



SANDOZ

Biopharmaceuticals

a Novartis company



Effect of Naming on Competition and Innovation

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Washington, DC

10 December 2013

Agenda

1 **Development of Biosimilars: Background**

2 Impact of Naming on Biosimilars

Access to biologics is a growing issue around the world



Almost one-quarter of 46 European countries do not provide access to biologics for arthritis¹



Cancer patients twice as likely as general population to go bankrupt a year after their diagnosis²



Canadian children with juvenile idiopathic arthritis may not receive "standard" care because pediatric coverage for biologic drugs is limited and inconsistent³



Only 50% of severe RA patients receive biologics across EU5, US and Japan⁴

¹ EULAR 2012: Annual Congress of the European League Against Rheumatism

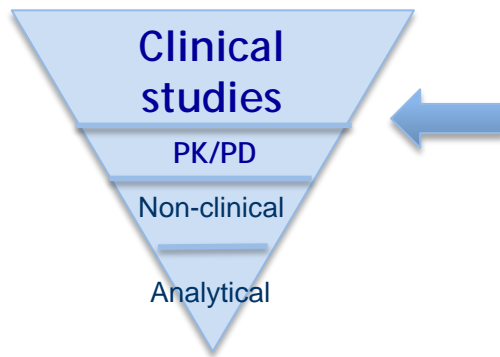
² Cancer diagnosis as a risk factor for personal bankruptcy, ASCO 2011

³ Access to biologic therapies in Canada for children with juvenile idiopathic arthritis. J.Rheum, September 2012

⁴ Stakeholder Insight: Rheumatoid Arthritis DMHC2592/ Published 09/2010

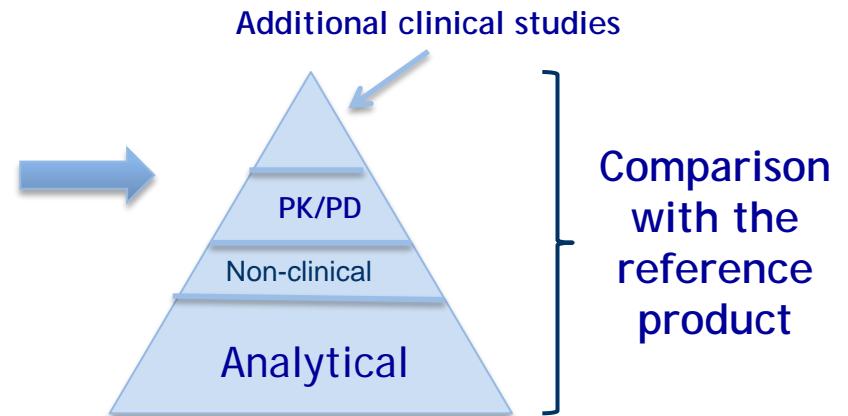
Biosimilar Development Turns the World Upside Down

Originator development



The world turned upside down....

Biosimilar development

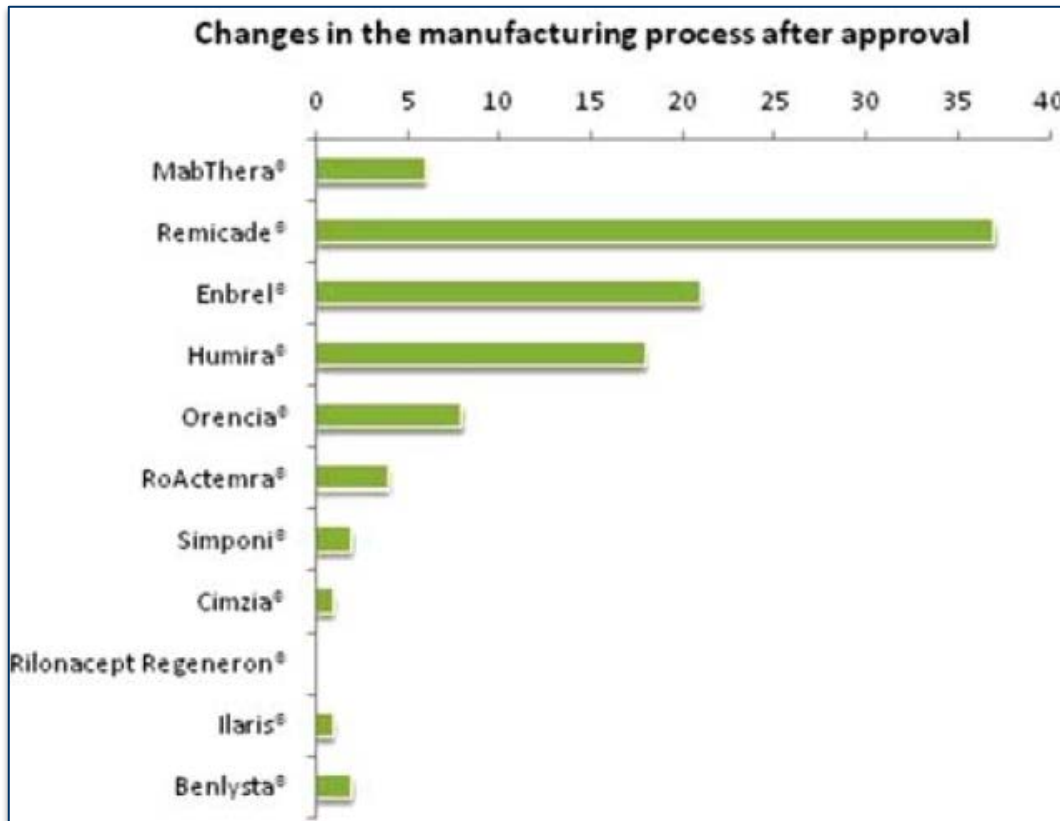


- **Several trials >1000 pts , replication needed**
- **Primary endpoint: ACR20 – 6 m min**
- **Secondary: ACR50, ACR70, DAS28, Remission, HAQ**
- **Structural damage (6-12 mon with 12 mon F/U)**

- **One study 200-600 pts**
- **Primary endpoint at 3-6 months: DAS28**
- **Secondary: averaged score over time, ACR20, 50, etc**
- **Immunogenicity key**

Figure inspired by Judith Macdonald, APEC conference, Seoul Sept 2013

EMA regulator C. Schneider documented extent of manufacturing changes



- Changes include e.g.**
- Change in the supplier of a cell culture media
 - New purification methods
 - New manufacturing sites

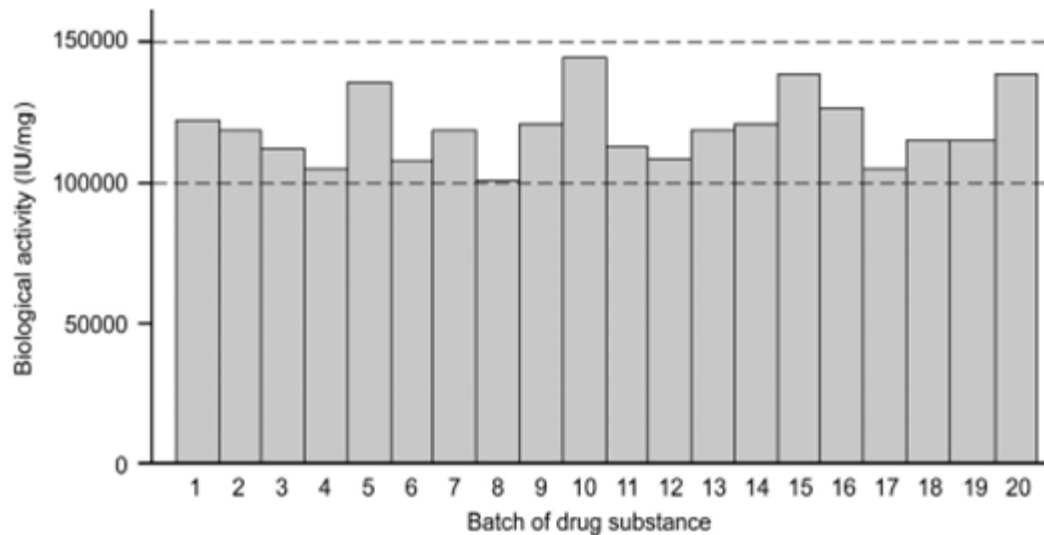
Source: C Schneider, Ann Rheum Dis March 2013 Vol 72 No 3

Number of changes in the manufacturing process after approval for monoclonal antibodies (mAbs)/cepts authorised in rheumatological indications (A). Products in order of date of approval in Europe (from MabThera, authorised on 2 June 1998 for the initial authorisation in oncology, to Benlysta, licensed on 13 July 2011)

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“Similar but not identical”

- „Non-identity“ 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)

EMA regulators say clinicians shouldn't be concerned about "Similar, but not identical"

"..the "similar but not identical" paradigm of biosimilars appears to fuel uncertainties about [biosimilars]. However, this principle is not new to biotechnology; even consecutive batches of originator products are never identical to each other...this is normal and is why adequate controls on batch consistency have to be imposed."

Weise et al. Blood 2012; 120: 5111-5117



Revised EMA Q&A further validates principles of biosimilar development



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 September 2012
EMA/837805/2011

Questions and answers

Questions and answers on biosimilar medicines (similar biological medicinal products)

*“The **active substance** of a biosimilar and its reference medicine is **essentially the same biological substance**, though there may be minor differences due to their complex nature and production methods. **Like the reference medicine, the biosimilar has a degree of natural variability**. When approved, its variability and any differences between it and its reference medicine **will have been shown not to affect safety or effectiveness.**”*

Recent approval of biosimilar infliximab in Europe

EU summary of product characteristics (SMPC Annex I, 2013)

1. What Remsima is and what it is used for

Remsima contains the active substance called infliximab. Infliximab is a type of protein of human and mouse origin.

Remsima belongs to a group of medicines called “TNF blockers”. It is used in adults for the following inflammatory diseases:

- Rheumatoid arthritis
- Psoriatic arthritis
- Ankylosing spondylitis (Bechterew’s disease)
- Psoriasis

Remsima is also used in adults and children 6 years of age or older for:

- Crohn’s disease
- Ulcerative colitis

Remsima works by blocking the action of a protein called ‘tumour necrosis factor alphas’

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The biosimilar concept works

- Sandoz marketed biosimilars:
 - >100.000.000 days of patient exposure with safety profiles comparable to their reference products^{1,2,3,4}
 - Zarzio[®] is #1 daily G-CSF in Europe, having surpassed the original products
 - Sandoz is the global #1 in biosimilars with >50% market share in 2012
 - 18 products representing 5 molecules approved by EMA
 - First biosimilar monoclonal antibody (Inflectra[™]/Remsima[™] *infliximab*) approved by EMA in September 2013
- Even complex biosimilars can be developed successfully today

¹ PSURs : biosimilar HX575 Feb 2013; biosimilar EP2006 Jan 2013 and biosimilar Growth Hormone Aug 2012 (Dr. Sreedhar Sagi, Sandoz International, Holzkirchen, sreedhar.sagi@sandoz.com)

² Romer, T. *et al.* Horm Res 2009; 72: 359-369

³ Gascon P. *et al.* Support Care Cancer 2013 Aug 1: DOI: 10.1007/s00520-013-1911-7 and Sandoz data on file (Dr. Matthew Turner, Sandoz International, Holzkirchen, matthew.turner@sandoz.com)

⁴ Apro M. GaBI Journal 2013; 2: 38–41 and Sandoz data on file (Dr. Matthew Turner, Sandoz International, Holzkirchen, matthew.turner@sandoz.com)

Agenda

1 Development of Biosimilars: Background

2 **Impact of Naming on Biosimilars**

The current pharmacovigilance system includes redundant means of biologic identification

- Brand names

“In the U.S. medication-use system, health care providers rely on the proprietary name as the critical identifier” - FDA Guidance on Evaluation of Proprietary Names Feb 2010

- INN (USAN in US)

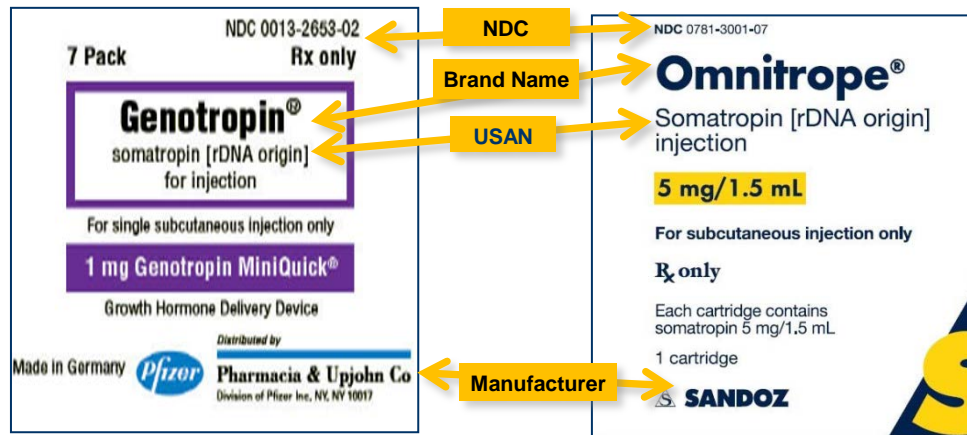
- Manufacturer

- NDC

- Lot number

- Within billing systems

Unique NDC or J-code will be captured *



The current system works. Incomplete or inaccurate data collection must be addressed for all products not just biosimilars

Product names, not INNs, are used in reports on Sandoz' biosimilar products

<p>Binocrit®/ Abseamed®/ Epoetin Alfa Hexal®</p> <p>Total Spontaneous (HCP, Non-HCP) ADRs through 28 Feb 2013: <u>166</u></p> <p>Reported as:</p> <ul style="list-style-type: none"> • Binocrit®: 91 • Epoetin Alfa Hexal®: 10 • Abseamed®: 62 • epoetin alfa: 1 • erythropoetin: 2 <p>~Patient exposure (days) = 66,898,161 (8/2007-2/2013)</p>	<p>Omnitrope® (including US)</p> <p>Total Spontaneous (HCP, Non-HCP) ADRs through 25 Feb 2013: <u>1067</u></p> <p>Reported as:</p> <ul style="list-style-type: none"> • Omnitrope®/Scitropin®: 1059 • somatropin: 8 (6 of 8 received from HA, no follow-up) <p>~Patient exposure (days) = 33,235,331 (10/2005 – 8/2012)</p>	<p>Zarzio®</p> <p>Total Spontaneous (HCP, Non-HCP) ADRs through 28 Feb 2013: <u>126</u></p> <p>Reported as:</p> <ul style="list-style-type: none"> • Zarzio®: 108 • Filgrastim Hexal®: 8 • GCSF: 1 (via HA) • filgrastim: 9 (4 of 9 from clinical trials) <p>~Patient exposure (days) = 3,456,506 (2/2009-1/2013)</p>
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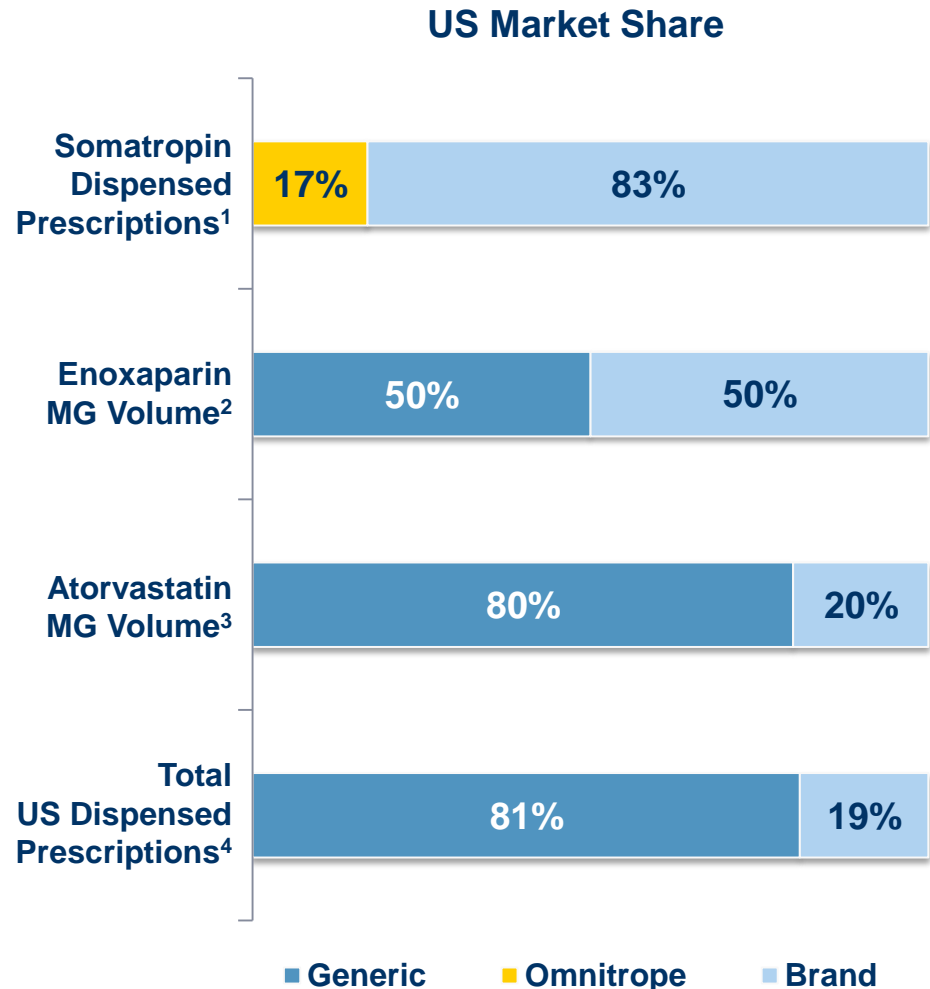
US market penetration by a highly similar somatropin molecule (Omnitrope®) lags generic biologic and small molecule penetration



- Seven somatropin products with FDA approval for treatment of growth hormone deficiency
- All somatropin products share same USAN
- Omnitrope® (somatropin [rDNA origin]) approved in 2006 via section 505(b)(2) of the FD&C Act
- Reference product is Genotropin® (somatropin [rDNA origin])

¹Wolters Kluwer Source PHAST Prescriptions Monthly + Kaiser Permanente Oct-2012; ²IMS Health National Sales Perspective, Nov-2012 YTD (Sanofi-Aventis/Winthrop vs. generics); ³IMS National Sales Perspective, Nov-2012; ⁴IMS Health National Prescription Audit, Nov-2012 YTD, branded generics disaggregated

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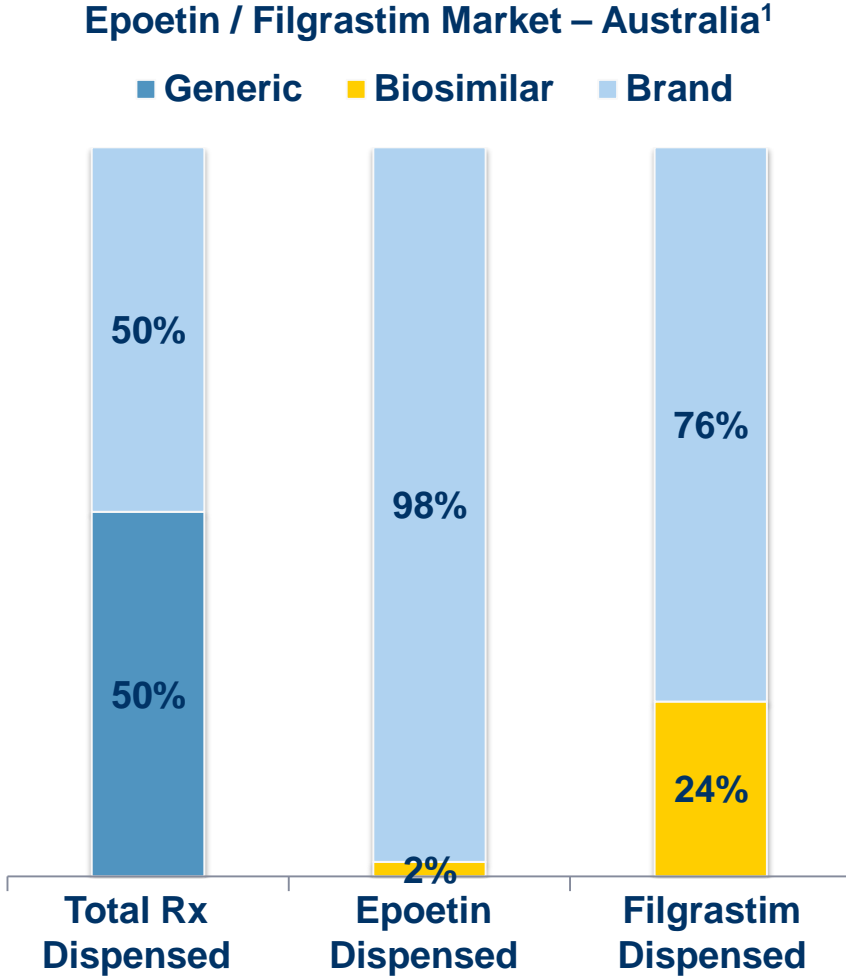




Different (local) non-proprietary names can further reduce market penetration and consumer access

Australia epoetin and filgrastim market case examples

- The non-proprietary name is a key differentiator in prescribing practice
- 3 epoetin molecules available in Australia – with 3 differing local non-proprietary names
 - Biosimilar epoetin lambda from Novartis sold as Novocrit in Australia
- 3 filgrastim molecules available – with 1 local non-proprietary name
- Requirement for different local non-proprietary names contributes to low biosimilar penetration of epoetin market
- Recent approvals of biosimilar filgrastim by Hospira and Teva have the **same INN** as the Amgen’s originator product. This is contributing to a significantly higher uptake in hospital distribution channels of the biosimilars



¹IMS Health MIDAS Volume database 2012

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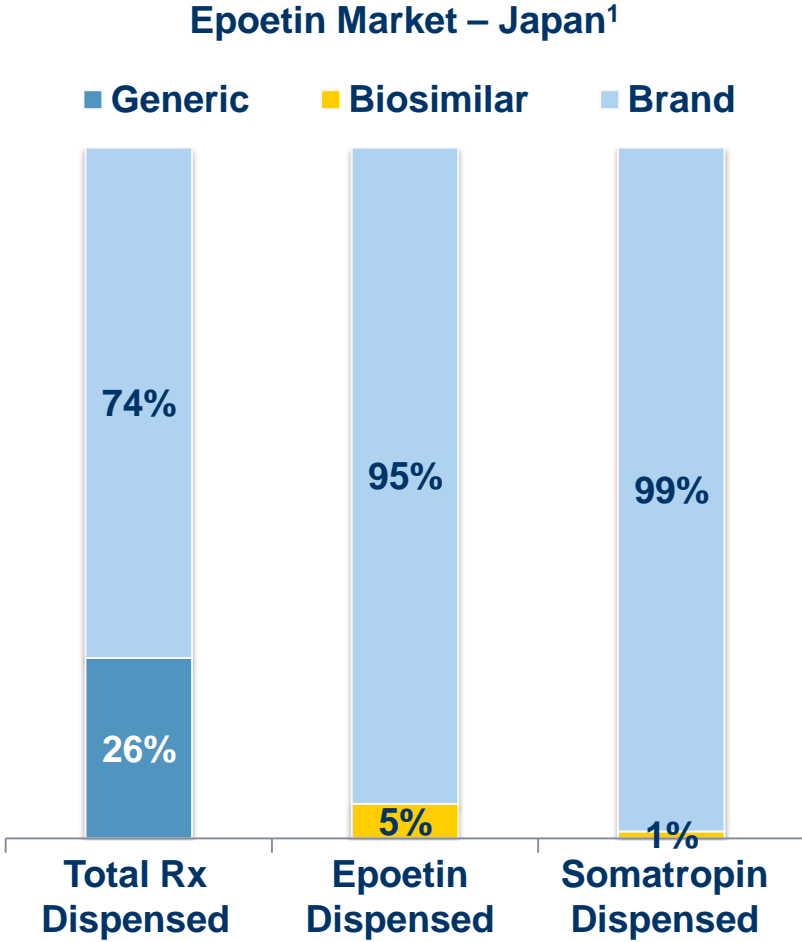




Different (local) non-proprietary names can further reduce market penetration and consumer access

Japan epoetin market case example

- HCPs are required to prescribe by local non-proprietary name
- 3 epoetins available – with 3 differing local non-proprietary name
- 6 somatropins – with 2 differing local non-proprietary names
 - 5 branded independent products with the INN “somatropin” – not compared to each other
 - “SOMATROPIN BS SAND” sold by Sandoz
- Requirement for different local non-proprietary names contributes to low biosimilar penetration of epoetin market



¹IMS Health MIDAS database 2012

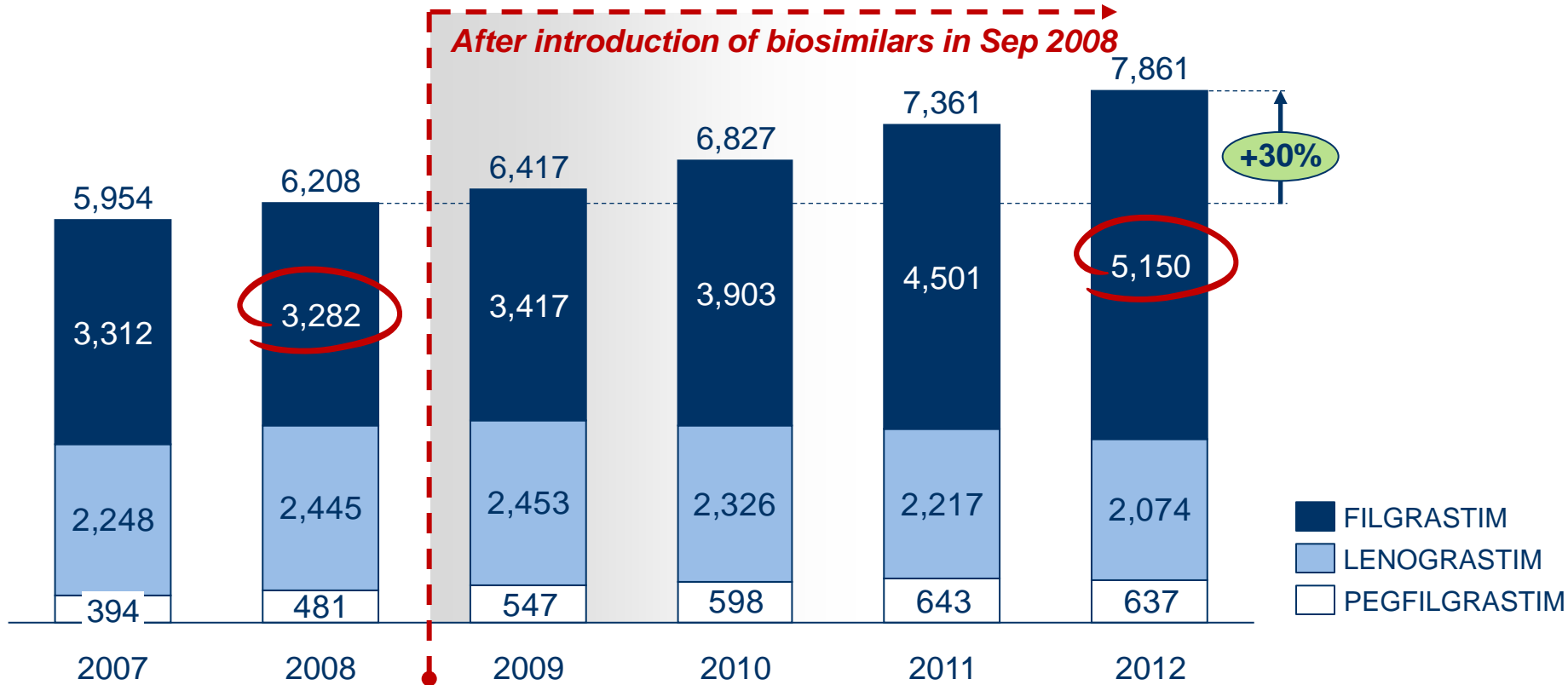
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At the same time, introduction of filgrastim biosimilars in Europe has significantly increased uptake of G-CSF



Total G-CSF market volume in Europe by year
Number of syringes in thousands



1st cycle treatment + optimal dose & duration = enhanced access for cancer patients

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Note: Data covers full year sales / Source: IMS

Summary

- Each biological product is clearly identified by its brand name
- The INN identifies the active substance and is not suitable for product identification
- Different INNs for biosimilars lead to confusion of physicians and discrimination of biosimilars, potentially impacting affordability and patient access
- The current naming system for biologics works well and should not be dismantled

“Developing Oncology Biosimilars: An Essential Approach for the Future” *

J Abraham: Semin Oncol. 2013 Dec;40S1:s5-S24

“Improving patient access to cancer therapies such as biologics and reducing healthcare costs are key initiatives of the US Government; the integration of approved biosimilars into clinical practice will be instrumental in accomplishing these goals.”

*Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH

Back up slides

Comparability and biosimilarity: same scientific principle

Biosimilar Concept

- Scientific principles underlying the comparability exercise required for changes in the manufacturing process of a given biological product and for the development of a biosimilar are the same
- Similar physicochemical characteristics prerequisite for reduction in non-clinical and clinical data requirements

The BfArM is a Federal Institute within the portfolio of the Federal Ministry of Health

Martina Weise, Federal Institute for Drugs and Medical Devices (BfArM), Germany, and **Vice Chair, EMA Biosimilar Medicines Working Party**
“Biosimilars – Why Terminology Matters”: Presentation at 10th EGA International Symposium on Biosimilar Medicines, 19-20 April, 2012, London, page 5.
Presentation declared as “personal views”, not official views of BfArM or EMA’s BMWP.

How to handle “drifts” of quality attributes in the originator biologicals?

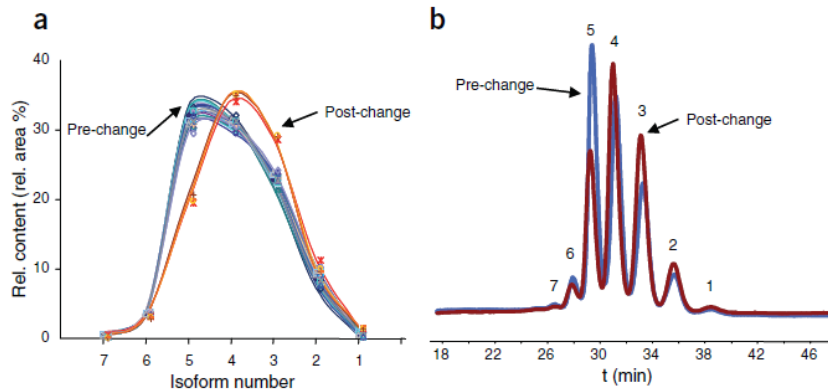


Figure 1 Comparison of the pre- and post-change Aranesp batches measured by capillary zone electrophoresis. (a) Relative content of the individual isoforms of the pre-change ($n = 18$) and the post-change ($n = 4$) batches. (b) Representative electropherograms; peaks are labeled with the isoform number.

- Oral reports from clinicians: Originator biologicals have been “interchanged” in patients for years in clinical practice (erythropoietins etc.)
- Has **extrapolation** of indications and **substitutions** already been practised for years when licensing changes in manufacturing?

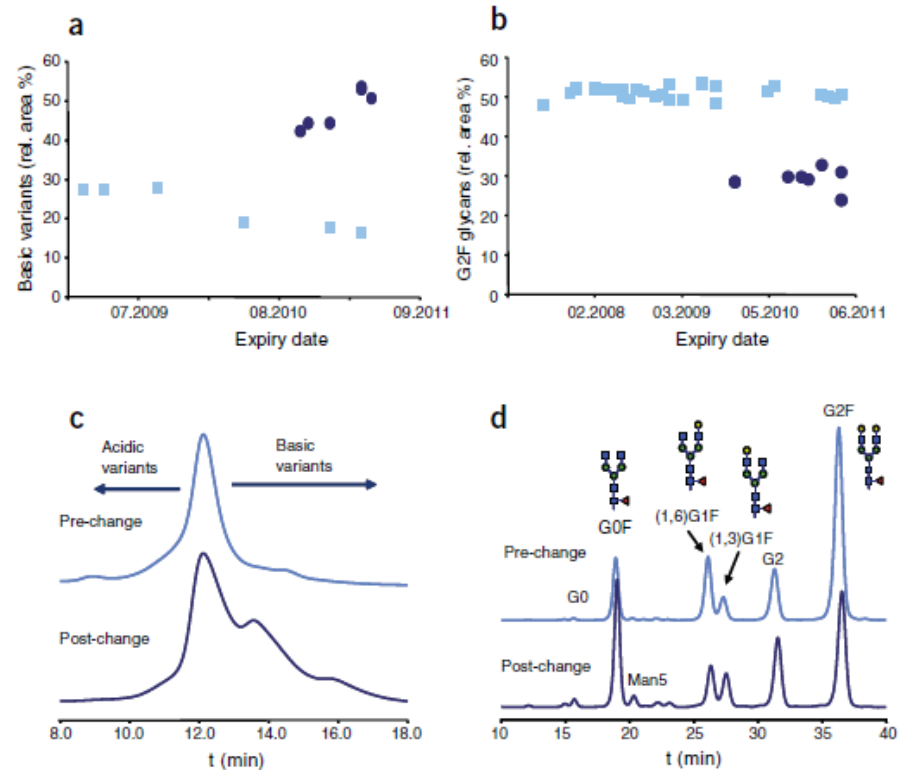


Figure 3 Comparison of the different pre- and post-change batches of Enbrel. (a) Relative amounts of basic variants of the pre-change ($n = 6$) and the post-change ($n = 6$) batches as measured by CEX. (b) Relative amount of the G2F glycan of the pre-change ($n = 25$) and the post-change ($n = 9$) batches.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

Schiestl M et al: Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nat Biotechnol.* 2011 Apr;29(4):310-2.

ASBM* Presents New European Survey Findings on Biosimilars and the Importance of Nonproprietary Naming

Friday, November 22nd, 2013

“The key findings showed that nonproprietary names matter to patient safety.”

- **Key findings from the survey include:**
- 53% of physicians surveyed felt that ***an identical nonproprietary name implies identical structure*** – which will not be the case for biosimilar medicines
- 61% of surveyed physicians said ***that identical nonproprietary names imply*** that the medicines are approved for the same indications – which is not necessarily the case
- 24% of reporting physicians record only the non-proprietary name of the biological product in the patient record

The responses of the European physicians ***demonstrate the need for distinguishable nonproprietary names to be given for all biologics***. Biosimilars, in contrast to generic drugs, may have different structure and therapeutic profile, and be approved for different indications than the reference product.

More and more biologic medicines, both innovative and biosimilar, are being approved around the world. ***How these products are named will clearly play an important role*** in facilitating global pharmacovigilance and the safe use of these medicines

*Alliance for Safe Biological Medicines: funded by Amgen, BIO, and Genentech

Take-aways from ASBM “survey”:

- The term “Identical” is abused to instill fear and foster misunderstanding
- One can take advantage of **leading questions and misinformation in a survey** to produce a desired outcome
- Naming DOES matter and using a different non-proprietary name does communicate a different product
- A different nonproprietary name will cause doubt in healthcare providers (the desired outcome)

Aranesp^{®1} (darbepoetin alfa)

Manufacturing changes

- Description of changes (see EPAR Aranesp[®] July 2008²):
 - Re-establishment of master cell bank
 - Change from roller bottle (RB) manufacturing process to a more scaleable high throughput (HT) process using cells in suspension
 - Change of cell culture medium
 - Change was rated as “Replacement of a biological substance or product of biotechnology with one of a slightly different molecular structure. Modification of the vector used to produce the antigen/source material, incl. new master cell bank”
- Submitted line extension contained comparability exercise including quality, non-clinical, and clinical data

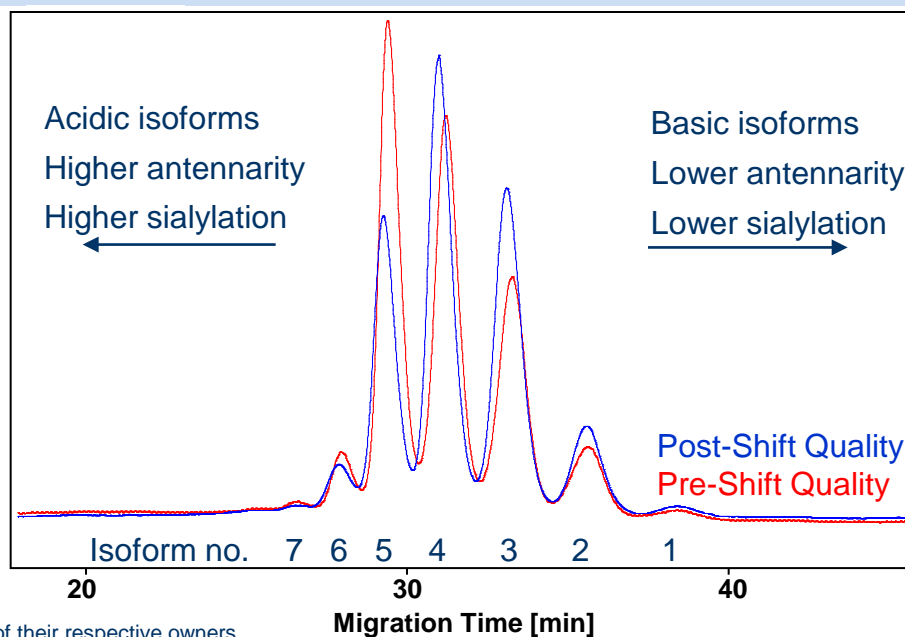
¹ All trademarks are the property of the respective owner

² Doc. Ref. No.: EMEA/478499/2008

Aranesp[®] (darpepoetin alfa):

Manufacturing Changes - Quality shift of the EU originator product

- Monitoring EU sourced batches of Aranesp[®] revealed a shift in the glycoisoform distribution measured by capillary zone electrophoresis
- Method separates glycoisoforms with different charge-to-mass ratios (e.g. different antennarity, sialylation, etc.)
- Indication of the altered, but comparable quality, resulting from the manufacturing changes approved for EU and published in the EPAR 2008 for Aranesp[®]?



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Aranesp[®] (Darbepoetin alfa)

EPAR on Manufacturing Changes - *Nonclinical Aspects*

Description	Outcome
<p>⑩ In vitro binding assay</p>	<p>⑩ Comparable results</p>
<p>⑩ Single dose PK study in male beagle dogs</p> <p>⑩ 4 week repeated (3x/week) tox study in beagles → For toxicity, PK, PD, Immunological measurements</p>	<p>⑩ PK: No meaningful changes between HT and RB after single and multiple dose (tox study); <u>25% higher exposure (AUC) of HT after 4 weeks of application not considered biologically relevant</u> → PK comparability on a pre-clinical level can be assumed</p> <p>⑩ PD: No meaningful differences between HT and RB → Comparability confirmed</p> <p>⑩ Tox: No meaningful differences between HT and RB & no unexpected toxicities → comparability shown at level of general tox.</p> <p>⑩ Antigenicity: <u>Lower serum Ab levels</u> with RB-material. However, Antibodies (Ab) detected in the same number of animals → <u>comparable immunogenic potential</u></p> <p>⑩ Neutralizing capacity: Assessed by bioassay AND marked decrease in reticulocytes in some of the dogs as indirect indicator of possible formation of NABs (in some cases findings of assay and hematology did not fit, e.g. due to possible iron deficiency)</p>

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Aranesp[®] (Darbepoetin alfa)

Manufacturing Change - *Clinical Aspects (product from 2000 L scale)*

Description	Outcome
<p>⑩ Phase I comparative PK study (randomized, 2-way, open-label, crossover, SC) with 2 single doses in 48 healthy volunteers</p>	<p>⑩ PK: Primary endpoint within predefined acceptance criteria (80%-125%); Secondary endpoints also comparable; No IV PK study requested by CHMP since SC route demonstrated equivalent PK profiles & SC route more sensitive to possible changes concerning HT product's PK profile</p> <p>⑩ Clinical safety: <u>No notable differences</u> in incidence of adverse events between RB and HT; no neutralizing antibodies</p>
<p>⑩ Pivotal Phase III comparative efficacy study (controlled, randomized, in 446 CKD haemodialysis patients, SC or IV, maintenance)</p>	<p>⑩ Efficacy (362 subjects): Both primary endpoints show comparable efficacy of RB and HT (only 35/37 patients on SC treatment)</p> <p>⑩ Conclusion of equivalent efficacy between RB and HT for SC route of administration by taking the SC PK profiles and supportive efficacy data from safety study into consideration</p> <p>⑩ Clinical safety : Comparable safety profile between treatment groups, <u>no neutralizing antibodies</u></p>
<p>⑩ Single arm safety study with HT (open label, in 1172 CKD patients)</p>	<p>⑩ Safety data from this (uncontrolled) study regarded as supportive only, as was the comparison to safety data from five historical trials (comparison difficult).</p> <p>⑩ However, <u>no new safety signal</u> emerged and overall safety profile consistent with underlying disease and severity, <u>no NABs</u></p>

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* No PD study (PD parameters not critical since Phase III efficacy/safety studies provided)

Aranesp[®] (darbepoetin alfa)

EPAR on Manufacturing Changes - Conclusions

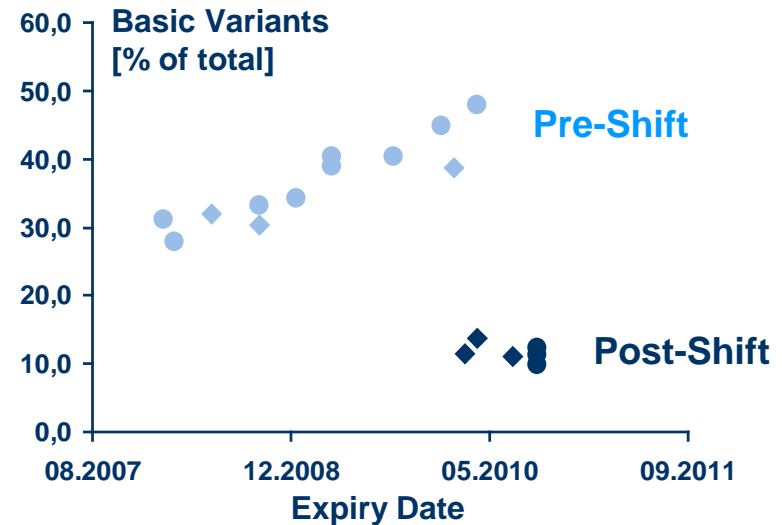
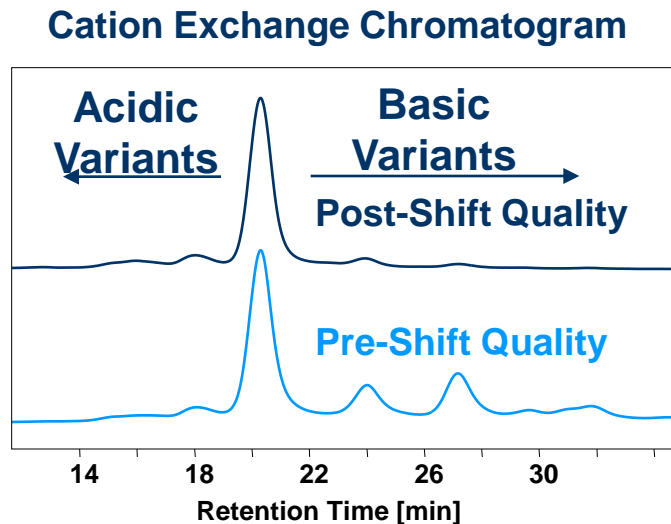
- Aranesp[®] manufacturing process was significantly changed
- The manufacturing change resulted in a considerable shift in certain quality attributes of the Aranesp[®] product marketed in EU
- The change was approved based on demonstrated comparability of quality, non-clinical, and (limited) clinical data
- This example clearly demonstrates that even considerable differences after a manufacturing change can be thoroughly evaluated using a risk based approach
- The studies and requests described in the EPAR demonstrate the rigor regulators apply in such assessments

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MabThera[®] / Rituxan[®] (rituximab):

Structural differences (charge variants) – comparable product

- Monitoring batches of MabThera[®] and Rituxan[®] revealed a 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
- Indication of a change in the manufacturing process?

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MabThera[®] / Rituxan[®] (rituximab):

Summary: *Structural and functional differences – comparable product*

- Monitoring batches of MabThera[®] and Rituxan[®] revealed a shift in several quality attributes.

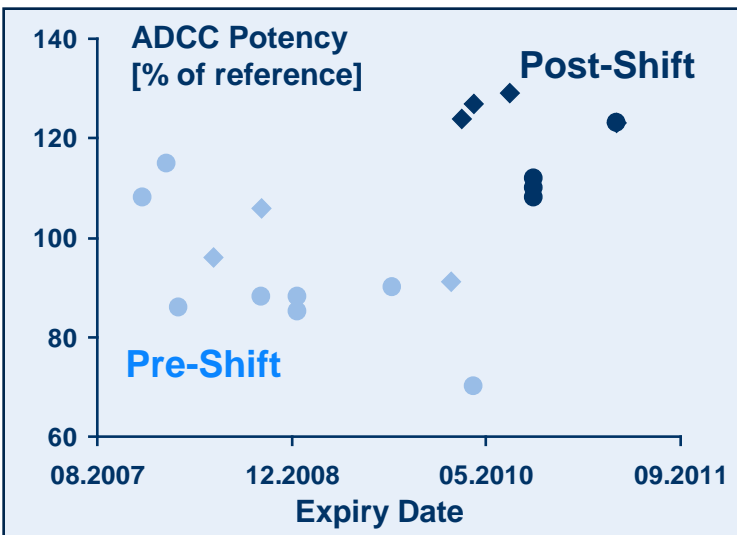
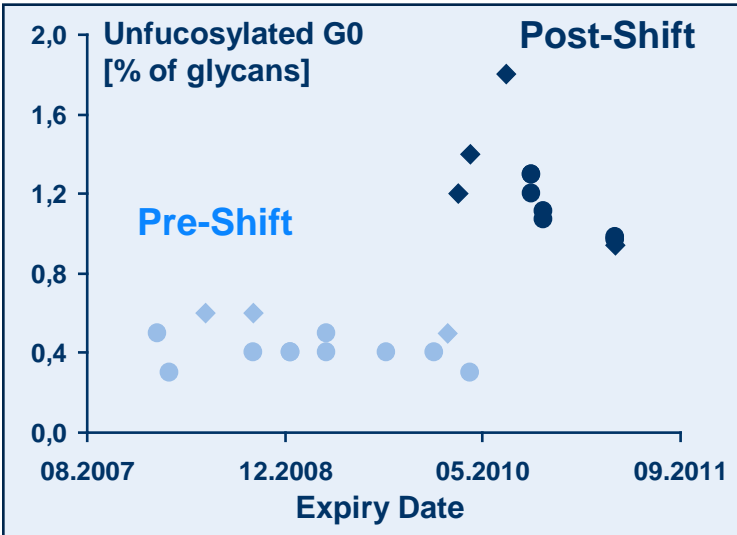
	Pre-Shift Quality	Post-Shift Quality
Basic charge variants [% of total mAB]	27.9 – 47.9	9.8 – 13.8
Unfucosylated G0 glycan [% of total glycans]	0.3 – 0.6	0.9 – 1.8
ADCC Potency [% of reference]	70 – 115	108 – 129

- Both rituximab qualities are sold under the same marketing license
- The same safety and efficacy profile is therefore expected
- Indicates that pre- and post-shift product qualities can be considered comparable
- Remark: INN remained unchanged

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Understanding the target: Variability is significant

Comparison of the different pre- and post-change batches of Rituxan®/Mabthera®

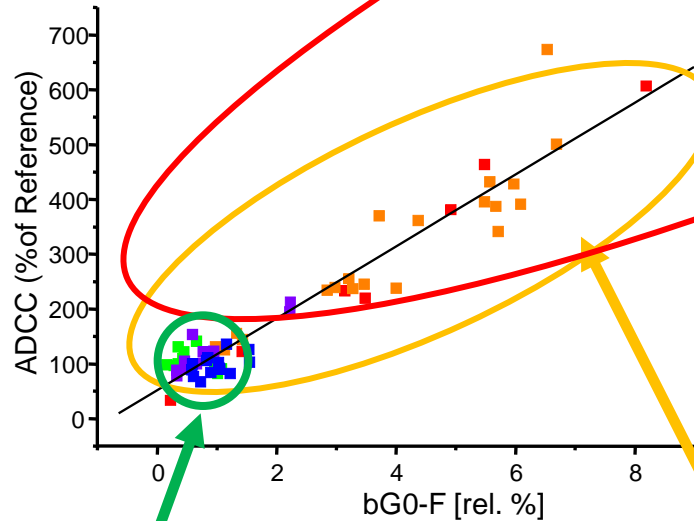


Schiendl, M. et al., *Nature Biotechnology* **29**, 310-312, 2011

- Monitoring batches of an approved mAb revealed a shift in quality attributes
- Shift in glycosylation (structure) pattern results in different potency in cell-based assays (function)
- Indication of a change in the manufacturing process
- Such shifts observed in several original products
- Products found to be equally safe and effective post-shift by regulators (EMA, FDA)

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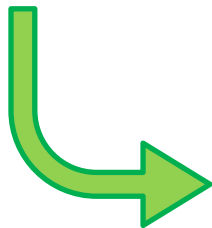
Defining the target: Variability in reference biologic defines very narrow goal posts for biosimilarity



Variability of reference product

Variability observed during cell line development

Biologically possible variability



Very narrow goalposts for biosimilar

