SATELLITE SYMPOSIUM EAHP 2015

BIOSIMILARS IN INFLAMMATORY DISEASE: A VALUE PERSPECTIVE

25 March 2015
16:15–17:45
Hall 6

SATELLITE SYMPOSIUM EAHP 2015

20th Congress EAHP: 25th March 2015: Hamburg

Michael Sobanja
Symposium Chair

Disclosures

- I received unrestricted research grants or acted as a speaker for a range of pharmaceutical companies and a number of commercial companies that operate in the health and healthcare environment.
  - Including but not limited to: Abbvie, Amgen, BMS, Celgene, GSK, Janssen, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, Servier, UCB

Housekeeping

- Please ensure your mobile phones are switched off or on silent
- Please do not leave any personal belongings unattended in the meeting room

Symposium Objectives

- Review the regulatory and policy environment for biosimilar agents and how it is evolving
- Discuss the importance of long-term data on value decisions in inflammation
- Review the role of Pfizer in the evolving environment

Agenda

Biosimilars: how they are regulated	**Dr Rieke Alten**
Understanding the role of long-term data in cost predictability	**Professor João Fonseca**
The role of Pfizer in the evolving environment	**Sylvie St-Laurent**
Panel discussion	**All**
Chair's summary	**Michael Sobanja**

Introductions

Michael Sobanja
Policy Director, NHS Alliance, UK

Dr Rieke Alten
Schlosspark–Klinik, Teaching Hospital of Charité, Berlin, Germany

Professor João Eurico Fonseca
University of Lisbon, Portugal

Sylvie St-Laurent
Senior Director, International Public Affairs, Pfizer

Your questions

- Questions will be taken during the panel discussion at the end of the symposia
- Questions can be submitted at any time using the question cards in your programme book
- Alternatively, you can ask your question using the aisle microphones

There is an evaluation form inside your programme book

Please fill this out at the end before leaving the symposium

The challenges with maintaining equitable health systems

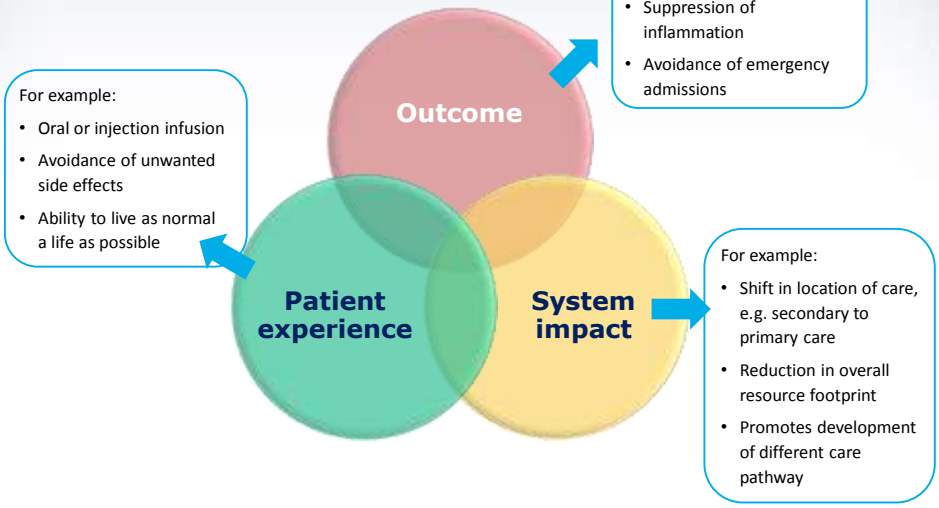
- Growing and ageing populations
- Growing demands on health care systems
- Growing health inequalities
- Increasing complexity of interventions
- Increasing costs & worsening economic conditions
- More informed and demanding patients

Key questions that drive the quest for value

- Affordability
- Necessary care
- Appropriate quality

These questions are answered differently across countries (and times)

Key measures of value



What do I think of as a Biosimilar?

A biosimilar is a structurally similar version of an approved biological medicine with demonstrated ***similarity*** in physicochemical, biological and immunological characteristics, efficacy and safety, based on an appropriate study.

Biosimilars are variously termed:

- Similar Biotherapeutic Products (WHO)[1]
- Similar Biological Medicinal Products (EU/TGA)[2]
- "Biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product" (US FDA)[3]
- Follow-on biologics (PMDA, Japan)[4] and subsequent entry biologics (Health Canada)[5]

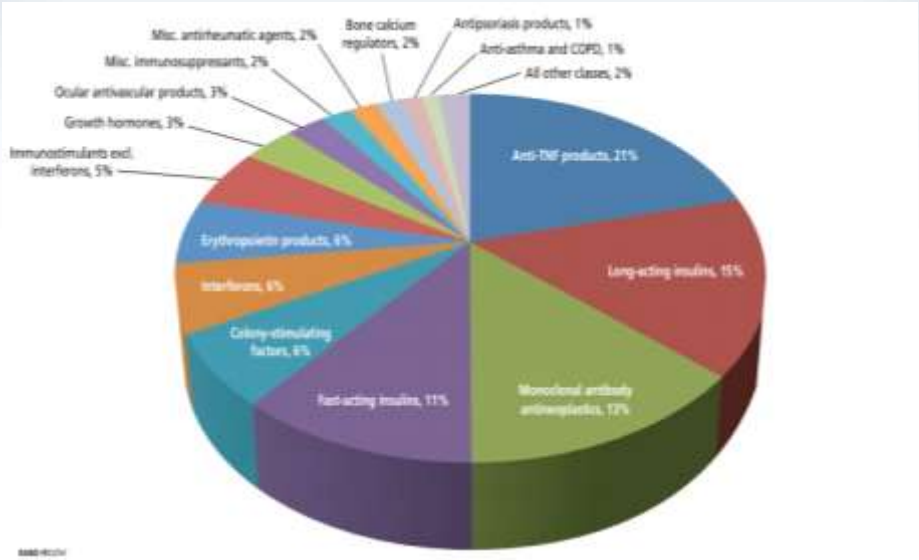
1. WHO. Guidelines on evaluations of similar biotherapeutic products (SBPs). 2010. 2 . EMA. Guideline on similar biological medicinal products. 2014. 3. US FDA. Guidance for Industry. 2014. 4. PMDA. Advanced review with electonic data promotion group. 2015.5. Health Canada. Fact Sheet: Subsequent Entry Biologics in Canada, 2009.

Definitions

EMA definition**	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.
FDA definition*	The term 'biosimilar' or 'biosimilarity', in reference to a biological product means: • The biological product is **highly similar to the reference product** notwithstanding minor differences in clinically inactive components • There are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product

**US FDA. Guidance for Industry. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product. May 2014.*
***Guideline on similar biological medicinal products. EMA Committee for Medicinal Products for Human Use (CHMP). CHMP/437/04 Rev 1. 23 October 2014.*

Potential cost savings across biologic classes (US)



http://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf last accessed 11 March 2015

EMA overarching guideline

- Scope
  - In principle: biosimilar concept applicable to any biological medicinal product.
  - In practice: Only for products that can be thoroughly characterised.
- Biosimilarity should be established at all levels (Q/S/E) using a reference medicinal product authorised in the Community on the basis of a complete dossier.
- Active substance should be similar to the reference medicinal product in molecular and biological terms.
- The pharmaceutical form, strength and route of administration should be the same as for the reference.
- The specific medicinal product given to the patient should be identified in order to support pharmacovigilance monitoring.

CHMP/437/04 Rev. 1 Dated October 2014 Effective 30 April 2015

Guideline on similar biological medicinal products. EMA Committee for Medicinal Products for Human Use (CHMP). CHMP/437/04 Rev 1. 23 October 2014.

Stepwise assessment for totality of evidence

- Quality (structure & function)
- Safety
- Efficacy

So, back to value...

- Biosimilar medicines may offer a less-costly alternative to existing biologic medicines that have lost their exclusivity rights (e.g. patents, data protection, etc.) and enhance competition
- As a result, the availability of biosimilar medicines may improve access to biological medicines for more patients and contribute to the financial sustainability of healthcare systems
- Thus, their availability offers potential economic benefit to healthcare systems while addressing the issue of new treatment options brought about by advances in medical science
- Biosimilars have the potential to be an important addition to the current originator biologics armamentarium for the treatment of inflammatory disease

European Commission: What you need to know about Biosimilar Medicinal Products, a consensus information paper 2013
http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf

Biosimilars: How they are regulated

Rieke Alten, MD

Schlosspark-Klinik Charité, University Medicine Berlin
Department Internal Medicine, Rheumatology, Clinical Immunology

25 March 2015 16:15–17:45 CCH – Congress Center Hamburg, Germany

Conflict of interest

- RA has received research grants and honoraria from the speakers bureau from Pfizer

Biosimilars: how are they regulated?

- Approval of a Biosimilar: Clinical trial requirements; EMA Guidance
- Which population is tested and how?
- Phase III Clinical data. Efficacy & Safety
- Extrapolation of clinical data across indications
- Interchangeability/substitution
- Post-approval pharmacovigilance and long term follow-up
- Biosimilar Regulations in Europe, in the US and beyond

Monoclonal antibodies are larger and more complex than simple biologics

- Challenges in development of biosimilars for monoclonal antibodies
  - Inherently structural complexity of the molecules[1-4]
  - Complexity and variability of the manufacturing process[5]
    - Even originators might not be the same as when they were introduced[5]
  - Evolving regulatory pathways[6]

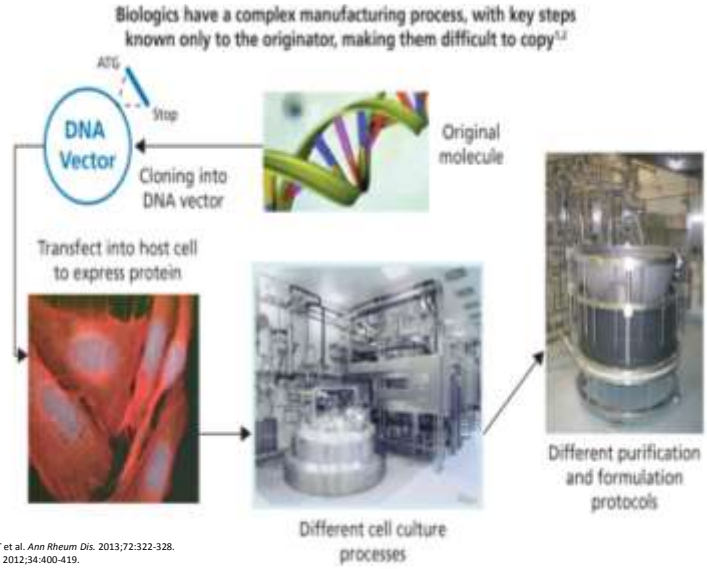
Insulin ← Simple

Erythropoietin

Monoclonal antibody Complex →

1. Schellekens H, Moors E. *Nat Biotechnol*. 2010;28:28-31. 2. Humalog Prescribing Information. Indianapolis, IN, USA: Eli Lilly and Co.; 1996, 2013.
3. Epoetin alfa (Procrit) Prescribing Information. Horsham, PA, USA: Janssen Products LP; 2000.
4. Infliximab (Remicade) Prescribing Information. Horsham, PA, UDA: Janssen Biotech, Inc.; 2013. 5. Dörner T et al. *Ann Rheum Dis*. 2013;72:322-328. 6. EMA web site. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c Accessed May 30, 2014.

Biosimilars differ from originator due to manufacturing complexities



1. Adapted from: Dörner T et al. *Ann Rheum Dis.* 2013;72:322-328.
2. Ahmed I et al. *Clin Ther*. 2012;34:400-419.

Clinical study design for biosimilars vs originators

- A well-designed study should:
  - Have a suitable patient population, with as little interpatient variability as possible
  - Be designed to show biosimilarity (comparison)
    - Have just two arms: originator vs biosimilar
  - Use an adequate primary endpoint
  - Have sufficient study length to be clinically relevant
    - 15 weeks or more for anti-TNFα in RA
  - Use adequate statistical analysis
    - No hypothesis testing, such as student *t*-test or ANOVA
    - Demonstrate equivalence, or at least noninferiority

Dörner T et al. *Ann Rheum Dis*.2013;72:322-328.
Park W et al. *Ann Rheum Dis*. 2013;72:1605-1612.
Yoo DH et al. *Ann Rheum Dis*. 2013;72:1613-1620.

Key differences in clinical trial requirements for originators and biosimilars

Study Parameter	Originator	Biosimilar
Patient population	Any	Sensitive[a] and homogeneous patient population
Clinical design	Superiority vs standard of care	Comparative vs originator (equivalence studies)
Study endpoints	Clinical outcomes data accepted (or established surrogates)	Validated endpoint from clinical trial and/or sensitive, clinically validated PD marker
Safety	Acceptable risk/benefit profile vs standard of care	Similar safety profile to originator
Immunogenicity	Acceptable risk/benefit profile vs standard of care	Similar immunogenicity profile to originator
Extrapolation	Not allowed	Possible if justified

[a] Sensitive: able to detect a clinically meaningful difference in response.

EMA. Guideline on similar biological medicinal products containing monoclonal antibodies:Non-clinical and clinical issues. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/ WC50028686.pdf. Accessed July 21, 2014.

EMA's abbreviated pathway to biosimilar approval: quality, nonclinical, and preclinical studies

Assessment	Originator Biologic	Biosimilar
Quality	• Individual quality assessment[a]	• Individual quality assessment[a] • Comprehensive comparison with reference product
Nonclinical/ Preclinical	• Full preclinical program	• Abbreviated program; tolerance, PK/PD

- Nonclinical physiochemical and biological characterisation is required to address structural, functional, and immunogenicity concerns before efficacy and safety trials
- The nonclinical portfolio must provide comparability data that are almost superimposable with the originator, through the use of 'fingerprint'-like analyses to detect differences between highly complex monoclonal antibodies

[a] Consisting of analytical techniques, characterisation (physicochemical, biological activity, immunochemical, purity), and specifications.

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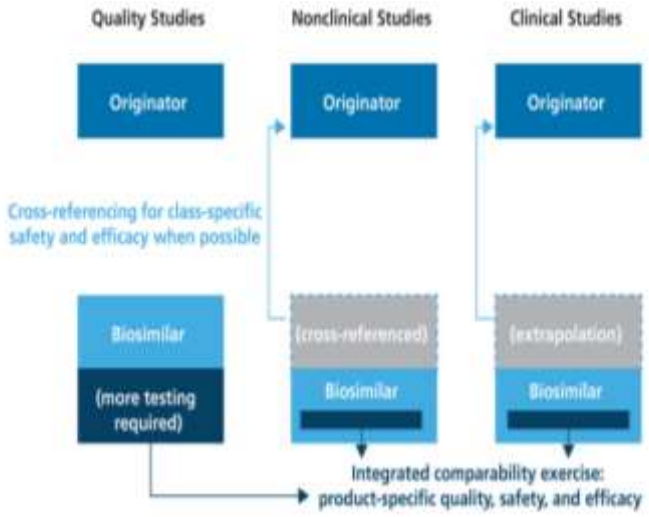
1. EMA. http://www.ema.europa.eu/docs/en_GB/ document_library/Scientific_guideline/2013/06/WC500144124.pdf. Accessed July 21, 2014.
2. Dorner T et al. *Ann Rheum Dis.* 2013;72:322-328.

EMA dossier requirements for biosimilars compared to originators



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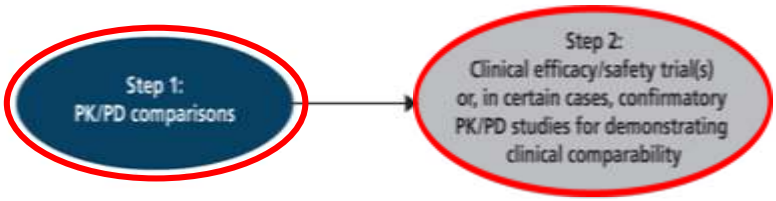
Adapted from: Schneider CK et al. *Nature Biotechnol.* 2012; 30:1179-1185.

EMA guidance on biosimilar monoclonal antibodies: mandated clinical testing

- When sufficient changes to the originator occur, clinical testing is required[1,2]



- No dose-ranging studies are needed

1. EMA. Similar Biological Medicinal Products Containing Biotechnology Derived Proteins as Active Substance: Non-Clinical and Clinical Issues. CHMP/BMWP/42832/2005.February 22, 2006.
2. Dörner T et al. *Ann Rheum Dis.* 2013;72:322-328.

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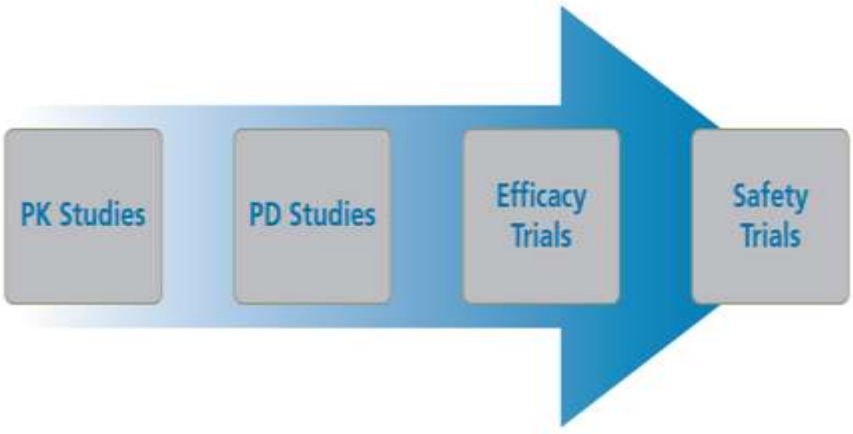
Clinical comparability: a stepwise procedure



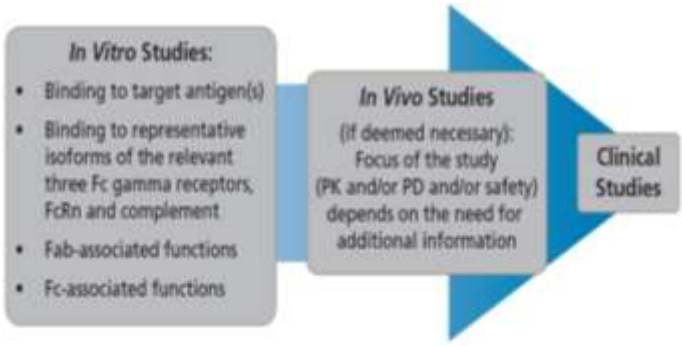
European Medicines Agency (EMA). Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/ Scientific_guideline/2013/06/W500144124.pdf. Accessed July 21, 2014.

Comparative PK/PD studies for biosimilars

Comparative PK Studies	PD Studies
Preferred: Single-dose crossover study in healthy volunteers, in a sensitive and homogeneous population	**Recommended:** PD markers should be added to PK studies whenever feasible
Alternate: Study in patients with few factors that cause major inter-individual or time-dependent variations	**However,** comparative efficacy trials are normally required to demonstrate clinical comparability
• **PK parameters** should be defined and justified beforehand; they vary for single- and multiple-dose studies • **Required CI** for ratios of drug concentration (AUC and C_{max}) comparisons between biosimilar and originator: 80%-125%	**Comparative PK/PD Studies** may be sufficient to demonstrate clinical comparability if • A clear dose-response relationship is demonstrated • Selected PD marker/biomarker is an accepted surrogate and can be related to patient outcomes

EMA. Guideline on similar biological medicinal products containingbiotechnology-derived proteins as active substance:Non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_libraryScientific_guideline/2013/06/WC500144124.pdf. Accessed July 21, 2014.

Nonclinical comparability studies: a stepwise approach for biosimilar mAbs



Are *in vivo* studies necessary? Some factors to be considered:

- Presence of relevant quality attributes not detected in the originator product
- Presence of quality attributes in significantly different amounts vs the originator product
- Relevant differences in formulation

EMA. Guideline on similar biological medicinal products containing monoclonal antibodies: Non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC50128686.pdf. Accessed July 21, 2014.

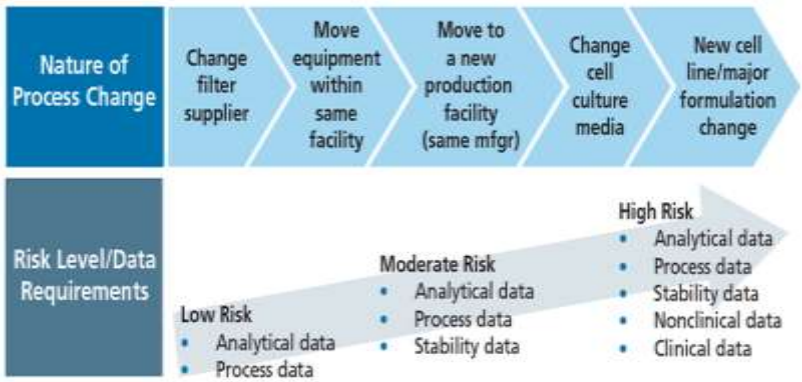
Comparability exercises for biosimilars

- Quality and cell-based assay comparisons are the most important parts of the comparability exercise
  - More sensitive to detect differences vs clinical studies
- **So how relevant are potential quality differences for the clinical endpoints?**
- **The answer is that the regulators will have to decide that, based on past experience in comparability exercises**

EMA. Guideline on similar biological medicinal products containing biotechnology-derivedproteins as active substance: Quality issues (revision 1). http://www.ema.europa.eu/docs/en_GB/documnt_library/Scientific_guideline/2012/05/WC500127960.pdf. Accessed July 21, 2014.

Comparability requirements with manufacturing changes

- The need, extent, and nature of nonclinical and clinical comparability studies will be determined on a case-by-case basis in consideration of various factors that may be associated with risk

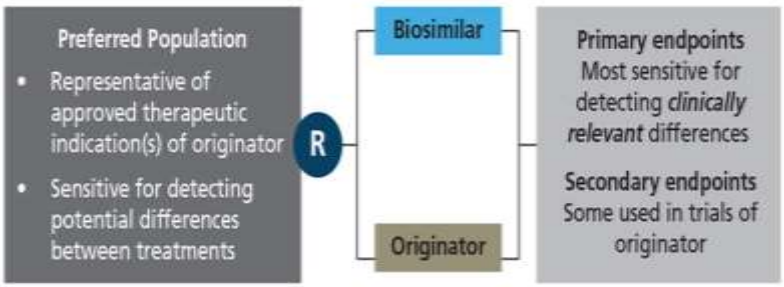


EMA. Guideline on comparability ofbiotechnology-derived medicinal products after a change in the manufacturing process: Non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003935.pdf. Accessed July 21, 2014.
Lee JF et al. *Curr Med Res Opin.* 2012;28:1053-1058.

Phase III Studies

Phase 3 efficacy trials for biosimilars: recommended study design

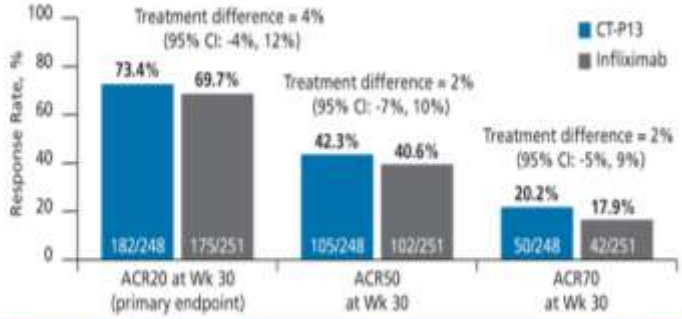
- Randomised, double-blind, parallel-group trial with adequate power
- Equivalence design preferred
- Noninferiority design acceptable in some cases
  - Strong scientific rationale
  - Possibility of increased efficacy excluded on scientific/mechanistic grounds



EMA. Guideline on similar biological medicinal products containing biotechnology-derivedproteins as active substance: Non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf. Accessed July 21, 2014.

PLANETRA: clinical efficacy and safety of biosimilar vs originator infliximab in RA

- Randomised, double-blind, parallel-group study
- Objective: Demonstrate the efficacy and safety of CT-P13 vs originator infliximab when coadministered with MTX in patients with active RA



- *Safety*: There were no clinically meaningful differences in safety data between CT-P13 and infliximab
- *Immunogenicity*: Antibodies to infliximab were detected using INX tag in 48.4% (n = 122) and 48.2% (n = 122) of patients for CT-P13 and INX, respectively, at week 30

Yoo DH et al. *Ann Rheum Dis*.2013;72:1613-1620.

PLANETAS: PK for biosimilar vs originator infliximab in AS

- Randomised, double-blind, multicentre, parallel-group prospective study
- Objective: Compare the PK, safety, and efficacy of CT-P13 and originator infliximab in patients with AS

Overall Steady State PK Between Weeks 22 and 30

Parameter*	Treatment	N	Geometric Mean	Ratio of Geometric Means, % (90% CI)
PK population				
AUC, μgh/mL	CT-P13 INX	112 110	32765.8 31359.3	104.5 (94.3-115.8)
$C_{max,ss}$, μg/mL	CT-P13 INX	113 110	147.0 144.8	101.5 (94.7-108.9)
ADA-negative subset				
AUC, μgh/mL	CT-P13 INX	84 86	37505.2 36266.9	103.4 (94.6-113.1)
$C_{max,ss}$, μg/mL	CT-P13 INX	85 86	153.9 146.9	104.7 (97.2-112.9)

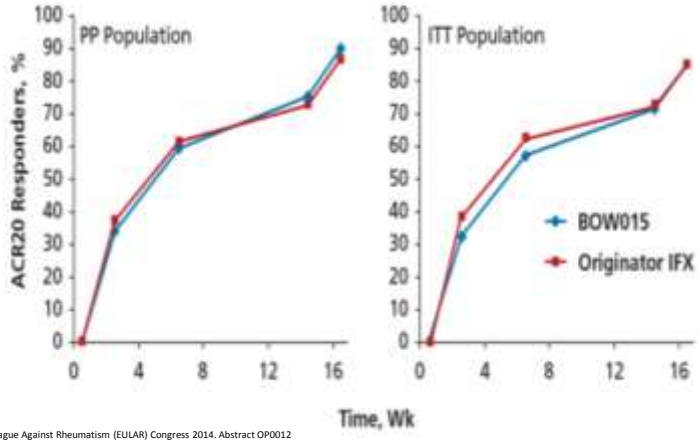
ADAs to infliximab with active AS patients were detected in 9.1% (n = 11) and 11.0% (n = 13) of patients for CT-P13 and INX at week 14 and 27.4% (n = 32) and 22.5% (n = 25) of patients for CT-P13 and INX, respectively, at week 30

* Observed AUC and $C_{max,ss}$ were analysed using an analysis of covariance with treatment as a fixed effect and region and baseline BASDAI score fitted as covariates. Point estimates and 90% CI for difference on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

Park W et al. *Ann Rheum Dis*.2013;72:1605-1612.

Biosimilar candidate infliximab: pipeline results in RA

- Phase 3, double-blind, active-comparator trial comparing efficacy and safety of biosimilar IFX BOW015 to originator IFX in patients with active RA (N = 189)
- Primary endpoint was ACR20 response at wk 16 within a 23% equivalence margin



Kay K et al. European League Against Rheumatism (EULAR) Congress 2014. Abstract OP0012

Biosimilar candidate etanercept: pipeline results in RA

- Phase 3, double-blind, RCT comparing efficacy and safety of biosimilar etanercept HD203 to originator etanercept in patients with active RA (N = 294)
- Primary endpoint was ACR20 response at Wk 24

ACR20 at Wk 24 and Wk 48

Endpoint	HD203	Originator Etanercept	Difference (95% CI)	P*
24-wk PPS	83.48% (96/115)	81.36% (96/118)	2.12 (–7.65, 11.89)	.6706
FAS	79.10% (106/134)	75.56% (102/135)	3.55 (–6.45, 13.55)	.4870
48-wk PPS	86.27% (88/102)	81.90% (86/105)	4.37 (–5.57, 14.31)	.3905

Bae SC et al. EULAR Congress 2014. Abstract OP0011.

*Pearson's chi-squared test.

Safety & Immunogenicity

Safety and immunogenicity data

- **Safety data** needs to be collected pre- and post-launch[1]

Prelaunch

- Create dossier of anticipated risks based on originator
- Address safety concerns related to infusions
- Address possibility of immunogenicity from differences in manufacturing process

Postlaunch

- Compare type, frequency, and severity of safety issues to originator
- Immunogenicity studies

- **Immunogenicity studies** should be performed with same assay format and schedule as the reference product
- EMA requires that immunogenicity of biosimilars be evaluated in the **most sensitive patient population** to detect possible differences in immunogenicity[2]

1. EMA. Guideline on similar biological medicinal products containingbiotechnology-derived proteins as active substance:Non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf. Accessed July 21, 2014.
2. Lee H. *AAPS J*. 2014;16:22-26.

The rationale for immunogenicity evaluation with biosimilars

- EMA requires that immunogenicity of biosimilars be evaluated in most sensitive patient population to detect possible difference in immunogenicity[2]
  - Population for which immunogenicity is suppressed may not serve as basis for extrapolation to other indications (eg, RA not sensitive population due to use of MTX)[1]

1. Brinks V. *GaBI Journal*.2013;2:188-193. 2. Lee H. *AAPS J*. 2014;16:22-26.

Extrapolation

Extrapolation of biosimilars in rheumatic diseases: before and after approval*

Concern	EMA	FDA	WHO
1. Mechanism of action may be distinct in each indication	If mechanism of action differs between indications or are not fully understood, separate clinical trials may be necessary		Clinically relevant mechanism of action and/or the involved receptors should be the same for the different indications
2. For a given mechanism of action, several mechanisms may exist	Almost superimposable biologic data for all functional aspects of the agent must be provided, even if not considered clinically relevant. Where mechanism of action are not fully understood, separate clinical trials may be necessary		
3. Risk of under-treating/varied safety profiles among patient groups	Use a patient population and clinical endpoint most sensitive to detect clinically meaningful differences in efficacy/safety		Use a sensitive clinical test model able to detect potential differences from reference products
4. Individual patient characteristics may influence the response	Use a homogeneous population	Consider comorbidities, concomitant medications, and intersubject variability	Safety and immunogenicity profiles should be sufficiently characterised

* Extrapolation is not permitted in Canada, Mexico, and Venezuela.

Dörner T et al. *Ann Rheum Dis*.2013;72:322-328.
Dranitsaris G et al. *Drugs*. 2011;71:1527-1536.
Azevedo VF et al. *Value Health Regional Issues*.2012;1:228-234.

Justification for extrapolation of indications according to EMA

Extrapolation of indications is needed to provide a cost-effective biosimilar

Extrapolation can be justified on a case by case basis (according to guidance) with

- Sufficient clinical experience
- Consistent scientific literature

- **Similar mechanism of action in the sought indications**
  - Target/receptor localisation and expression
  - Binding affinity
  - Concentration-response relationship (intracellular signalling pathways)
- PK/PD and biodistribution data
- Expected adverse events in various indications
- Expected immunogenicity in various indications

EMA. Guideline on similar biological medicinal products containingbiotechnology-derived proteins as active substance:Non-clinical and clinical issues. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/06/WC500144124.pdf. Accessed July 21, 2014.
EMA. Guideline on similar biological medicinal products containing monoclonal antibodies. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf. Accessed July 21, 2014.

Interchangeability and substitution

Interchangeability and substitution of biosimilars

- The EMA mandate does not include recommendations about **interchangeability** of biosimilars and originators
- In Europe, agreements to **switch a patient from an originator product to a biosimilar** are entirely left to the national authorities
- **Available data on switching** should be carefully assessed during the review of adverse reaction reports as part of the risk management plan

EMA. http://www.ema.europa.eu/docs/en_GB/document_library/ Scientific_guideline/2013/06/WC500144124.pdf. Accessed July 21, 2014.

Considerations regarding interchangeability and substitution

- There is no agreement between world regulatory agencies on whether originators and biosimilars are interchangeable[1,2]
- More studies are needed to demonstrate that the risk of changing the biosimilar for the originator or vice-versa is not significant
- If switching is permitted at the pharmacy level, the clinician should be informed which product a patient is receiving

- Norway is funding a large randomised, double-blind parallel-group study (NOR-SWITCH) to see the impact of switching[3]
- Study will examine innovator infliximab (Remicade) and biosimilar infliximab (Inflectra/Remsima)
  - Recruiting patients with RA, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn's disease and chronic plaque psoriasis
  - Primary outcome measure will be occurrence of disease worsening

1. Dörner T et al. *Ann Rheum Dis*.2013;72:322-328.
2. World Health Organization (WHO), Expert Committee on Biological Standardization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs). Sixtieth report(19-23 October 2009). WHO Technical Report Series No. 977. http://apps.who.int/medicinedocs/en/d/Js19941en/. Accessed September 23, 2014.
3. ClinicalTrials.gov. http://clinicaltrials.gov/show/NCT02148640. Accessed September 23, 2014.

Pharmacovigilance and long term follow-up

Biosimilars and the role of pharmacovigilance

- Biosimilars need a stringent pharmacovigilance system, due to[1,2]
  - Immunogenicity
  - Unknowns regarding data for ethnic groups, children, patients with comorbidities, etc
- European Union, US, and several countries in Asia have very stringent pharmacovigilance systems[1-3]
- Emerging countries in Latin America, Southeast Asia, Africa, and Eastern Europe have a lot of variability in their systems[1-3]

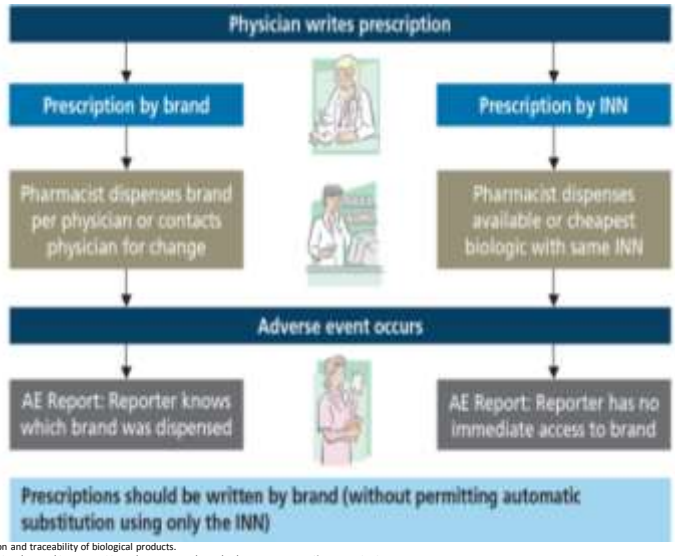
1. Yadav S. *Indian J Pharmacol* 2008;40(suppl 1):S4-S9.
2. Pirmohamed M et al. *BMJ.* 2007;335:462.
3. System for Improved Access to Pharmaceuticals and Services. Pharmacovigilance. http://siapsprogram.org/approach/pharmaceutical-systems/pharmacovigilance/. Accessed September 23, 2014.

Pharmacovigilance: long-term follow-up of safety of biosimilars

- Clinical safety of biosimilar, including benefit-risk ratio, is monitored closely during post-approval phase
- Risk management plans for biosimilar developed in accordance with EU legislation and pharmacovigilance guidelines should address:
  - Identified and potential risks
  - Immunogenicity
  - Specific safety monitoring
  - Risk minimisation activities
- If treatment-related adverse reactions suspected, **name and batch number of medicinal product should be identified** in an adverse event report for traceability

EMA. http://www.ema.europa.eu/docs/en_GB/document_library/ Scientific_guideline/2013/06/WC500144124.pdf. Accessed July 21, 2014.

Pharmacovigilance: the problem of biosimilar traceability



De Veene P et al. Identification and traceability of biological products. http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2012/05/WC500127936.pdf. Accessed July 21, 2014.

Biosimilars regulations in Europe, the US and beyond

Biosimilar regulations in the EU and the US

Critical Element	EMA Guidelines	FDA Guidelines
PK studies	Single-dose, comparative human studies	Comparative human studies
PD studies	Combine with PK studies where a clinically relevant PD endpoint is available; otherwise, nonclinical evaluation required	Comparative human studies, where clinically relevant measures are available
Efficacy	Highly sensitive, dose-comparative PD studies may be sufficient; otherwise, at least one adequately powered equivalence trial	At least one adequately powered equivalence trial
Safety	At least one adequately powered equivalence trial	At least one, adequately powered equivalence trial
Immunogenicity	Must be assessed during the safety trial	At least two comparative trials, one pre- and one post-marketing

Based on: Dörner T et al. *Ann Rheum Dis*. 2013;72:322-328.

Biosimilar recommendations in rheumatology: ACR and EULAR

ACR Recommendations[1]: "Interchangeability and substitution of biologics and biosimilars should not be permitted until strong and thorough evidence supporting the biosimilarity of these products to reference biologics becomes available."

"... A biosimilar proven effective for one indication may not necessarily be effective for a second indication for which the reference biologic has been shown to be effective."

EULAR[2]**: No formal recommendations on extrapolation**

"An infliximab biosimilar cannot be regarded as 'another TNF inhibitor' in patients with an insufficient response to infliximab. ... This recommendation was voted for by 97% of the members."

1. American College of Rheumatology. Position Statement: Biosimilar. 11/2011. https://www.rheumatology.org/ACR/practice/clinical/position/biosimilars.pdf. AccessedSeptember 23, 2014.
2. Smolen JS et al. *Ann Rheum Dis.* 2014;73:492-509.

Introduction and use of biosimilars in the treatment of inflammatory rheumatic diseases *Position paper of German Society of Rheumatology (DGRh)*

- **Each biologic must have a different international non-proprietary name.**
- **A pharmacist should not change the prescription** from the original preparation to a biosimilar or vice-versa without the knowledge and/or instruction of the physician.
- **Side effects must be documented precisely in central registries (e.g. RABBIT registry)** and clearly assigned to specific products (original biologic, biosimilars).
- As long as there is no long-term data on specific indications, an **uncontrolled switch of products with each prescription between the original product and/or different biosimilars should be avoided in order to not increase possible immunogenicity due to different manufacturing processes.**
- **DGRh refuses an uncontrolled exchange between biologics due to cost reasons.**
- **DGRh considers a switch from an original product to a biosimilar which is approved only for non-rheumatic indications** (e.g. Rituximab for Non-Hodgkin Lymphoma) **as problematic as long as there are no long-term data of these biosimilars in rheumatic core indications**, because the immunological pathogenesis and concomitant medication (and thus the immunogenicity of the biologic) can influence the safety and long-term efficiency in different ways.
- **DGRh refuses forced prescription quota for biosimilars at present and in any form** as long as the required long-term data for biosimilars is not available in pharmaceutically independent central registries as mentioned above (e.g. RABBIT registry).

H.-M. Lorenz, J. Braun, K. Krüger, M. Schneider, Z Rheumatol 2014;73:784–786
Press release: http://dgrh.de/?id=9681

Opinion of the German Rheuma-Liga, Federal Association e.V. on the Introduction of Biosimilars in Germany

- Patient safety must always be of top priority when biosimilars are introduced to the market
- Extrapolation of study data in one indication to other indications is seen as critical
- Biosimilar products must be clearly identifiable by name (e.g. brand name)
- Close monitoring of effects and in particular of side effects (for all biosimilars in all indications) must be ensured after approval (e.g. RABBIT registry)
- Exchange between biosimilar and reference product must be medically justified
- In German pharmacies, interchangeability is not possible in the framework of discount contracts
- No exchange based on price policy
- Start of biosimilar treatment with great caution, in particular in indications which are only approved by extrapolation

Deutsche Rheuma-Liga, https://www.rheuma-liga.de/biosimilars
(Version: 20 June 2014)

Conclusions

- Biosimilars are highly regulated but non-identical versions of an originator biologic
  - This is due to the complexity of their molecules and manufacturing, especially for monoclonal antibodies
- EMA has created an abbreviated pathway for the approval of biosimilars based on a comparability exercise
- The comparability exercise is designed to exclude relevant differences via quality and nonclinical, as well as clinical, testing
  - Quality and cell-based assay comparisons are critical to this exercise
  - Deciding whether a difference has an impact is difficult
  - This is usually not resolved until the outcome of comparative clinical studies is available

Conclusions

- For the clinical development of biosimilars, at least one PK study and one Phase 3 trial must be part of the clinical package
  - A PK/PD study is preferred if valid pharmacodynamic data are available, especially if PD endpoints are accepted as surrogate markers for efficacy or safety
  - An efficacy Phase 3 trial for biosimilars should be run in a sensitive, homogenous population with sensitive endpoints
- In Europe, interchangeability and substitution are entirely left to the national competent authorities

SATELLITE SYMPOSIUM EAHP 2015

THANK YOU FOR YOUR ATTENTION!

Understanding the role of long-term data in cost predictability

João Eurico Fonseca

Lisbon
Academic Medical Centre

Rheumatology
Research Unit

Lisboa
Portugal

Disclosure

Session sponsored by Pfizer
The contents are of my own responsibility,
with no intervention from the sponsor.

I received unrestricted research grants or acted as a speaker
for Abbvie, Amgen, BMS, Celtrion, Celgene, Janssen, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Servier, UCB

The most crazy jokes about Portuguese (from Brazil!)

Lisbon University Experience of the day: The speed of light…

Avoid reinventing the wheel!

Presentation plan

1- Understanding the use of biologics in inflammatory diseases: Rheumatoid Arthritis (RA) as a case study

2- Long term data. Burden and long term benefits. The value of treating RA

3- Long term data demonstrate differences between real world costs and acquisition costs

4- The promise of biosimilars

5- Value of long term data for determining immunogenicity

6- Impact of dose escalation on cost

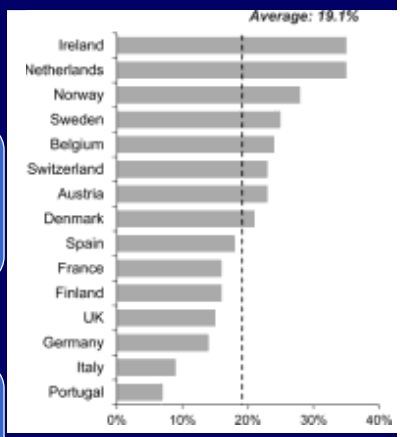
7- Traceability and registries

Rheumatoid Arthritis (RA): 0.5-1% prevalence and use of biologics in 10 to 40% of the patients

RA prevalence (0.5-1%)
Early Diagnosis

Conventional treatment
Disease Modifying Anti Rheumatic Drugs (DMARDS)

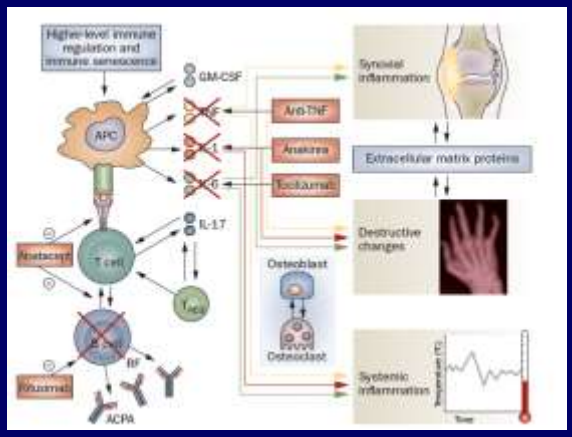
Biologics for the 30% non responders, after careful infectious risk assessment and prevention



Laires P et al. Eur J Health Econ 2013;14:875-85

9 Biologics approved in Rheumatoid Arthritis (RA)

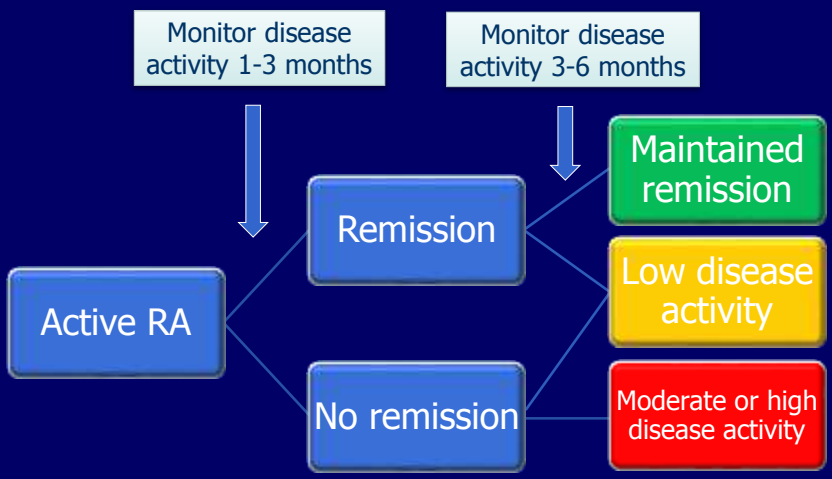
- TNF inhibitors
  - Infliximab
  - Etanercept
  - Adalimumab
  - Golimumab
  - Certolizumab
- Rituximab
- Abatacept
- Tocilizumab
- Anakinra



VanVollenhoven RF.Nat Rheum Rev. 2009

Sousa E, Fonseca JE, McInnes I, EULAR Compendium on Rheumatic Diseases

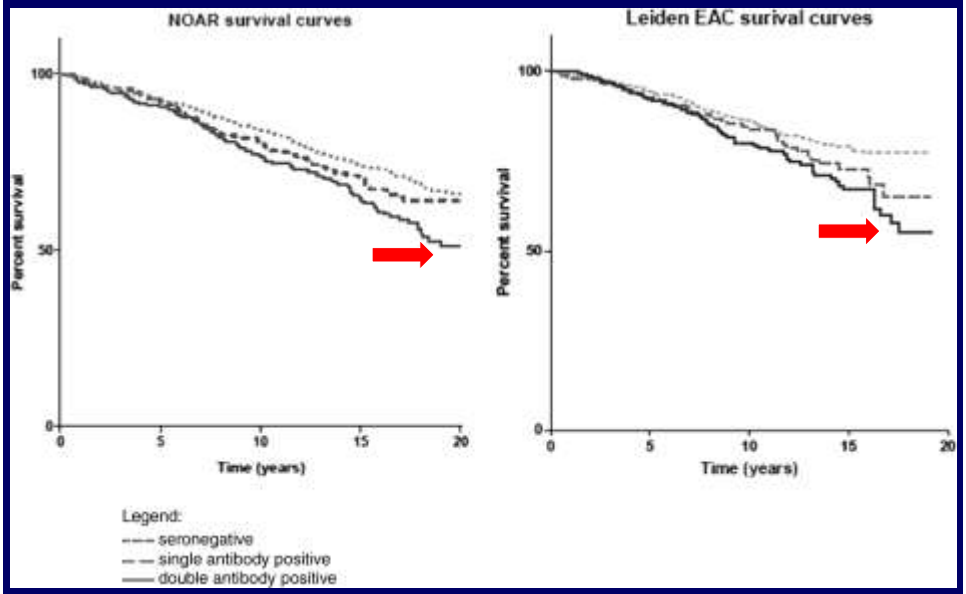
Rheumatoid Arthritis (RA) treat to target concept: the goal of remission and tight control



DAS28

Smolen J et al. Ann Rheum Dis 2010;69:631-637

Increased mortality in RA particularly in ACPA and RF double positive patients



Humphreys JH et al. Arthritis Res Ther 2014; 16: 483

Increased mortality in high disease activity RA patients

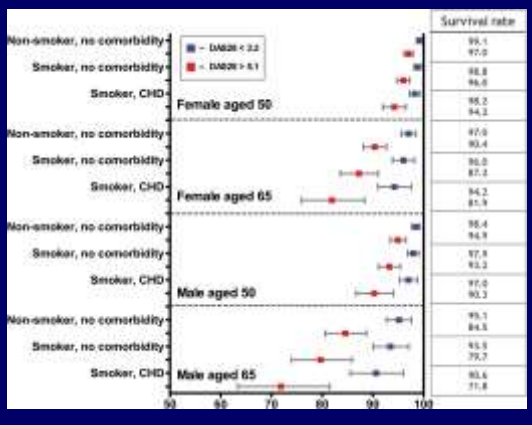


Table 2 Standardised mortality ratios (SMR) and life-years lost, in comparison with the German general population by groups of patients with different mean disease activity (DAS28) scores at follow-up

	Women			Men		
DAS28	Deaths	SMR (95% CI)	Lost life years (95% CI)	Deaths	SMR (95% CI)	Lost life years (95% CI)
<3.2	29	0,86 (0,58 to1,24)	−1,5 (−3,0 to 0,0)	13	0.54 (0.29 to 0,92)	−2,4 (−6,1 to1,3)
3,2–4,1	60	0,94 (0,72 to1,22)	0,0 (−1,4 to 1,4)	39	1,11 (0,79 to 1,52)	0,1 (−2,1 to 2,3)
>4,1–5,1	88	1,35 (1,09 to 1,67)	3,0 (1,1 to 4,9)	42	1,34 (0,96 to 1,81)	0,5 (−1,3 to 2,1)
>5,1	132	3,33 (2,79 to 3,95)	10,3 (8,9 to 11,6)	60	3,33 (2,54 to 4,30)	10,7 (8,9 to 12,6)
Total	309	1,53 (1,37 to 1,71)	2,7 (2,0 to 3,4)	154	1,41 (1,20 to 1,65)	1,9 (0,8 to 3,0)

Listing J et al. Ann Rheum Dis 2015; 74: 415-21

Mortality in RA patients reduced by anti TNF drugs and rituximab

	Unadjusted HR		Adjusted HR: 6 (rituximab 12) months risk window approach			Adjusted HR: Ever exposed approach				
	HR	95% CI	HR	95% CI	p Value	HR	95% CI	p Value	Deaths	PYRS
Prednisone most recent 12 months: 0 mg/d	Ref.		Ref.			Ref.			88	9036
1–5 mg/d	1.33	1.00 to 1.76	1.05	0.80 to 1.38	0.71	1.04	0.79 to 1.37	0.77	177	13 615
>5–10 mg/d	2.22	1.65 to 2.98	1.46	1.09 to 1.95	0.013	1.41	1.06 to 1.89	0.021	140	7086
>10–15 mg/d	3.95	2.61 to 5.98	2.00	1.29 to 3.11	0.0033	2.01	1.30 to 3.11	0.0030	37	1170
>15 mg/d	6.68	4.06 to 11.0	3.59	2.11 to 6.13	<0.0001	3.43	2.01 to 5.86	<0.0001	21	448
FFbH* in % of full function per 10% improvement	0.76	0.73 to 0.79	0.88	0.84 to 0.93	<0.0001	0.89	0.85 to 0.93	<0.0001		31 378
Methotrexate	Ref.		Ref.			Ref.			96†/78‡	7012†/6469‡
Other synth. DMARDs	2.53	1.95 to 3.28	1.14	0.86 to 1.51	0.36	0.98	0.60 to 1.59	0.92	126†/31‡	3513†/1581‡
TNFα inhibitors	0.77	0.61 to 0.98	0.64	0.50 to 0.81	0.0007	NA			182†	16 843†
Rituximab	1.01	0.70 to 1.46	0.57	0.39 to 0.84	0.0062	NA			36†	2599†
TNFα inhibitors or rituximab	NA		NA			0.77	0.60 to 0.97	0.0312	330‡	22 370‡
Other biologics	1.02	0.68 to 1.52	0.64	0.42 to 0.99	0.043	0.91	0.66 to 1.25	0.54	25†/51‡	1654†/2806‡
DAS28>4.1 for > 6 (12) months after discon- tinuation of a biologic without start of a new one	NA		NA			2.08	1.59 to 2.72	<0.0001	86‡	1812‡

Listing J et al. Ann Rheum Dis 2015; 74: 415-21

Increased sick leave, annual direct and indirect cost in working RA patients comparing to individuals without RA

Population Characteristic	US Civilian Noninstitutionalized Labor Force in 2010, Millions
Base population	139.064
Prevalent rheumatoid arthritis population	1.10
Incremental absence days	3.95
Incremental annual direct health care costs, $	5,174.28
Incremental annual indirect costs, $	579.17
Total incremental annual costs, $	5,753.45

Kleinman NL et al. J Occup Environ Med 2013; 55: 240-4

Improved function and decreased sick leave, disability and direct costs in RA patients in remission

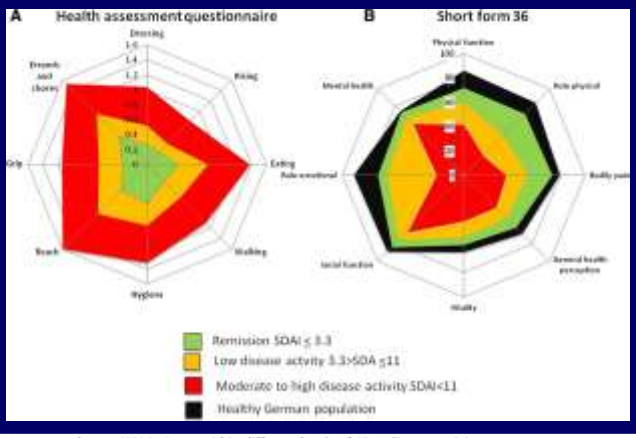
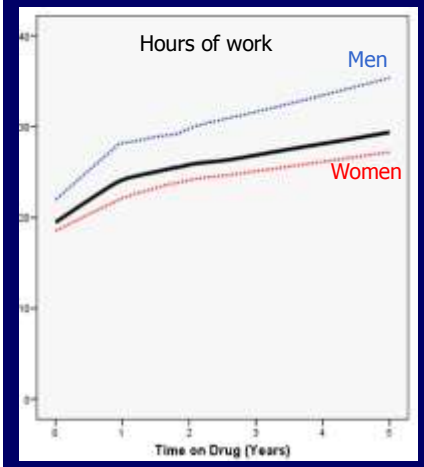


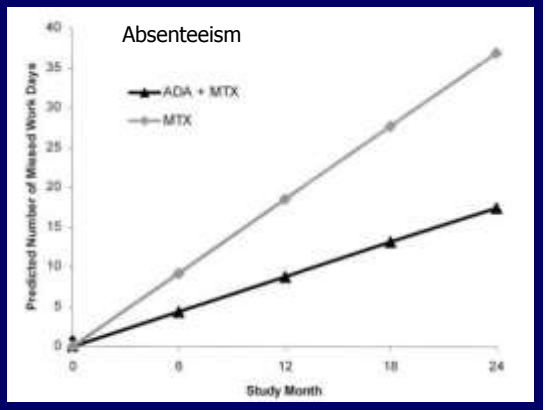
Table 3 Mean annual costs (SD) in Euros within different levels of SDAI disease activity

	Costs resource use	Treatment costs	Total direct costs	Costs sick leave	Costs work disability (HCA)	Costs work disability (FCA)
REM	€808.28 (2,491.24)	€539.64 (729.46)	€1,367.92 (2,621.94)	€1,285.2 (1,502.1)	€5,772.8 (3,388.7)	€917.5 (538.3)
LDA	€1,039.02 (2,561.41)	€603.93 (762.06)	€1,642.95 (2,644.7)	€1,874.2 (2,185.9)	€7,186.6 (4,864.9)	€1,142.1 (772.8)
MDA/HDA	€1,702.39 (3,500.74)	€637.85 (748.46)	€2,340.24 (3,686.89)	€3,291.9 (2,871.3)	€10,525.7 (6,129.2)	€1,672.5 (973.7)
P value	0.06	0.65	0.05	<0.01	<0.01	<0.01

Radner H et al. Arthritis Res Ther 2014; 16: R56

Hours of work gained and absenteeism reduced by anti TNF drugs

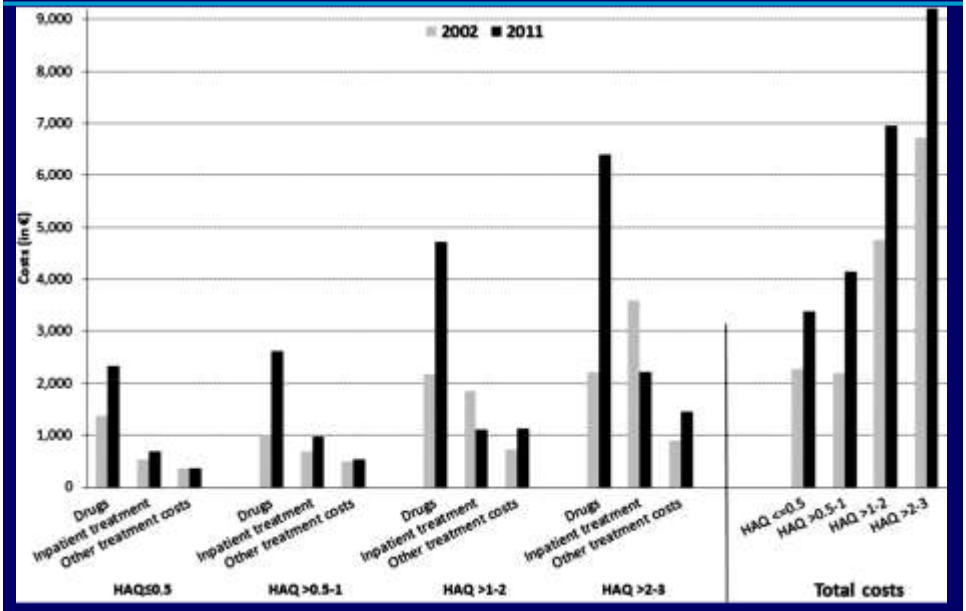




Augustsson et al, Ann Rheum Dis 2010; 69: 126

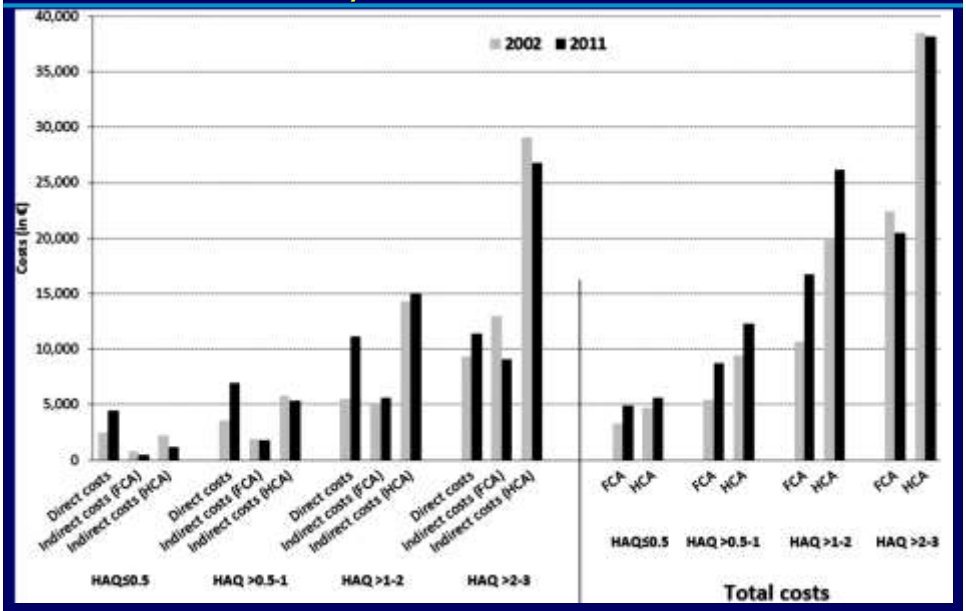
Augustsson et al, Ann Rheum Dis 2010; 69: 126

2000–2010 direct RA costs in Germany at current prices increased in all aspects particularly in the more disabled



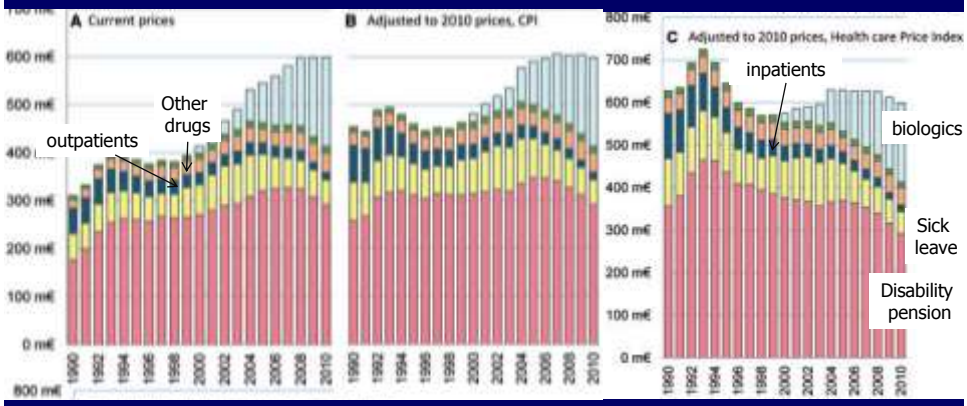
Huscher D et al. Ann Rheum Dis 2015; 74:738-45

2000–2010 increase in direct RA costs in Germany are offset by a decrease in indirect cost



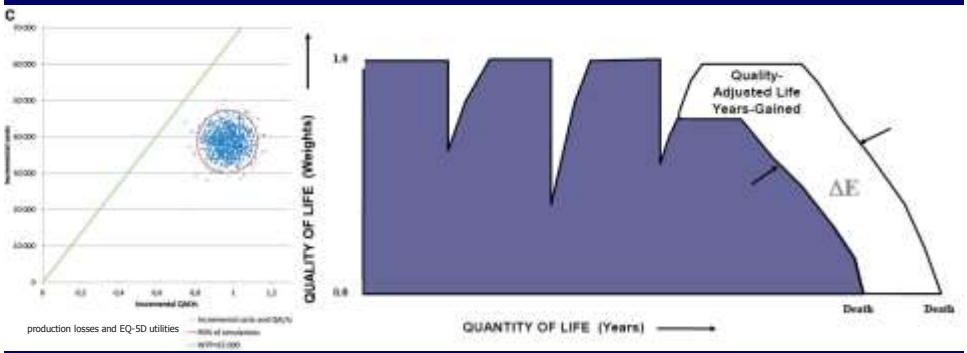
Huscher D et al. Ann Rheum Dis 2015; 74:738-45

1990–2010 RA costs in Sweden corrected for health care price are stable but sick leave and disability decreased



Kalkan A et al. Rheumatology 2014;53:153-60

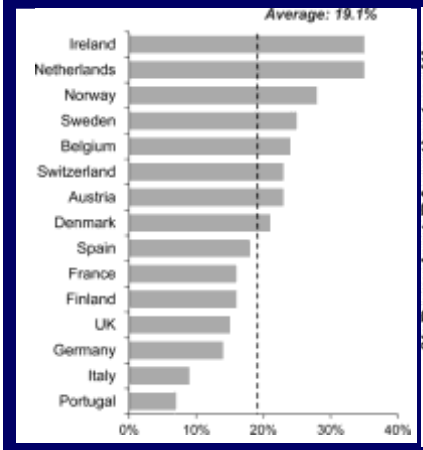
Anti TNF drugs are cost effective in RA accounting for EQ-5D and production losses. Probable Quality Adjusted Life Years Gained

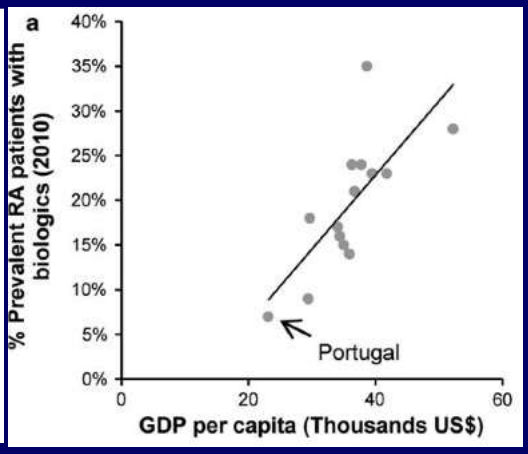


Kvame MV A et al. Model Rheumatol 2015;11:1-11

Adapted from Aslam Anis, personal communication 2011

…But cost is still an issue and there is a correlation between GDP and patients' access to biologics across countries





Laires P et al. Eur J Health Econ 2013;14:875-85

Equivalent efficacy and safety of infliximab biosimilar comparing to infliximab originator

Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study

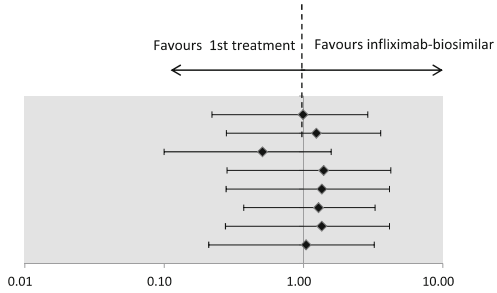
Dae Hyun Yoo,[1] Pawel Hrycaj,[2] Pedro Miranda,[3] Edgar Ramiterre,[4] Mariusz Piotrowski,[5] Sergii Shevchuk,[6] Volodymyr Kovalenko,[7] Nenad Prodanovic,[8] Mauricio Abello-Banfi,[9] Sergio Gutierrez-Ureña,[10] Luis Morales-Olazabal,[11] Michael Tee,[12] Renato Jimenez,[13] Omid Zamani,[14] Sang Joon Lee,[15] HoUng Kim,[16] Won Park,[17] Ulf Müller-Ladner[18]

Yoo D et al. Ann Rheum Dis 2013; 72: 1613-20

Comparable efficacy and safety in meta-analysis of infliximab biosimilar vs. other biologics

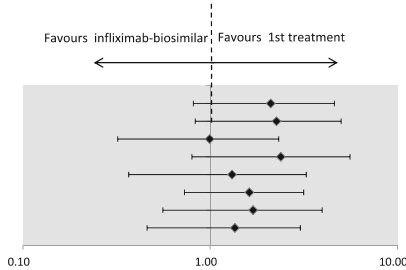
ACR20 at week 24

Comparison	OR (95% CI)
abataceptvs. infliximab-biosimilar	0.99 [0.22-2.89]
adalimumab vs. infliximab-biosimilar	1.24 [0.28-3.58]
certolizumabvs. infliximab-biosimilar	0.51 [0.1-1.58]
etanercept vs. infliximab-biosimilar	1.39 [0.28-4.24]
golimumab vs. infliximab-biosimilar	1.35 [0.28-4.13]
infliximab vs. infliximab-biosimilar	1.28 [0.37-3.26]
rituximab vs. infliximab-biosimilar	1.35 [0.28-4.14]
tocilizumab vs. infliximab-biosimilar	1.04 [0.21-3.22]



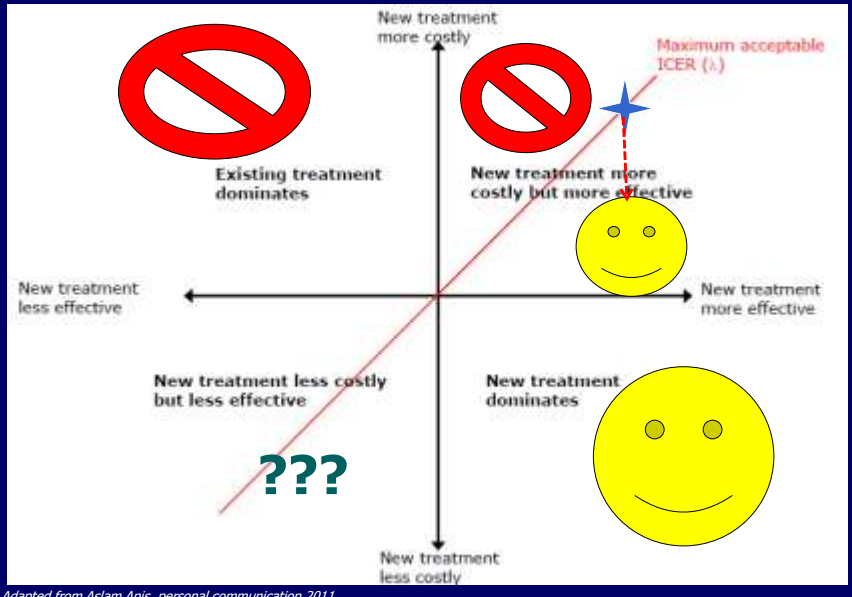
Serious AE at week 24

Comparison	OR (95% CI)
abatacept vs. infliximab-biosimilar	2.11 [0.81-4.61]
adalimumab vs. infliximab-biosimilar	2.26 [0.83-5]
certolizumab vs. infliximab-biosimilar	0.99 [0.32-2.32]
etanercept vs. infliximab-biosimilar	2.38 [0.8-5.59]
golimumab vs. infliximab-biosimilar	1.31 [0.37-3.26]
infliximab vs. infliximab-biosimilar	1.62 [0.73-3.16]
rituximab vs. infliximab-biosimilar	1.7 [0.56-3.96]
tocilizumab vs. infliximab-biosimilar	1.36 [0.46-3.03]



Baji P et al. Eur J Health Econ 2014; S1: S53-64

The promise of biosimilars: same efficacy, less cost



Adapted from Aslam Anis, personal communication 2011

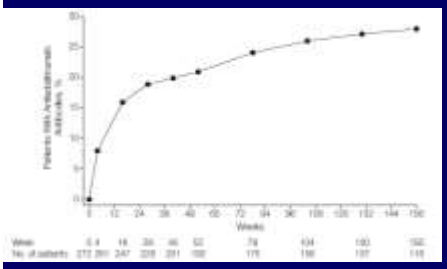
Small changes in structure, formulation and handling can affect immunogenicity: worries with biosimilars

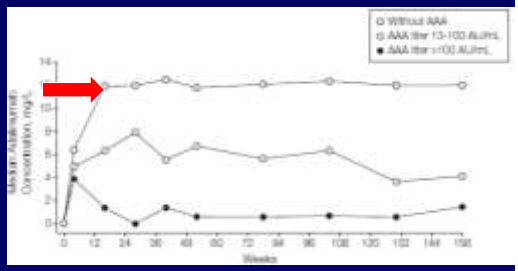
1. Schellekens H. Nat Rev Drug Discov. 2002;1:457-462. 2. Roger SD. Expert Opin Biol Ther. 2010;10:1011-1018.

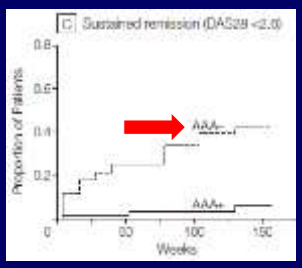
Consequences of immunogenicity

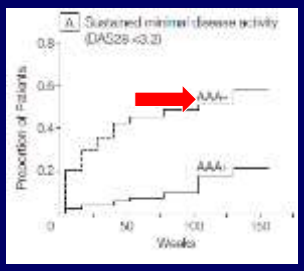
- Antibodies against drug appearing over months/years
- Lower levels of the drug
- Loss of efficacy over months/years
- Increase dose and frequency of the drug
- Immune complexes may lead to manifestations of immune mediated symptoms (lupus like, etc)
- Allergic reactions

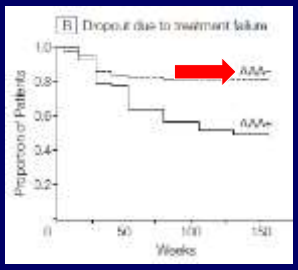
Immunogenicity take months/years to develop and affect drug levels and efficacy: leading to an increased dose!











Bartelds GM et al. JAMA 2011;305:1460-8

Increase in dose and/or frequency of infliximab administration raises costs

Table 1 Unit cost per item used in the model

Description	Cost (€)
Etanercept 50 mg/1 mL ×4 prefilled syringe 756€/Month	756.96
Infliximab 100 mg/vial 3mg/Kg (8/8W), average 70Kg, 426€/Month	426.00
Adalimumab 40 mg 762€/Month	381.39
Methotrexate 2.5 mg/tablet, 100 tablet bottle	3.57
Physician office visit[a]	5.00
Day care hospitalization[b]	85.00

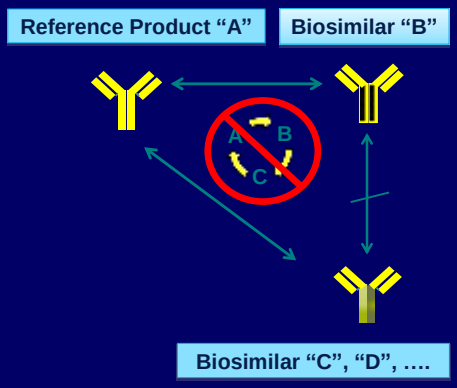
Annual cost in Euros

	New patients		Existing patients**
	Nonresponders	Responders*	Responders
Scenario 2 Dose escalation: 0% (etanercept), 0% (adalimumab), and 55% (infliximab) (Hellenic Registry[46])			
Etanercept	2,276 (NA)	9,845 (NA)	9,840 (NA)
Etanercept + MTX	2,278 (NA)	9,857 (NA)	9,852 (NA)
Infliximab + MTX	3,171 (NA)	11,238 (11,124–11,349)	10,397 (10,147–10,645)
Adalimumab	2,293 (NA)	9,921 (NA)	9,916 (NA)
Adalimumab + MTX	2,296 (NA)	9,932 (NA)	9,927 (NA)

Fragoulakis V et al. Clinecon Outcomes Res 2015; 7: 85-93

Tracking and Traceability

- Substitution may complicate effective pharmacovigilance as repetitive switching may subvert the ability to attribute adverse events to the appropriate agent.[1]
- Some adverse reactions, including immunogenic reactions such as pure red cell aplasia (PRCA), are delayed in onset and may develop only after several months of treatment.[2]



1. Dorner T. et al. Ann Rheum Dis. 2012;00:1-7.
2. Gershon, Sharon K, et al. New England Journal of Medicine. 2002;Vol. 346:1584-1585.

Insure traceability by avoiding automatic substitution, by prescribing by brand name and by using registers

The Portuguese Society of Rheumatology position paper on the use of biosimilars

João Eurico Fonseca, João Gonçalves, Filipe Araújo, Inês Cordeiro, Filipa Teixeira, Helena Canhão, José António Pereira da Silva, Sandra Garcês, Luís Cunha Miranda, Sofia Ramiro, Ana Roxo, Fernando M. Pimentel-Santos, Viviana Tavares, Adriano Neto, Alexandre Sepriano, Armando Malcata, Augusto Faustino, Cândida Silva, Catarina Ambrósio, Cátia Duarte, Cláudia Miguel, Filipe Barcelos, Helena Santos, Inês Cunha, João Carlos Ramos, José António Melo Gomes, José Bravo Pimentão, Lúcia Costa, Luís Maurício, Margarida Silva, Miguel Bernardes, Mónica Bogas, Paulo Clemente Coelho, Paulo Monteiro, Renata Aguiar, Rui André, Rui Leitão, Sofia Pimenta, Tiago Meirinhos, Susana Fernandes, Vera Las, Walter Castelão on behalf of Sociedade Portuguesa de Reumatologia

ACTA REUMATOL PORT. 2014;39:60-71

1- this position statement is contrary to automatic substitution;

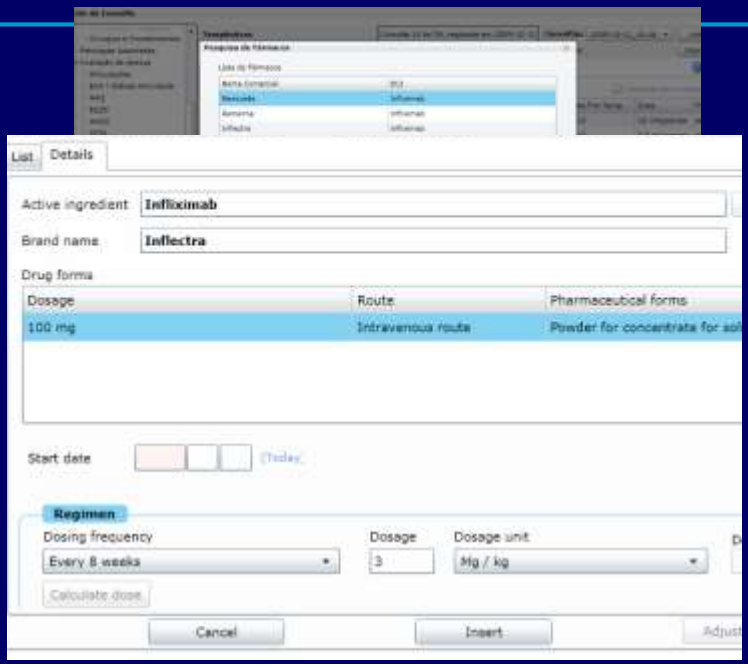
2- defends either a different INN or the prescription by brand name;

3- switching only based on physician decision and after patient information;

4- recommends the registration of all biosimilar treated patients in Reuma.pt for efficacy, safety and immunogenicity surveillance, following the strategy already ongoing for originators;

Registers should actively promote tracking of biosimilars

Registers should identify the brand name



Observational studies promoting formal evaluation of efficacy, safety and immunogenicity: How we did it?

Observational study approved by the ethical commission

New patients and patients on treatment with infliximab are invited to participate in the observational study and sign an informed consent

Efficacy, safety and immunogenicity formally evaluated

Conclusion

1. Biologics have had a major positive impact on morbidity, disability and mortality of RA, at long term
2. Adequate RA treatment reduce costs.
   Biologics are cost effective
3. Biosimilars constitute a promise of less costs with equal efficacy and safety
4. Immunogenicity and some adverse effects can take months/years to appear and impact on costs
5. Long-term data is crucial to capture comprehensive information on biosimilars including costs

Biosimilars – The Role of Pfizer in the Evolving Environment

EAHP 2015 Symposium

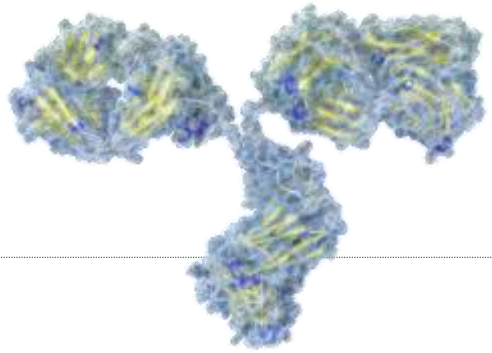
Hamburg – March 25, 2015

Sylvie St-Laurent
Corporate Affairs

Pfizer CORPORATE AFFAIRS

Overview

- Quick recap on biosimilar development
- Regulatory systems for biosimilars
- European regulations and policies
- Key to building physician and patient confidence



Many policy issues being debated – Why?

- Interchangeability
- Automatic substitution
- Switching
- Prescribing practices
- Inclusion in national registries
- WHO INN scheme?
- Tendering
- Quotas

Developing a biosimilar is like re-creating an “Old Master”

The reference product

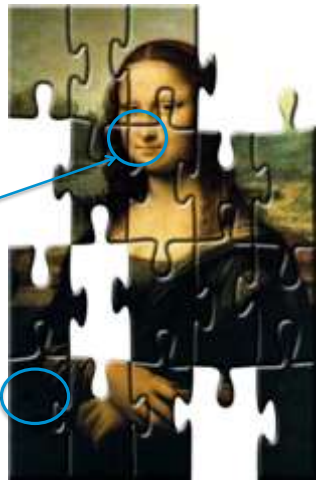
The biosimilar

There will be differences. But which differences matter?

= Only those that are clinically meaningful

Possibly **is** a “clinically meaningful difference”

Possibly **is not** a “clinically meaningful difference”



The development plan focuses on establishing similarity

(not clinical benefit)

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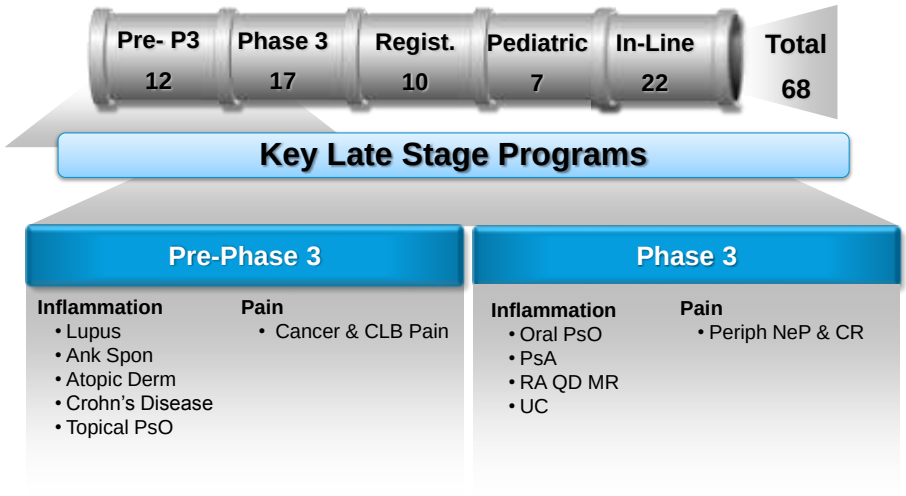
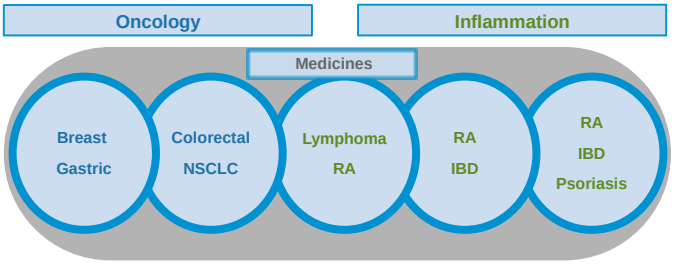
Pfizer has a rich history in biologic manufacturing

And a commitment to scientific innovation in Inflammation



Biosimilars: we're also investing in hard-to-make monoclonal antibodies



Phase III Clinical Trials Currently Recruiting	European sites
HER2+ metastatic breast cancer	✔
Neo-adjuvant breast cancer	✔
Rheumatoid arthritis	✔

Regulatory systems for biosimilars

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Biosimilars ≠ generics

Because biologics, including biosimilars, are larger and more complex molecules than small chemical medicines and generics, they are much more difficult to manufacture, not possible to replicate exactly, and are regulated differently:[1,2]

Small Molecule Drug

- Proof of quality
- Pharmacokinetic bioequivalence
- No substantial clinical data
- 2 years to develop[3], $1-2M costs

→ **Generics**

Biologic

- Proof of quality & similarity
- Pharmacokinetic bioequivalence
- Clinical safety and efficacy comparability data
- 5-9+ years to develop[3], $42-135M costs

→ **Biosimilars**

Biosimilars can never be identical copies of innovator biologics, and therefore need to be more closely regulated than generics

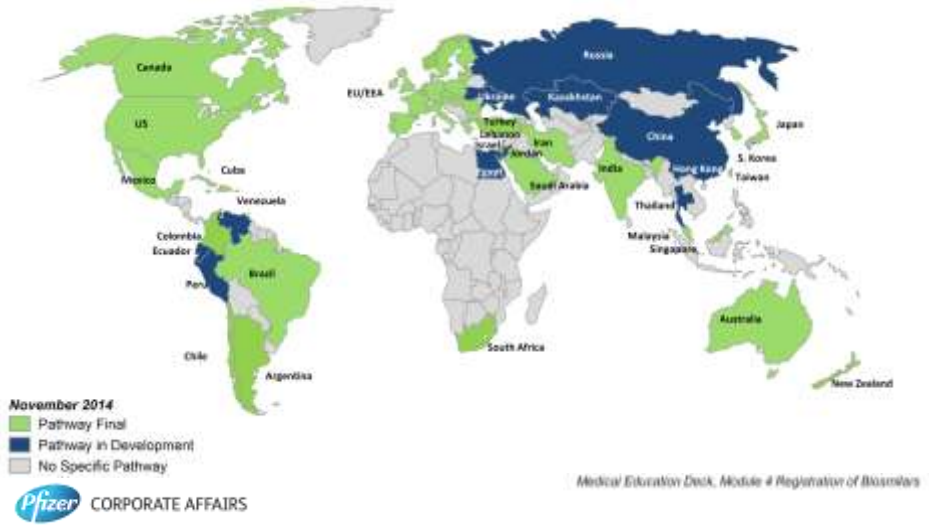
1. European Commission. What you Need to Know about Biosimilar Medicinal Products. A Consensus Information Paper 2013
2. Schellekens H et al. NDT Plus. 2009;2(suppl 1):i27-i36
3. GaBI. Development of Biosimilars. website. January 2011. Available at: http://www.gabionline.net/Biosimilars/Research/Development-of-biosimilars (accessed August 2014)

Regulatory: Biosimilars pathways evolving at different rates

Biosimilars are available in many countries

The definition of "biosimilar" can differ throughout the world

All biosimilars are not held to the same level of regulatory standards



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Medical Education Deck, Module 4 Registration of Biosimilars

Pathways aligned to the WHO's Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs)

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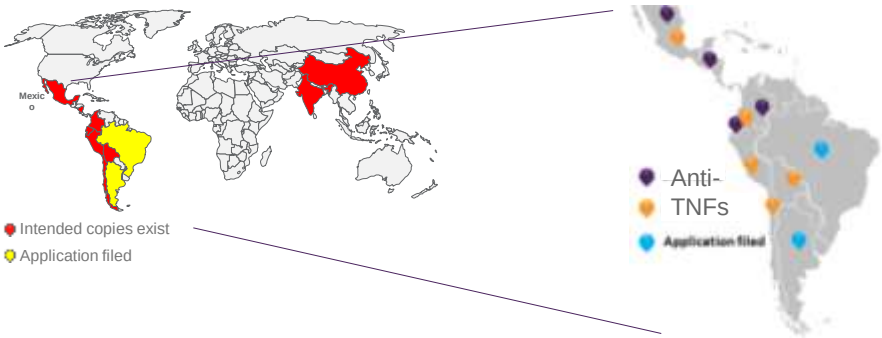
Given non-existent or delayed biosimilar regulatory laws, Intended Copies are present in several countries



•Biosimilars (*comparative development)

- Demonstrated similarity to reference product in physicochemical characteristics, efficacy and safety
- Consistent standards ensured via comparison to reference product which itself was approved to high standard

•Intended Copies (non comparative development)

- Copy not developed, assessed, and approved according to WHO regulatory guidelines and standards for biosimilars
- Therefore may have clinically signification differences in formulation, doses/dosing regimen, efficacy, safety and immunogenicity

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In Europe, some issues are regional; others national

EMA / European Commission

- Sets Regulatory Approval Standards
- Grants Marketing Authorisation
- Sets Guidance on Labeling, Naming & Pharmacovigilance

National Governments

- Determine if and which biosimilars are interchangeable
- Are responsible for enforcing prescription of biologics by brand name
- Set policies on access, such as automatic substitution
- Set policies on procurement, such as tendering and quotas

NOT ALL ISSUES ARE FULLY DECIDED

- **Both the innovative pharmaceutical industry and biosimilar manufacturers are heavily involved in these discussions with regulators and policy makers**
- **There is not a consensus on all issues**
- **Stakeholders (clinicians, patient groups, medical societies) tend to have lower level of input but are increasingly being asked to provide their views**

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Pfizer policy position - biosimilars

1. Innovators should be provided significant regulatory exclusivity to further biologics development and to support the continued flow of innovative medicines
2. The approval process for biosimilars should be rooted in statutory authority
3. The approval process for biosimilars should be grounded in assessment of the overall research and development program, from analytical through clinical trial data
4. Safety and effectiveness standards should be determined on a “product-by-product” basis, and not as a “one size fits all” standard
5. The reference product must be chosen based on stringent criteria
6. Interchangeability should be based on science and physician supervision, and the standard for interchangeability should be higher than that of biosimilarity
7. Biological medicines (including biosimilars) are not suitable for automatic substitution
8. Biosimilar names and labelling should be distinguishable from the innovator product
9. Biosimilars should be subject to rigorous post-marketing surveillance
10. Regulatory agencies worldwide should have consistency among approval processes

Pfizer believes regulators should require the highest standards for regulatory approvals to ensure development of high-quality, safe, and efficacious biosimilars

European Regulatory System for Biosimilars

- In 2005, the EU pioneered the "biosimilars" concept
- Recognized that biosimilars should not be regulated either like a new biologic, nor a generic
- Other regions including US/Japan/Canada/Australia built their regulatory framework on the EU model

- High regulatory standards
- Emphasis on pharmacovigilance
- Not all clinical trials of the original biologic have to be repeated
- Accepts 'extrapolation' on a case-by-case basis

- Labeling is identical to that of the reference product (generic approach)
- Original biologic and all approved biosimilars can share same INN (generic approach)

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Labeling

- In Europe, the biosimilar SmPC does not include any information on the clinical trials that were conducted to obtain approval – it replicates the original biologic label entirely which is often misinterpreted by physicians.

- Package Leaflets provide important safety information and instructions for patients on how to use a medicine. In Europe, they do not indicate that medicines are a biosimilar.

Physicians must be in a position to make informed decisions about the medicines they prescribe to their patients

Patients have a right to know which medicines they are receiving.

The lack of transparency sends the wrong message to medical community and patients.

Rather than instilling confidence to use biosimilars, this approach does not educate and may generate more questions.

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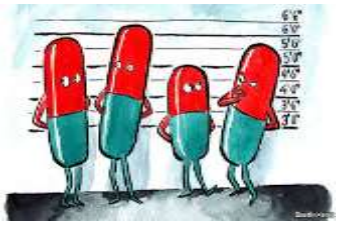
Summary of Product Characteristics -
A document approved as part of the marketing authorisation of each medicine

Naming (INN)

- Under current European legislation, biosimilars are not required to have a unique or distinguishable INN. This means that two or more medicines (the originator biologic medicine and all approved biosimilars) can share the same INN

- The adverse events associated with biologics can have significant clinical consequences, and some adverse events may be rare and difficult to detect in any traditional pre-market testing programme



This has led to the draft EMA recommendation to prescribe biological medicines by brand name and batch number in order to ensure traceability

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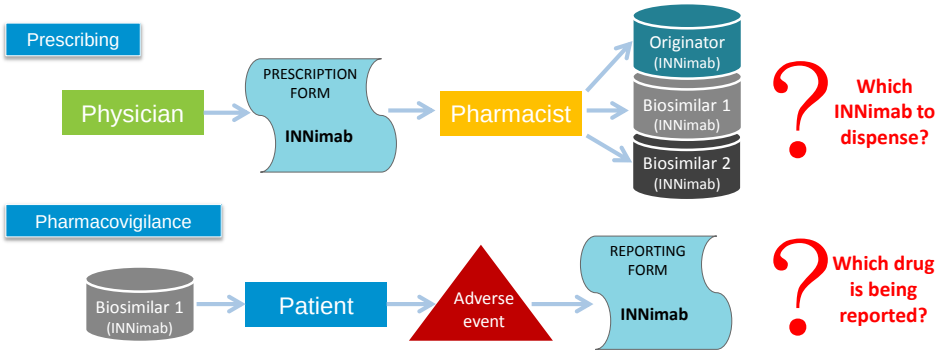
International non-proprietary names (INNs): A system designed by the WHO (World Health Organization), where an INN identifies a pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property. A non-proprietary INN is also known as a generic name.[1]

Regulatory considerations: Traceability

Use of the INN alone may cause confusion



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Dorner T, et al. Ann Rheum Dis 2013;72:322–328.

INN, international non-proprietary name.

So what's the problem?

- For cost-saving reasons, some European governments require physicians to use the INN when prescribing medicines. This is to ensure that the pharmacist dispenses the least expensive drug
- In the context of biological medicines, this can result in the unintended substitution of an original biologic (or biosimilar) with another biosimilar

We need multiple ways of identifying products, including the trade name, separate INNs, Marketing Authorisation Holder and lot / batch number in order to:

- Properly trace and assign all ADRs
- Prevent misattribution of safety issues to individual products while aggregating data to detect class effects

ADR = adverse drug reactions

A Global Naming System – Another option?

Ongoing discussion:

World Health Organization

- In July 2014, the World Health Organization (WHO) issued a draft proposal for assignment of biological qualifiers to ensure that all biological medicines are distinguishable
  - There is general support for this initiative but several clarifications/ additional guidance are needed on the proposed scheme
  - The voluntary nature of this scheme could result in a "mixed" system in which some markets adopt the proposal in full, partially, or not at all
  - The EMA has so far said Europe does not need this
  - However other regulators (Japan, Australia) which previously created their own naming system are supportive

Switching – Lack of policy coherence

On the one hand, a recognition that biologics are different

- No EU member-state has explicitly authorised interchangeability or substitution
- 19 of 31 European countries have either laws or guidelines against automatic substitution of biologics
- Medical societies are unanimously opposed to automatic substitution

Yet non-medical switching can happen for other reasons

- In 24 countries, tenders include biologics, mainly in hospitals; the risk of switching stable patients exists in 11 countries
- In 17 countries, biologics are included in mandatory or recommended INN prescription
- 15 countries have reference pricing, and switches can happen 6 of those countries

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National Policies: Analysis - EU28 + Norway, Serbia, Switzerland (EBE – March 2014)

The key to creating trust in biosimilars:

- Clarity → Transparent labelling
- Consistency → Distinguishable names
- Coherence → Formal policies that prevent non-medical switching
- Carefulness → Until we have the clinical data on the long-term consequences of interchangeability and substitution, decision-makers need to be careful not to over-reach on issues of interchangeability, switching and procurement policies

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Europe has led the way … still a bit more to do

- *Europe has strongly supported the development of biosimilars*
- *It has developed robust approval standards and strict pharmacovigilance principles to ensure patient safety*

- Pfizer has a stake in the success of biosimilars and we need a set of regulations and policies that:
  - Support their uptake
  - Reflect the complexity of biologics
  - Recognize that these are early days for biosimilars
  - Respect the right of the physician to choose the treatment that is most appropriate for their patient

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Your questions

- You can ask your question using the aisle microphones
- Alternatively, you can still submit a question card to one of the hostesses

SATELLITE SYMPOSIUM EAHP 2015

Michael Sobanja

CHAIR'S SUMMARY

Please remember to fill out your evaluation form

- Please leave this on your seat for collection

SATELLITE SYMPOSIUM EAHP 2015

THANK YOU

SATELLITE SYMPOSIUM EAHP 2015

BIOSIMILARS IN INFLAMMATORY DISEASE: A VALUE PERSPECTIVE

25 March 2015
16:15–17:45
Hall 6