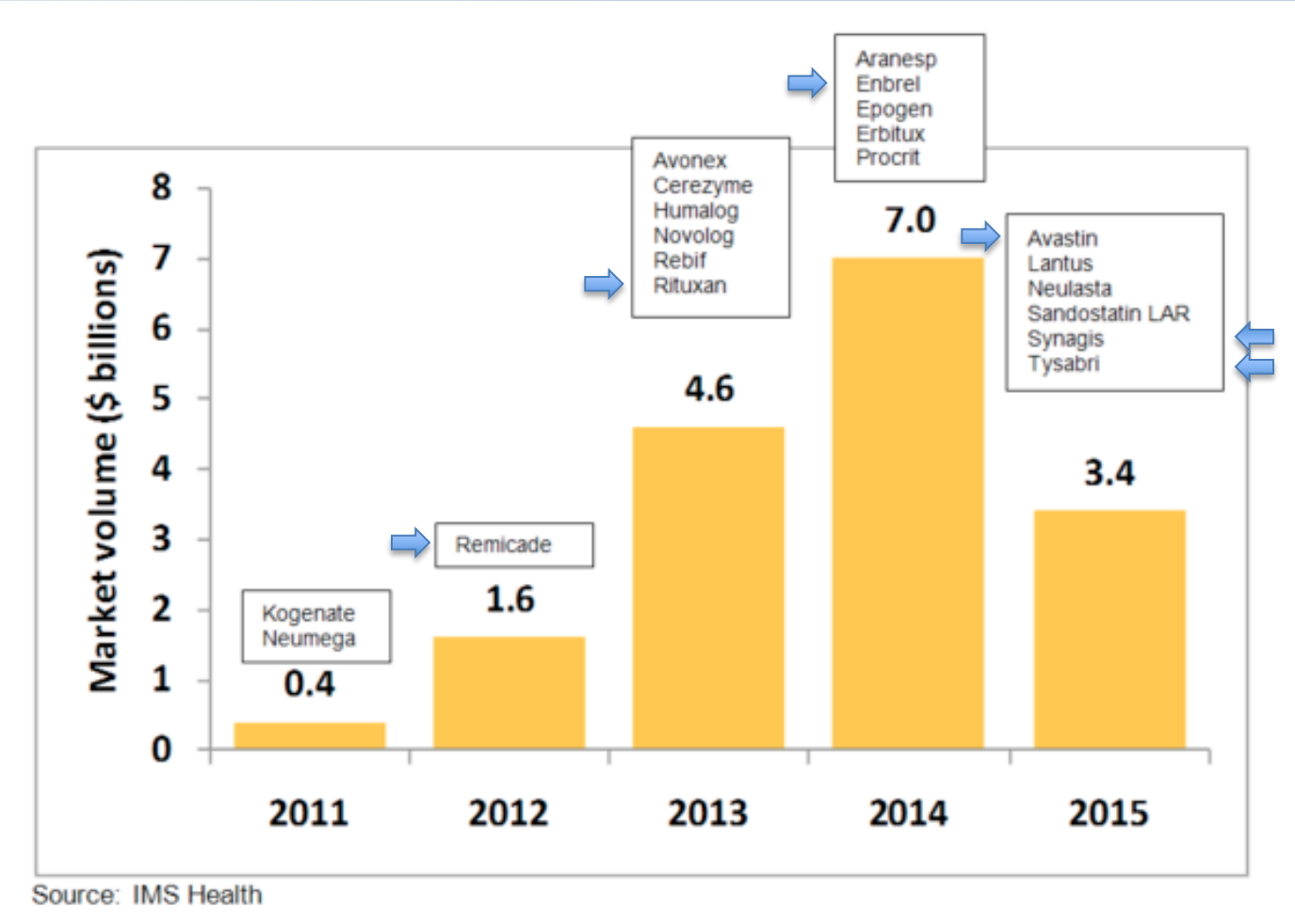
Currently available biosimilars (cont'd.)

Company	Drug class	Biosimilar	Approval/Launch (year)	Country
Novo Nordisk	rGlucagon	GlucaGen	1998	US[1]
Ratiopharm	rhG-CSF	Ratiograstim	2008-09	EU
	rhG-CSF	Filgrastim ratiopharm	2008	EU
Sandoz	rhGH	Omnitrope	2004/06/09	Australia/Eu&US[1] /Japan&Canada
	rhEPO	Binocrit	2007	EU
	rhG-CSF	Zarzio	2009	EU
Stada	rhEPO	Silapo	2007	EU
Teva/Ferring	rhGH	Teva-tropin	2005	US[1]
Teva	rhG-CSF	Tevagrastim	2008	EU
Upsher Smith	rSalmon calcitonin	Fortical	2005	US[1]

[1] FDA approval via 505(b)(2)

Source: Cheng Hou *et al., J. Chem. Technol. Biotechnol.* **86**, 895-904 (2011)

US patent expiries 2011-15 by market volume
Based on 2007 US retail sales



mAbs and Fc fusion proteins

Enbrel: Nov 2011 US patent office action extends US patent protection to 2028

US regulatory pathway
The challenge

- Biologics are structurally much more complex and heterogeneous than small organic molecules
- How to provide sufficient analytics to completely define something that is essentially "acceptably heterogeneous"
  - Measurement of bioequivalence
  - Length of product exclusivity

US regulatory pathway

- Patient Protection and Affordable Care Act
  - Signed 23 Mar 2010
  - Within this legislation is the Biologics Price Competition and Innovation Act of 2009 (BIPCA) which creates abbreviated approval pathway [Section 351(k)] for biologics
  - Key provisions
    - 12 years exclusivity from the date reference material is first produced (irrespective of patent landscape) for innovator companies
    - No biosimilar submissions to FDA within first four years
    - Two avenues for approval
      - "Highly similar" if it closely resembles the reference product and if safety, purity and potency show no clinically meaningful difference
      - "Interchangeable" if it is expected to produce the same clinical outcome as reference product in a given patient
      - Unclear how these will be interpreted

FDA guidance

- Three guidances were issued by FDA on 9 Feb 2012
  - Scientific considerations
  - Quality considerations
  - Biosimilars: Questions and answers

Reference: Koslowski *et al.*, Developing the nation's biosimilars program. *NEJM* **365**, 385-388 (2011)

Draft guidance
Scientific considerations

- Biosimilar application for licensure will be submitted as "351k application"
- FDA will take a risk-based "totality-of-the-evidence" approach to assess data as evidence of biosimilarity to originator product

Draft guidance
Quality considerations

- Overview of analytical factors to be considered in submitting a 351k application
- Emphasizes importance of extensive analytical, physicochemical and biological characterization in demonstrating biosimilarity
  - Seems to allow for minor differences in clinically inactive components, e.g., new formulation and container/closure possible

Draft guidance
Questions and answers

- Addresses anticipated questions in biosimilar product development, e.g.
  - How to request meetings with FDA?
  - How to address differences in formulation from reference product?
  - How to request exclusivity?

Challenges for biosimilars

Strategies and Sandoz' experience

Strategy
Alternative technologies

- Opportunity to move away from traditional CHO-based cell culture
  - Transgenic plants and animals
    - Atryn® (rh antithrombin) from GTC Biotherapeutics, approved by FDA in 2009
    - GTC is focused on follow-on products with potentially improved ADCC
  - Glycoengineered yeast *(Pichia pastoris)*
    - Merck (GlycoFi acquired 2006)
    - Technology capable of eliminating microhetergeneity of glycoforms in glycoproteins
  - PER.C6
    - Capable of very high density growth (16E7 cells/mL)
    - Enables lower culture volume and single use bioreactor technology (e.g., ≤2 kL)
- Benefit: improved cost and product quality
- Challenge: product comparability may be more difficult to justify
  - Contaminant profile
  - Product variants

Strategy
Improved production efficiency

- Closely match innovator's expression system
- Cut costs through manufacturing efficiency gains and reduced licensing and patent encumbrances
  - Increased production titer
  - Single use bioreactors
  - Simplified downstream process = increased robustness, higher overall process yield
  - Shorter process = higher productivity/yr
- New stable cell line required
  - DHFR and GS as selectable markers in CHO, NS0
    - While original patents now expired, patents on improvements can make use of "state of the art" technology proprietary
  - PDL uses non-proprietary selection system
    - Xanthine-guanosine phosphoribosyl transferase *(gpt)* from *E. coli* and cholesterol-independent NS0
    - 20-60 pg/cell-day reported

Analytical characterization
Acceptable changes in quality attributes

Schiestl *et al. Nat. Biotechnol.* **29**, 310-312 (2011)

- Quality variation in innovator products
  - Aranesp® (engineered analog of hEPO)
  - Rituxan®/Mabthera® (ch anti CD-20 mAb)
  - Enbrel® (TNFR Fc fusion protein)
  - All glycoproteins in which glycan structure impacts function
- Market-sourced
  - EU 2007-2010 (Aranesp, Rituxan/Mabthera)
  - EU/US 2007-2010 (Enbrel)
- Causes of quality changes in marketed products
  - Batch-to-batch variability
  - Process drift
  - Manufacturing process changes

Analysis of Aranesp® commercial lots
Charge isoforms by CZE

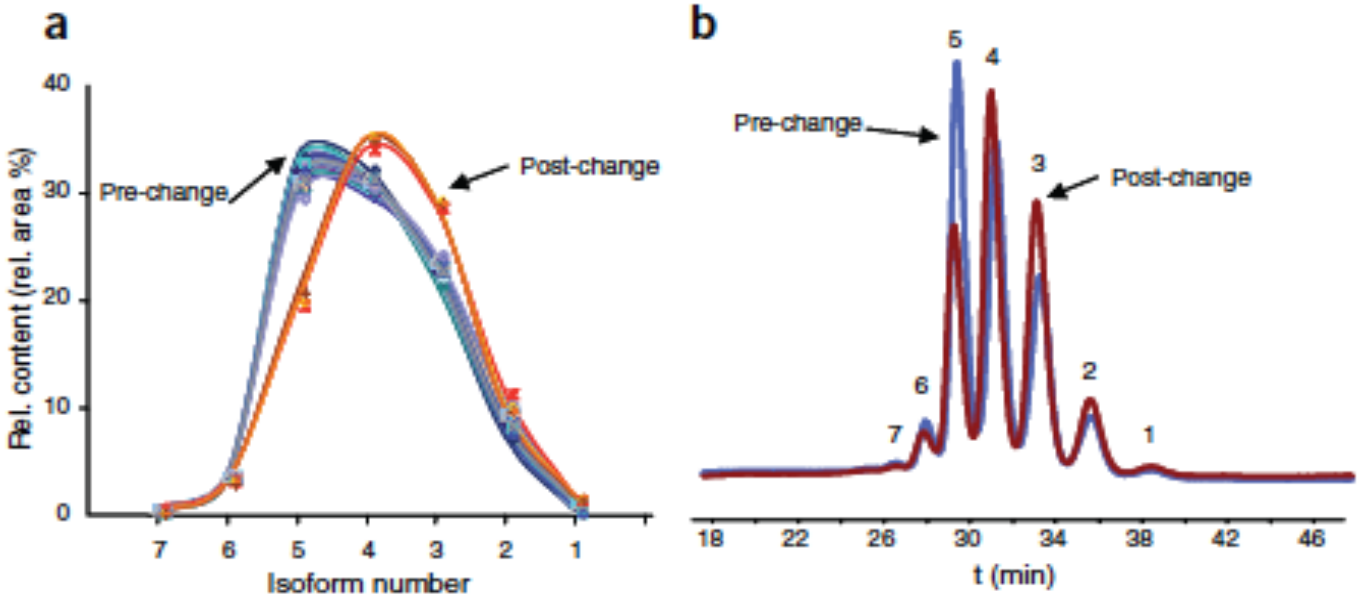


Figure 1 Comparison of the pre- and post-change Aranesp batches measured by capillary zone electrophoresis. (**a**) Relative content of the individual isoforms of the pre-change ($n = 18$) and the post-change ($n = 4$) batches. (**b**) Representative electropherograms; peaks are labeled with the isoform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

(a-b) 22 batches tested

High batch-to-batch consistency

Abrupt shift suggests manufacturing process change (2008, EMA)

Analysis of Rituxan®/Mabthera® commercial lots CEX, ADCC, glycoforms

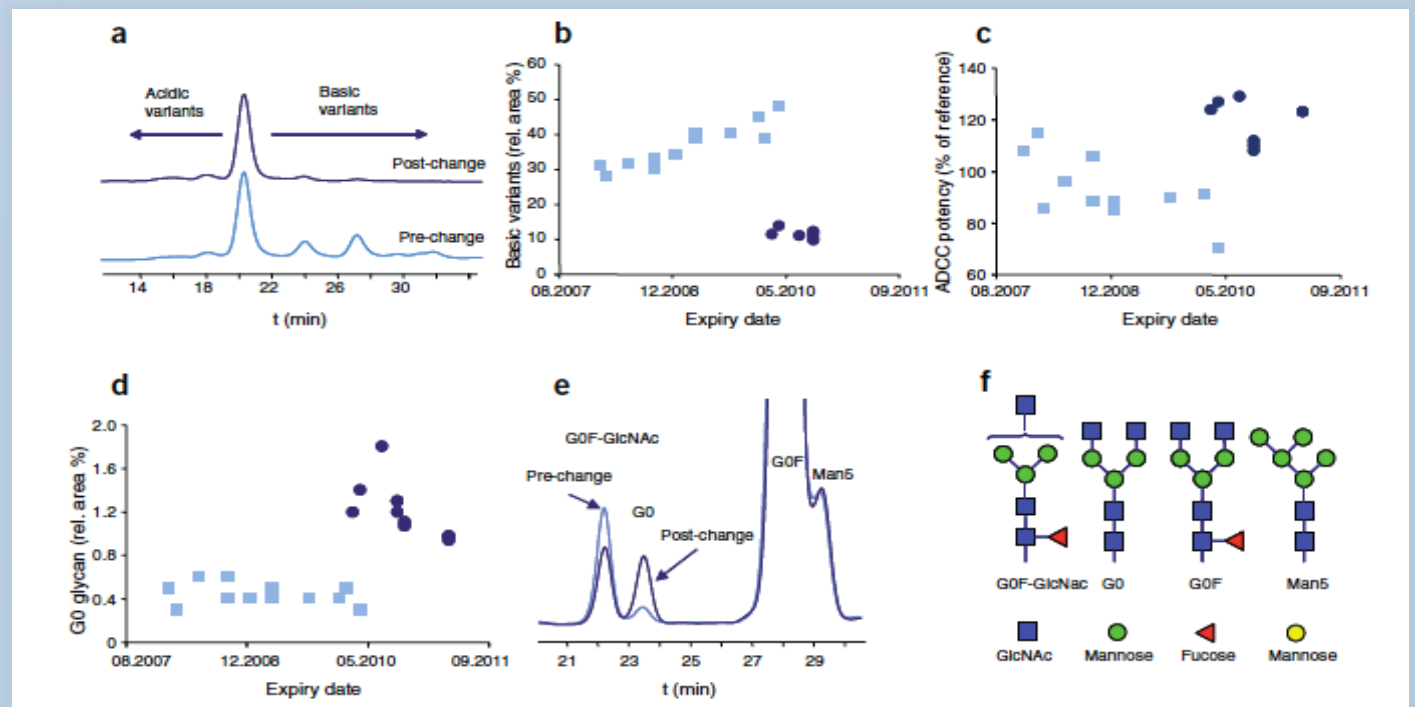


Figure 2 Comparison of the different pre- and post-change batches of Rituxan/Mabthera. (**a**) Exemplary CEX chromatograms. (**b**) Amount of basic variants of the pre-change ($n = 12$) and post-change ($n = 6$) batches as measured by CEX. (**c**) ADCC potency of the pre-change ($n = 11$) and post-change ($n = 8$) batches. (**d**) Relative amount of the G0 glycan of the pre-change ($n = 13$) and post-change ($n = 11$) batches. (**e**) Exemplary glycan mapping chromatograms. (**f**) Glycan legend.

(b) 18, (c) 19, (d) 24 batches tested

Abrupt shift suggests manufacturing process change

- Decrease in C-terminal lys and N-terminal gln (CEX)
- Increase in G0/G0F

Analysis of Enbrel® commercial lots
CEX, glycoforms

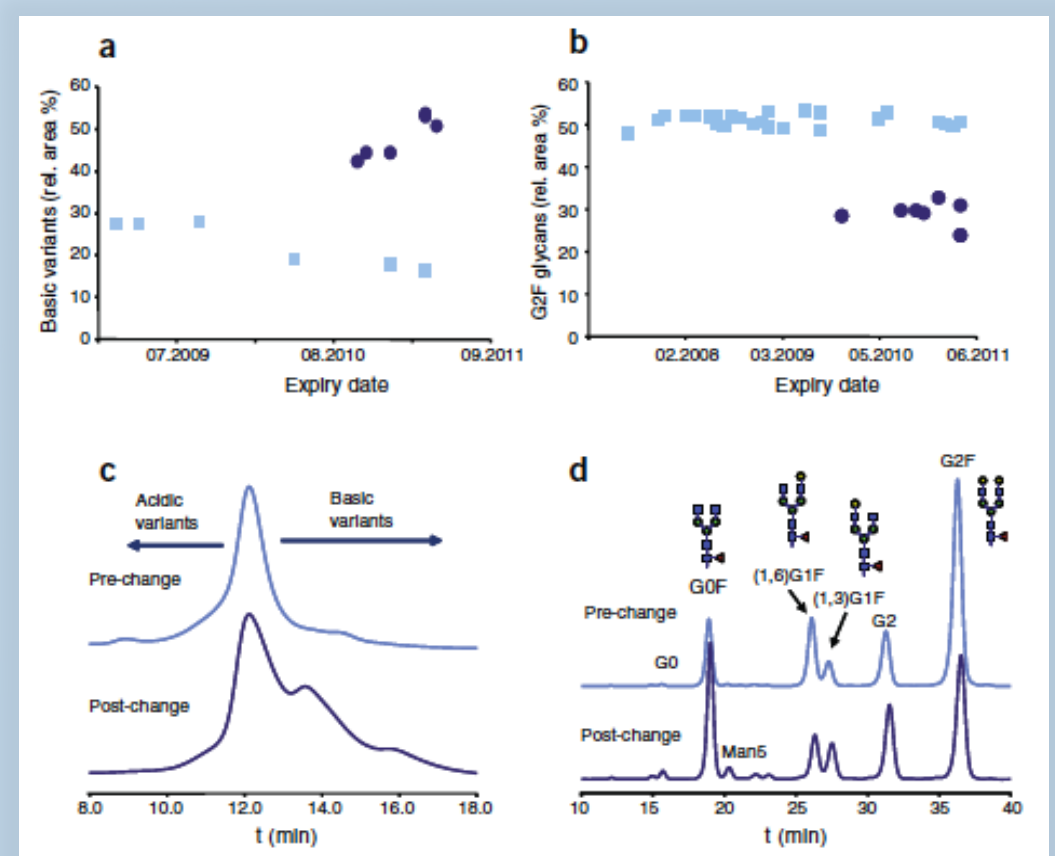


Figure 3 Comparison of the different pre- and post-change batches of Enbrel. (**a**) Relative amounts of basic variants of the pre-change ($n = 6$) and the post-change ($n = 6$) batches as measured by CEX. (**b**) Relative amount of the G2F glycan of the pre-change ($n = 25$) and the post-change ($n = 9$) batches. (**c**) Exemplary CEX chromatograms. (**d**) Exemplary glycan mapping chromatograms.

(a) 12, (b) 34 batches tested

Abrupt shift in 2010 suggests manufacturing process change

- Increase in basic variants
- Decrease in G2F

Summary
Sandoz' experience

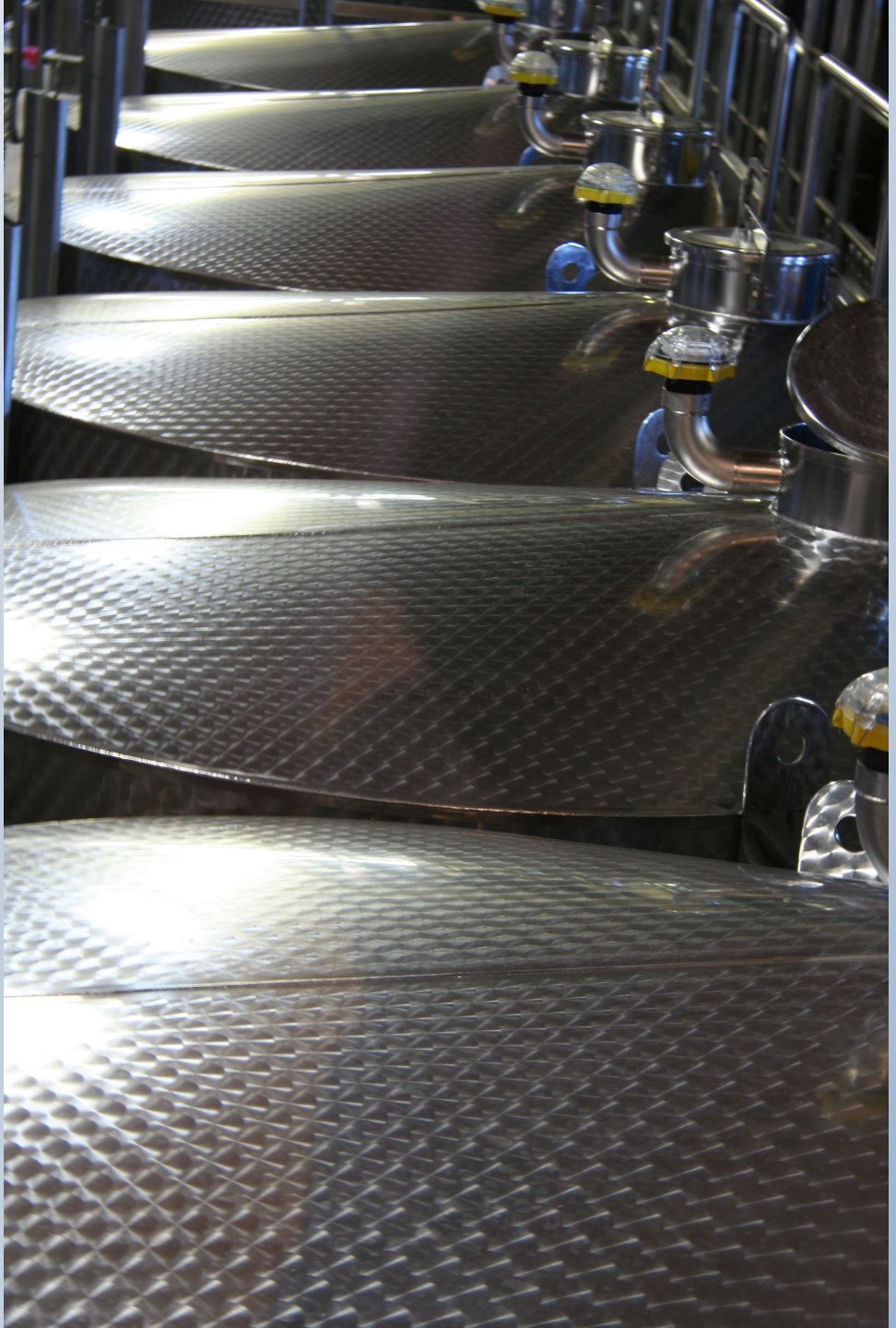
- Substantial alterations in glycan profiles for all tested products
- For **Aranesp**, changes in charge isoforms (sialylation?)
- For **Rituxan/Mabthera**, variation in ADCC among batches (G0 vs. G0F)
- For **Rituxan/Mabthera** and **Enbrel**, changes in basic variants (C- term lys; N-term gln)
- Abrupt shifts suggest manufacturing process changes
- Magnitude of quality differences observed represents acceptable variation for innovator product under licensed product label

Reference: Schiestl *et al. Nat. Biotechnol.* **29**, 310-312 (2011)

Conclusions

- A biosimilar shows no clinically meaningful difference in safety, purity and potency compared to the innovator product
  - Potential to improve the *process* for better production efficiency and lower cost
- With US regulatory pathway proposed, biosimilars going forward will be considered for approval by FDA under 351(k)
- Biobetters—enhanced versions of the innovator product—will remain under BLA
- To guide biosimilar development, Sandoz' experience indicates that innovator product variability should be considered to establish acceptable ranges for critical product quality attributes


ANGOLA
ZAMBIA
NORTH LUANGWA N.P.
SOUTH LUANGWA N.P.
LOWER ZAMBEZI N.P.
MALAWI
Lilongwe
KAFUE N.P.
Lusaka
MANA POOLS N.P.
Victoria Falls
Harare
Okavango Delta
CHOBE
MOREMI
HWANGE N.P.
ZIMBABWE
GORONGOSA N.P.
ETOSHA N.P.
SKELETON COAST N.P.
NAMIBIA
Maun
BOTSWANA
MOZAMBIQUE
TULI CIRCLE
Walvis Bay
Windhoek
Gaborone
KRUGER N.P.
NAMIB NAUKLUFT N.P.
KGALAGADI T.P.
SABI SAND
Sun City
Pretoria
Maputo
Johannesburg
SWAZILAND
FISH RIVER CANYON N.P.
SOUTH AFRICA
GTR ST LUCIA WETLAND
RICHTERSVELD N.P.
LESOTHO
Durban
Atlantic Ocean
KAROO N.P.
SHAMWARI
KWANDWE
ADDO N.P.
East London
Indian Ocean
Port Elizabeth
Cape Town
Knysna
George

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