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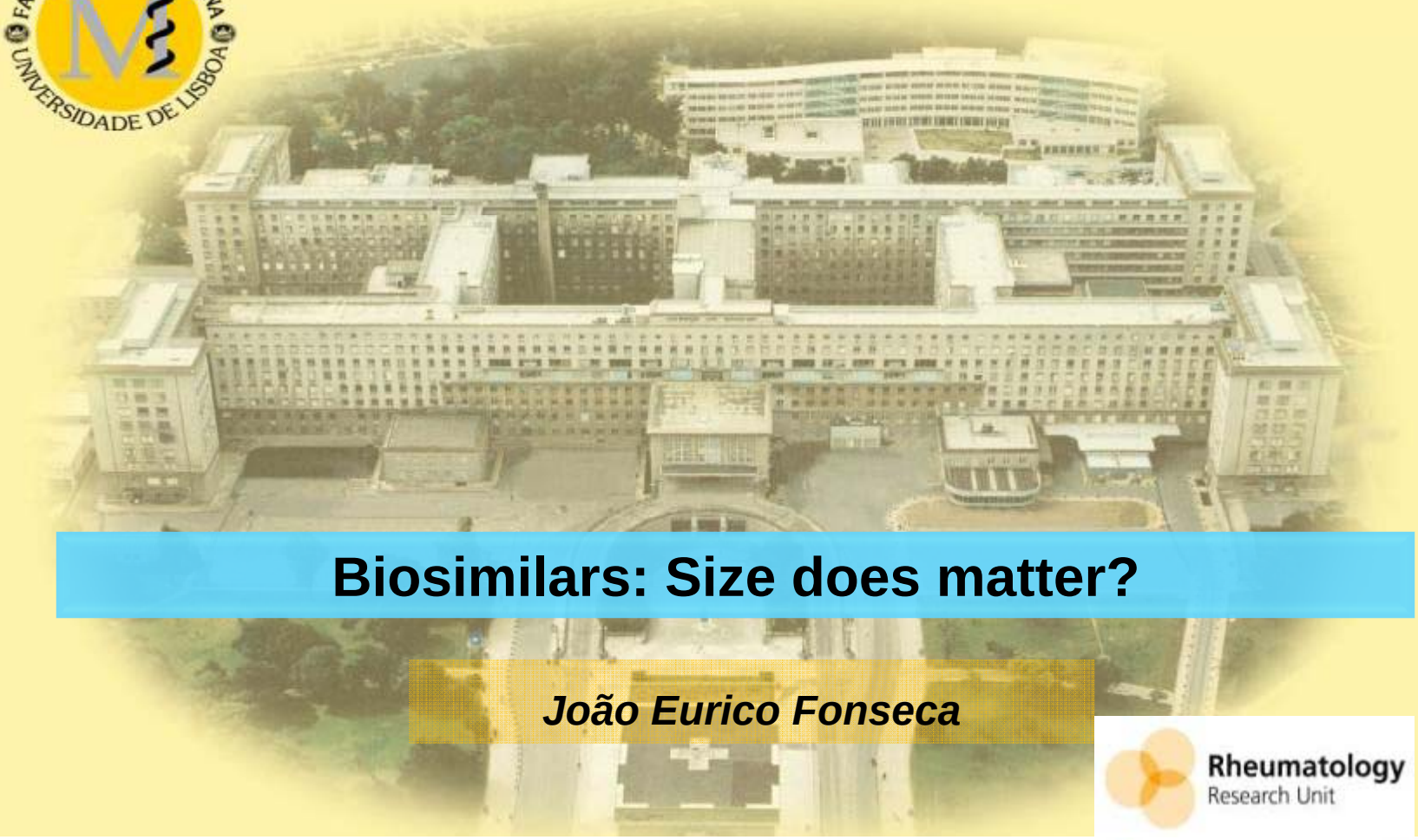
Innovative Medicines for Malaysia
1ST NATIONAL
BIO-THERAPEUTICS
CONGRESS – PUTTING PATIENT FIRST
22 NOVEMBER 2014



Biosimilars: Size does matter?

João Eurico Fonseca

Rheumatology Research Unit

CENTRO ACADÉMICO DE MEDICINA DE LISBOA

HOSPITAL DE SANTA MARIA — CENTRO HOSPITALAR LISBOA NORTE, EPE

Hospital Pulido Valente

Disclosure

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

Sharing experiences over the centuries

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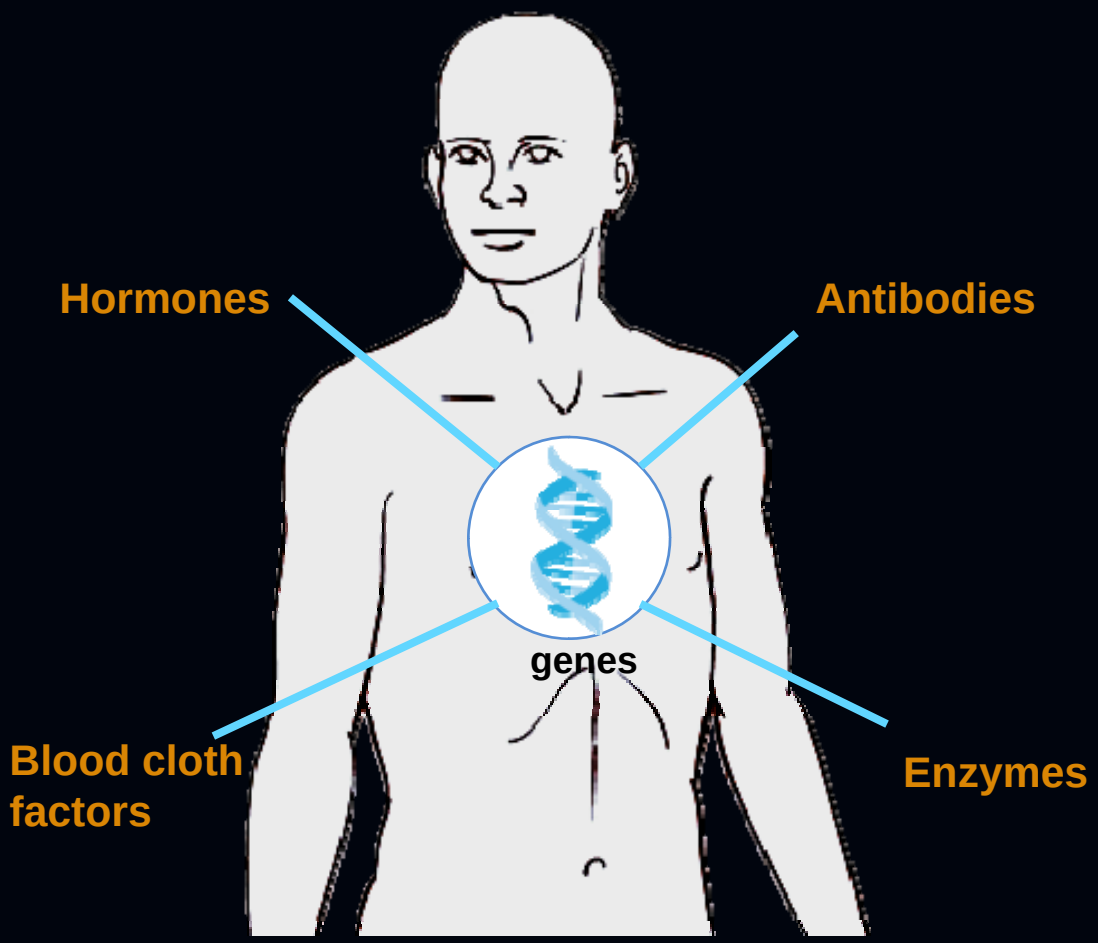
Outline of the presentation

- The heterogeneity of biologics
- Biosimilar concept
- Clinical data requirements
- Interchangeability, switching, substitution, tracking & extrapolation
- The rheumatology experience
- The Portuguese experience
- My opinion

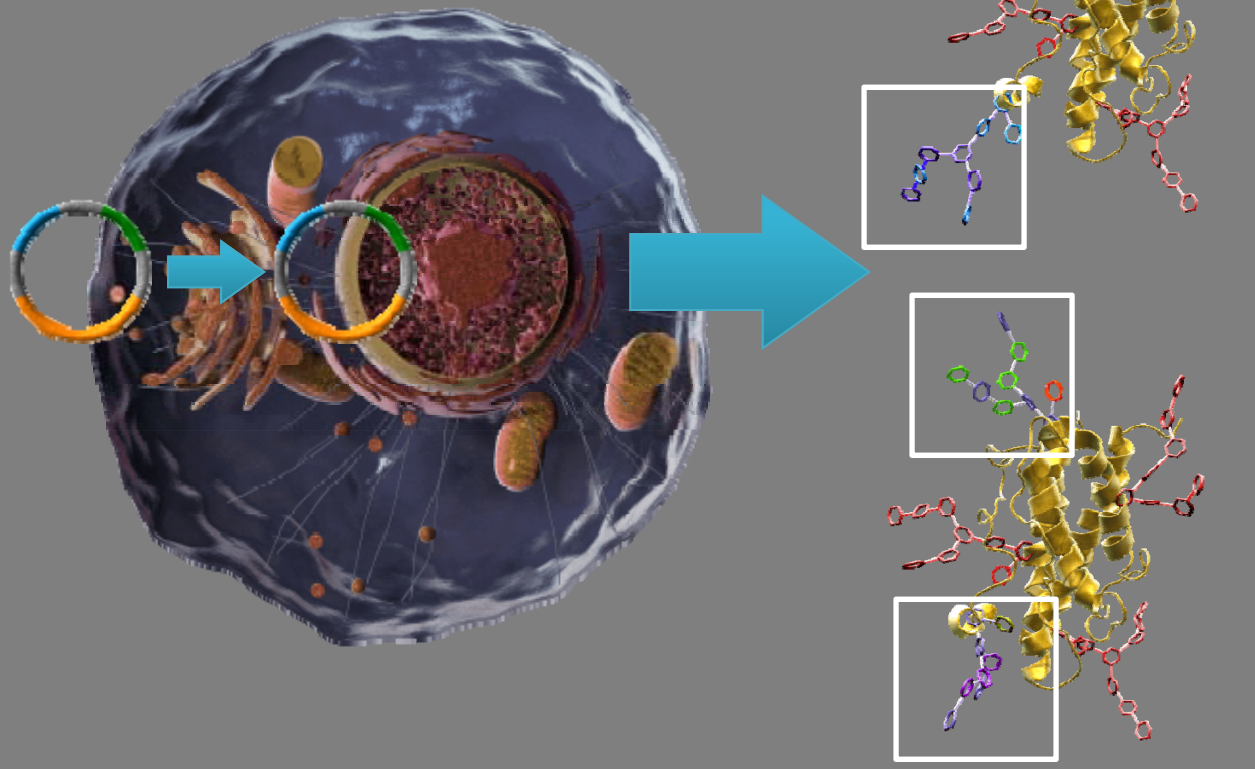
The Heterogeneity of Biologics

The most advanced lab: the human body!

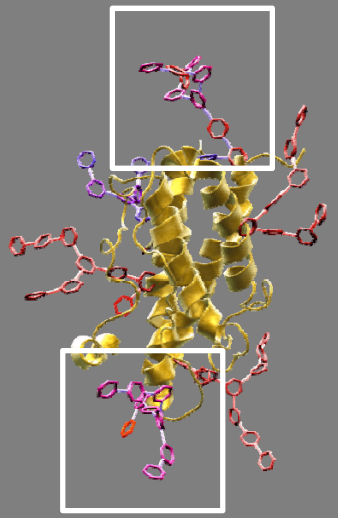


Biologics Are Produced Within Living Cells

DNA Sequence inserted by plasmid vector



Heterogeneity of Protein Product



Mellstedt H, et al. *Ann Oncol*. 2008;19:411-419.

Among biologics monoclonal antibodies are the most complex

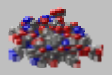
Small molecule

Aspirin

180 Daltons
2160 atoms

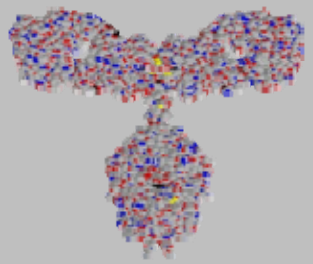
Biologics

Insulin (hormone)



6000 Daltons
72000 atoms

Adalimumab (monoclonal antibody)



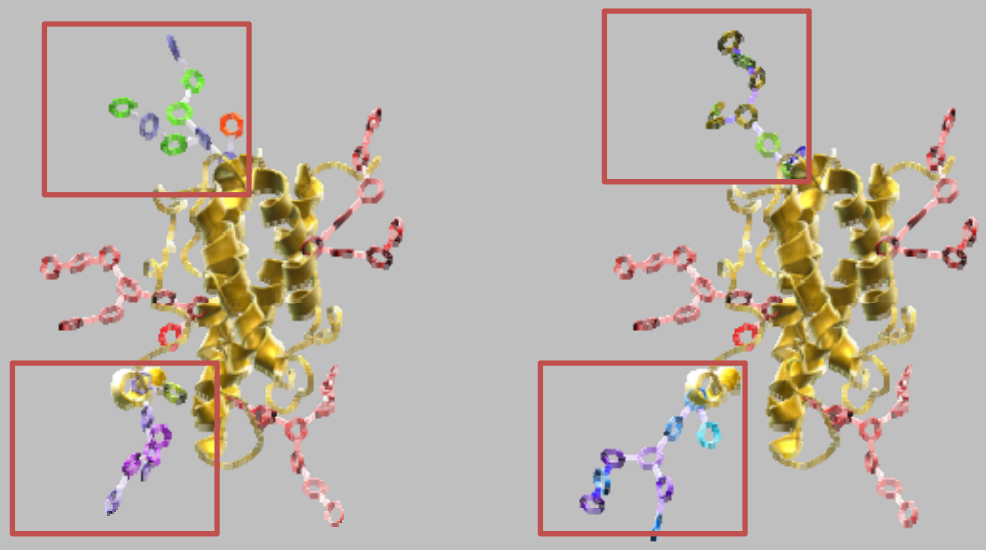
148,000 Daltons
1,776,000 átomos

Monoclonal antibodies are gigantic structures in comparison with conventional small molecules

Weight and number of atoms
one thousand
larger than conventional small molecules

Biologics Heterogeneity

- Each biologic protein product represents a mixture of closely related compounds[1,2]
- Post translational modifications can occur in response to even subtle changes in manufacturing process[1,2]



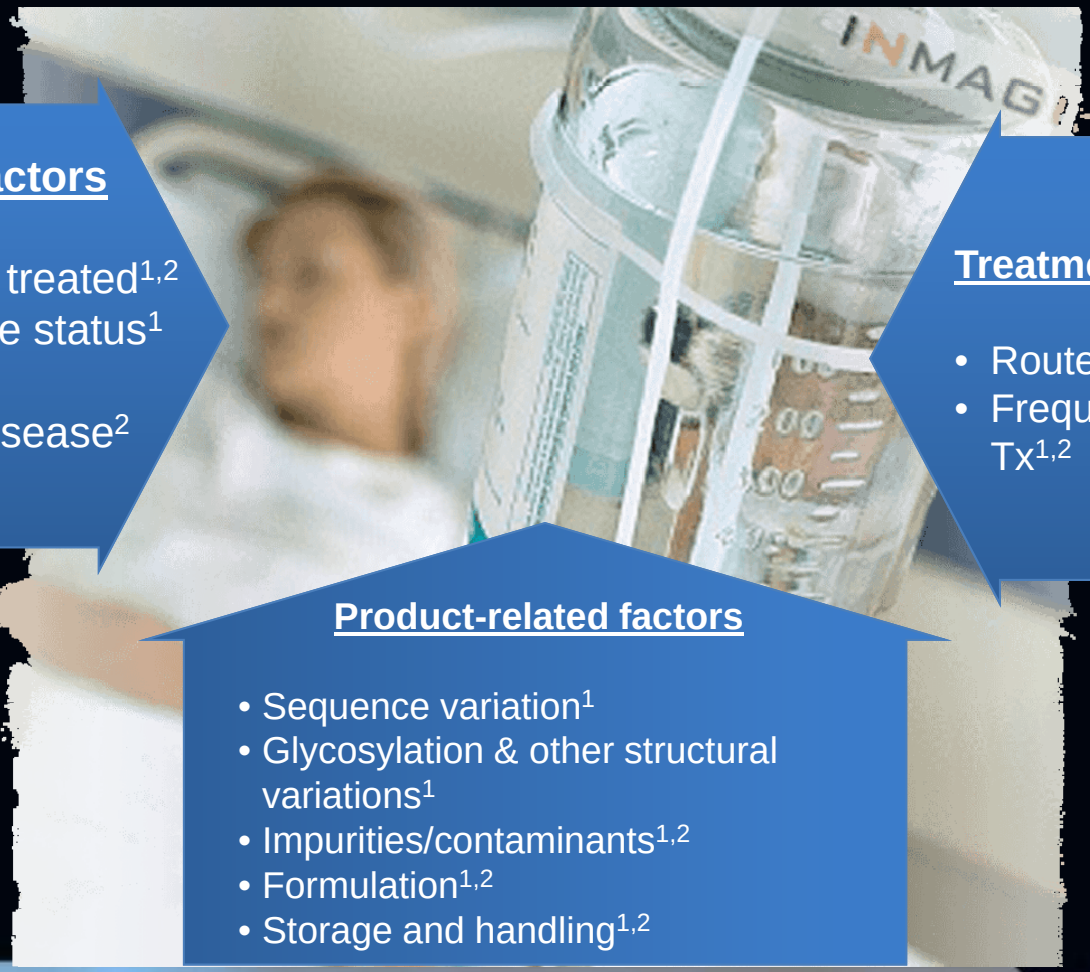
1. Kresse GB. *Eur J Pharm Biopharm.* 2009;72:479-486.
2. Schellekens H. *Clin J Am Soc Nephrol*. 2008;3:174-178.

Changes in Post-Translational Modifications can modify the Protein Product

Protein Modifications	Possible Consequences
Cleavage	Activation (e.g. hormones) Function: impaired interactions with receptors and/or ligands
Oxidation	Degradation , function and/or stability
Lipid attachment	Localization of proteins to membranes
Phosphorylation	Can activate or inhibit a protein
Charged Isoforms	Function (e.g. N- or C-terminal modifications,, deamidated amino acids)
Glycosylation (addition of sugar moieties)	**Immunogenicity: drug reactions and/or altered rate of clearance** **Function: interactions with receptors and/or ligands** **Clearance: half-life and serum concentration**

1. Domer T et al. Ann Rheum Dis 2013;72:322-328.
2. Goldsmith D. Nephrol Dial Transplant 2006; 21(Suppl 5):v1-v3.
3. Jefferis R. Nature Reviews Drug Discovery 2009;8:226-234.

Many Host and Treatment-Related Factors Affect Immunogenicity



Host-related factors

- Disease being treated[1,2]
- Patient immune status[1]
- Presence of concomitant disease[2]
- Genetics[1]

Treatment-related factors

- Route of administration[1,2]
- Frequency and duration of Tx[1,2]

Product-related factors

- Sequence variation[1]
- Glycosylation & other structural variations[1]
- Impurities/contaminants[1,2]
- Formulation[1,2]
- Storage and handling[1,2]

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

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Consequences of immunogenicity

- Allergic reactions
- Antibodies against the drug
- Lower levels of the drug
- Loss of efficacy
- Immune complexes that may lead to manifestations of other immune mediated diseases (lupus like, pure red cell aplasia…)

Process Change is not Simple:
Case Studies of Manufacturing Changes with Clinical Impact

Challenges Encountered In Late-Phase Development or Shortly After Product Approval

Product	Triggering Event & Outcomes Later Found In Humans	Impact
Omnitrope® (Biosimilar somatropin, rHGh)[1]	• New manufacturing facility added • High rate of anti-GH antibodies due to host cell proteins from new mfg site (60%)	• New facility's product not commercialized
Erythropoietin	• Change excipient and SC administration introduced. Interaction between polysorbate 80 with rubber in syringes. PRCA	• Rubber replaced by teflon • Stop SC administration
HX575 (Binocrit®) (Biosimilar epoetin alpha)[2]	• Additional SC administration route • Tungsten contamination from needle manufacturing process • Neutralizing drug antibodies with PRCA cases	• Clinical trial discontinued • New needle mfg process implemented
Myozyme/Lumizyme® (glucosidase alpha) [3,4]	• Scale up production capacity • Glycosylation differences altered PK profile	• New clinical trials required • New BLA as stand-alone product
Raptiva® (Efalizumab)[5]	• Change in production facility during RCTs • PK variations discovered during Ph III	• FDA mandated new phase III trials • FDA approval delayed by 2 years

PRCA: pure red cell aplasia; **HSA**: human serum albumin; **PFS**: pre-filled syringe; **BLA**: Biologics License Application

Small Changes Can Result in Immunogenicity and other unpredicted functional modifications

- Small, hard-to-measure differences in manufacturers'versions of a biologic can result in the generation of antibodies causing an unanticipated change in the body's immune response

- At the present time, there are no known *in vitro* analytical methods available that are capable of predicting the effect of changes in conformation on immunogenicity

Since immunogenicity cannot be accurately predicted or tested, extensive clinical testing and pharmacovigilance are required for all biologics.

Evaluation of Manufacturing Changes

Nature of process change	Change filter supplier	Move equipment within same facility	Move to new production facility (same manufacture)	Change cell culture media	New cell line or major formulation changes
Risk level/ Data requirements	Low Risk • Analytical data • Process data		Moderate Risk • Analytical data • Process data • Stability data		High Risk • Analytical data • Process data • Stability data • Non-clinical data • Clinical data

The nature of a manufacturing change determines the amount and type of supporting data required to evaluate comparability

The Concept of Biosimilars

Generics are exact copies of conventional small molecules, such as the case of NSAIDs

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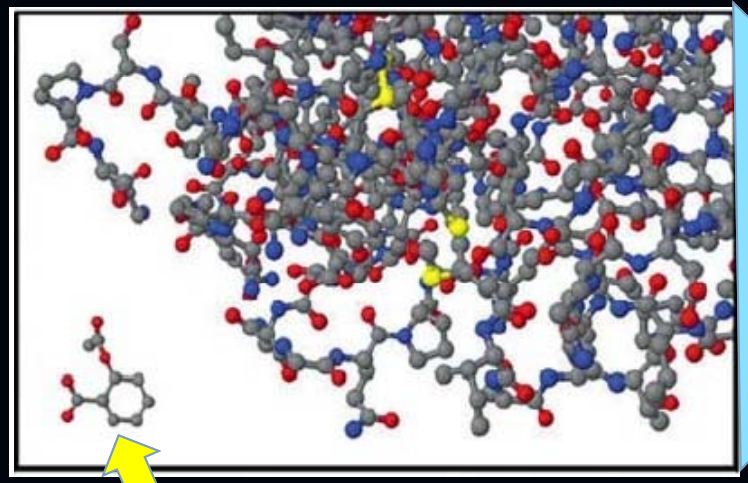
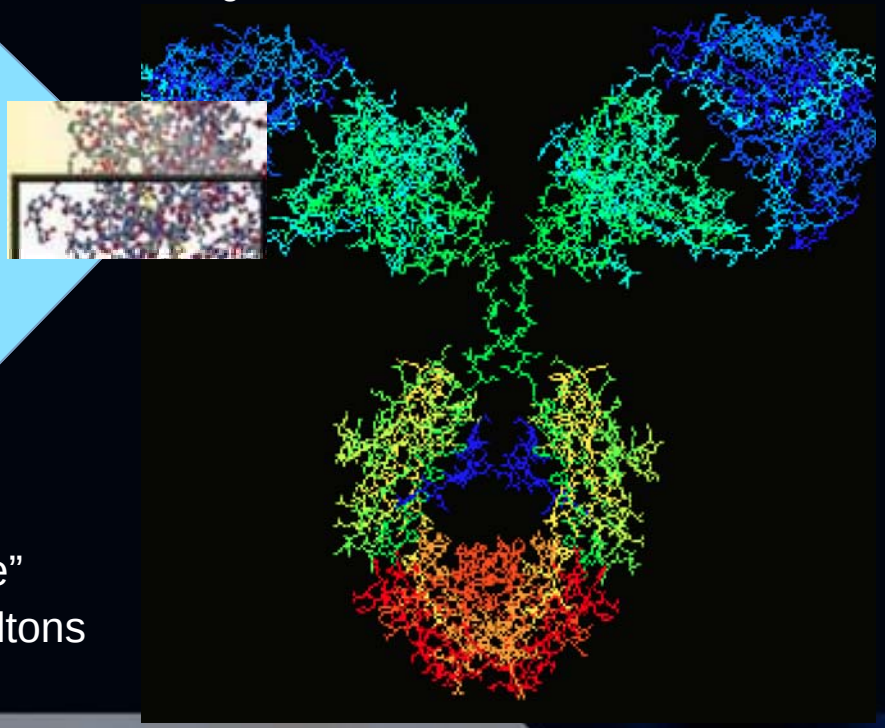
Biologics: Molecular Complexity does not allow exact copies as is the case for small molecules

Monoclonal Antibody:

- >1,000 Amino Acids
- > 6,400 Carbon Atoms
- Molecular Weight ≈ 150,000 Daltons





Aspirin:

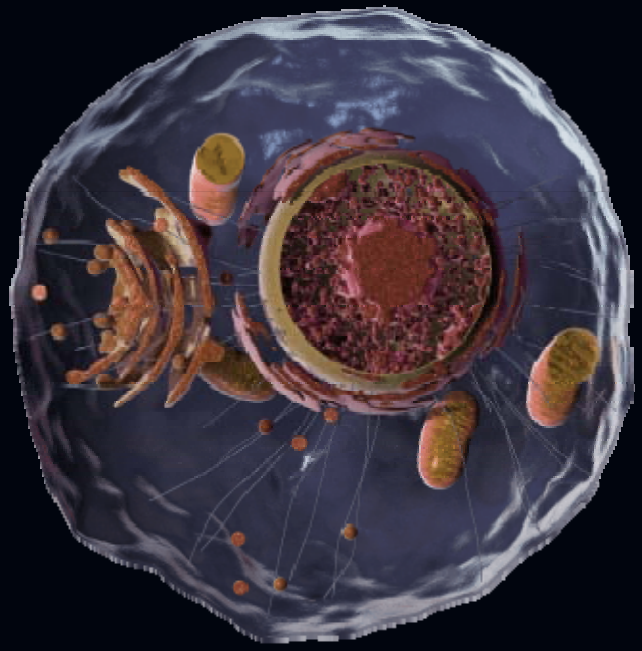
- Synthesized “small molecule”
- Molecular Weight = 180 Daltons

Adapted from Kozlowski J et al ,NEJM 365;5

On top of that, manufacturing of biologics is protected by industrial privacy, even after the end of the patent

When a patent falls the opportunity arrives for trying to develop a biological process that allows to replicate as similar as possible the original drug.

After due preclinical and clinical testing and regulatory approval this molecule is called a biosimilar: A biologic product similar to the original one but not entirely equal



The manufacturing process has to be developed in an autonomous way by the biosimilar company

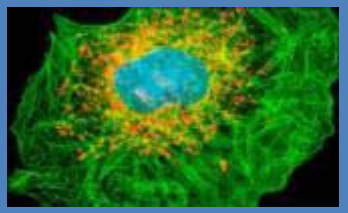
Two Different Processes Create Two Non-Identical Biologic Products

START

Both may use the same gene sequence

Different vectors to insert the gene

Different host cells to grow the protein

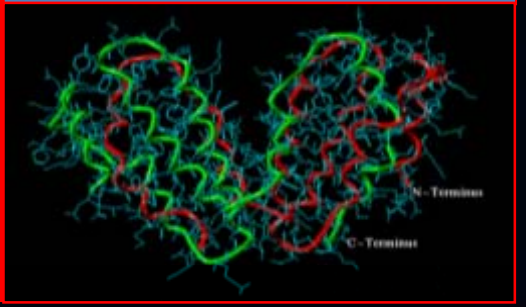


Different fermentation/ culture conditions

Different downstream processing

END

Non identical biophysical characteristics in final product



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Biosimilar Development

Relevant quality attributes are evaluated for the potential impact of process modifications on clinical safety and efficacy of the drug

Nature of process change	Different host cell line and cell culture media Different manufacturer and facility Different equipment and raw materials Different process conditions and specifications
Risk level/ Data requirements	<u>High Risk</u> • Analytical data • Process data • Stability data • Non-clinical data • Clinical data

The nature of biosimilar development requires extensive analytical, non-clinical and clinical data required to evaluate biosimilarity

Regulatory definition of a Biosimilar

- **EMA guidance:** Biosimilar sponsor is to **"generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the new similar biological medicinal product** and the chosen reference medicinal product authorized in the Community."[1]

- US FDA (BPCIA) definition: a follow-on biologic means
  - The biological product is **highly similar to the reference product,** notwithstanding minor differences in clinically inactive components; and
  - **No clinically meaningful differences exist** between the biological product and the reference product **in terms of the safety, purity, and potency**[2]

- **WHO definition:** "Similar Biotherapeutic Products" is a biotherapeutic product that is similar in terms of **quality, safety and efficacy** to an already licensed biotherapeutic product [3]

Biosimilars are those products that are "highly similar" to the reference biologic product based on submission of quality, safety and efficacy data: **clinical data requirements**

1.FDA Draft Guidances – Quality and Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance)
2. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
3. EMA: CHMP Guideline on Similar Biological Medicinal Products (October 2005

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Clinical Data Requirements

General Principles for Clinical Data Requirements[1,2,3]

- The purpose of the clinical component as part of the biosimilarity exercise is to demonstrate high similarity to the reference product, in one or more appropriate indications
- Generation of data must be done with the biosimilar product resulting from the manufacturing process as intended for commercial use
- Stepwise procedure: PK, PD →Clinical Efficacy/Safety (including immunogenicity) trials → Post-Marketing commitment(s)

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline on Similar Biological Medicinal Products (October 2005) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

PK, PD Data[1,2,3,4]

- Comparative human PK and PD (if there is a relevant PD measure) data are essential components of a biosimilarity exercise
  - These parameters cannot be predicted from analytical/nonclinical (including in vivo) studies
  - Experience gathered with small molecule generics teaches us that a highly similar PK to that of the reference product is an absolute requirement
  - For biosimilars, high PK or PD similarity does not establish “bioequivalence”
- Scientific justification for patient population
  - Healthy volunteers vs. patients
    - Relevance of population: more sensitive vs. more similar to “real-life” population, incl. co-medications and co-morbidities
    - Significant potential for ADRs/toxicity → studied in patients only
    - Used for rare/life-threatening diseases → studied in patients only

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf 4.EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012)

Safety and Effectiveness Data[1,2,3]

- Phase II-type trials are not required
  - Dosing schedule, including route of administration, have been defined by the reference product
- Type and extent of phase III data needed is influenced by:
  - Patient population, disease to be treated
  - Extent of knowledge on the reference product's:
    - Mechanism(s) of action
    - Clinical experience, risk/benefit profile
    - Established, sensitive clinical endpoints
  - Outcomes of CMC, pre-clinical, PK/PD biosimilarity exercise

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

Clinical Trial Design

- Comparative (head-to-head (H2H)), double-blind, randomized[1,2,3]
  - Other design(s) must be scientifically/statistically justified by the biosimilar sponsor
- Most sensitive disease condition and patient population within the chosen disease condition (the latter, if pertinent)[1,2,3,4]
- Size, duration and endpoints should allow[1,2,3]
  - Sufficient exposure
  - Detection of clinically relevant differences in safety (including immunogenicity) and effectiveness
- Clinical endpoint(s) different from, and more sensitive than, those used in the efficacy trials of the reference product may be used if scientifically justified[1,4]

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
4.EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012)

Clinical Trial Design[1,2,3,4]

- Equivalence designs (requiring lower and upper comparability margins) preferred for the comparison of efficacy and safety between the potential biosimilar and the reference biologic

- Non-inferiority designs (requiring only one margin)
  - May not exclude clinically important differences that indicate the products are not highly similar (“biobetter”)

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
4.EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012)

Immunogenicity Trials[1,2,3,4,5]

- Establishing that there are no clinically meaningful differences in unwanted immune response between a biosimilar and the reference product is a key element in the demonstration of biosimilarity

- Structural, functional, and animal data do not predict immunogenicity in humans
  - at least one clinical study comparing the immunogenicity of the biosimilar to that of the reference product will be necessary

- The extent and timing of the clinical immunogenicity program depends on
  - the extent of biosimilarity
  - the incidence and clinical consequences of immune responses for the reference product

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf 4.EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012) 5. EMA: CHMP Guideline on Immunogenicity Assessment of Monoclonal

Immunogenicity Trial Design[1,2,3,4]

- Comparative, parallel design
- Equivalence trials preferred
  - in case of lower immunogenicity, there should be a thorough experimental investigation and a scientific rationale as to **why** that is the case
- Assessment by state of the art, validated methods
  - Binding antibodies
  - Neutralizing antibodies
- Post-market assessment is usually necessary to detect less frequent immunogenicity-related events. Post approval safety studies, phase IV clinical trials and Registries

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3.EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012) 4. EMA: CHMP Guideline on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use (24 May 2012)

Interchangeability, Switching, Substitution, Tracking and Extrapolation

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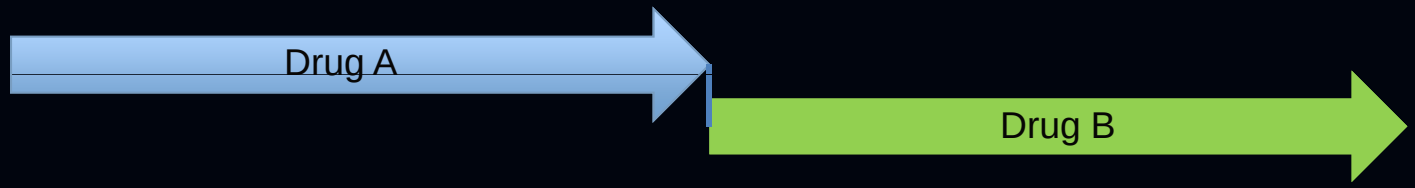
Interchangeability

- Interchangeability – Health or Regulatory Authority Designation
  - **US FDA:** (1) Expected to produce the same clinical result as the reference product in any given patient; (2) Repeated switching between biosimilar and reference product presents no greater safety or efficacy risk than continued use of the reference product[1]
  - **WHO:** Pharmaceutical product is one that is therapeutically equivalent to a comparator product and can be interchanged with the comparator in clinical practice[2]
  - **European Commission:** The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative or with the agreement of the prescriber[3]

1. BPCI Act. Biologics Price Competition and Innovation Act of 2009. Federal Register 2010; H.R. 3590-686-702; 2. WHO: Multisource (Generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability (2006); 3. European Commission: What you need to know about biosimilar medicinal products . Consensus Information Paper 2013.

Switching

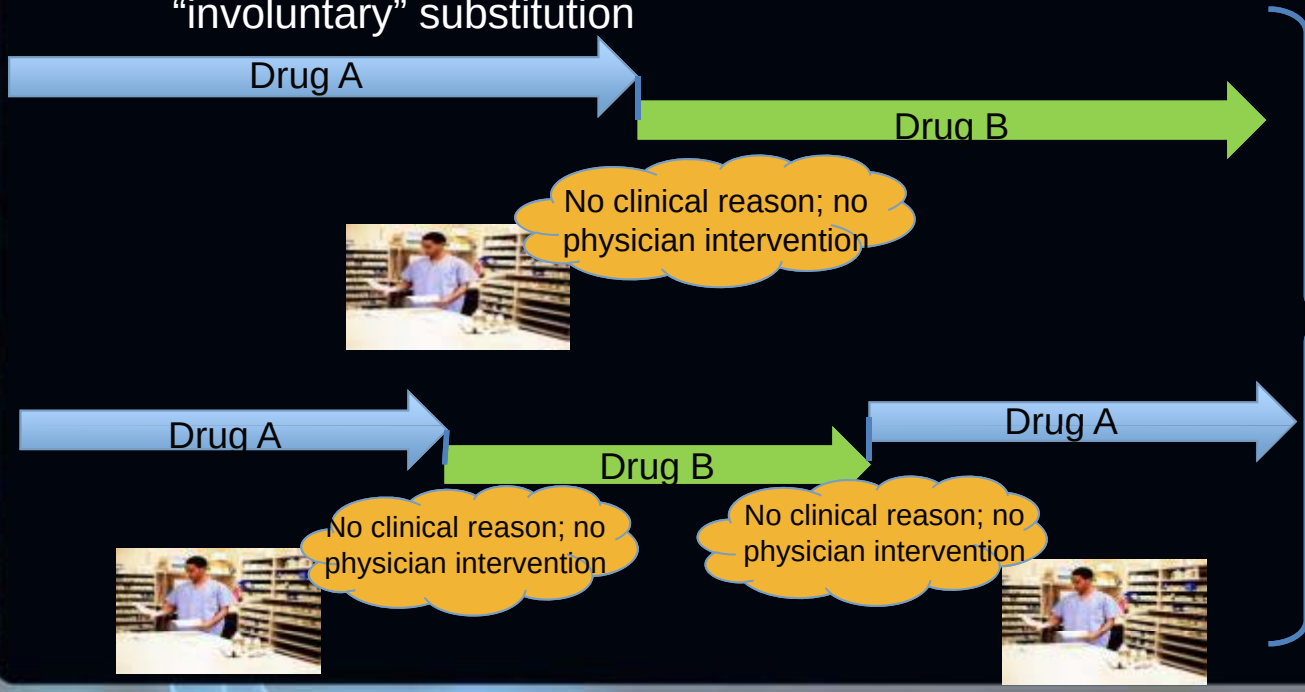
- Medical Switching - Treating Physician Decision
  - When a prescribing physician changes medication, usually because of efficacy or safety issue(s)



1. BPCI Act. Biologics Price Competition and Innovation Act of 2009. Federal Register 2010; H.R. 3590-686-702; 2. WHO: Multisource (Generic) pharmaceutical products: Guidelines on registration requirements to establish interchangeability (2006); 3. European Commission: What you need to know about biosimilar medicinal products . Consensus Information Paper 2013.

Substitution

- Substitution – Pharmacist Action
  - When a pharmacist substitutes a certain prescribed product by another equivalent product
  - If without the prescribing physician's involvement, it is considered "automatic" or "involuntary" substitution



Open questions:

1. Are drug A and B identical?
2. Ethical concern?
3. Need for washout period?
4. Tracking/ Traceability?

Interchangeability & Substitution / External Materials / March 2014

1. BPCI Act. Biologics Price Competition and Innovation Act of 2009. Federal Register 2010; H.R. 3590-686-702; 2. Dorner T. et al. Ann Rheum Dis 2012;72:322-328; European Comission: What you need to know about biosimilar medicinal products . Consensus Information Paper 2013. 4. Endrenyi L et al. Statist. Med. 2013,32, 434-441

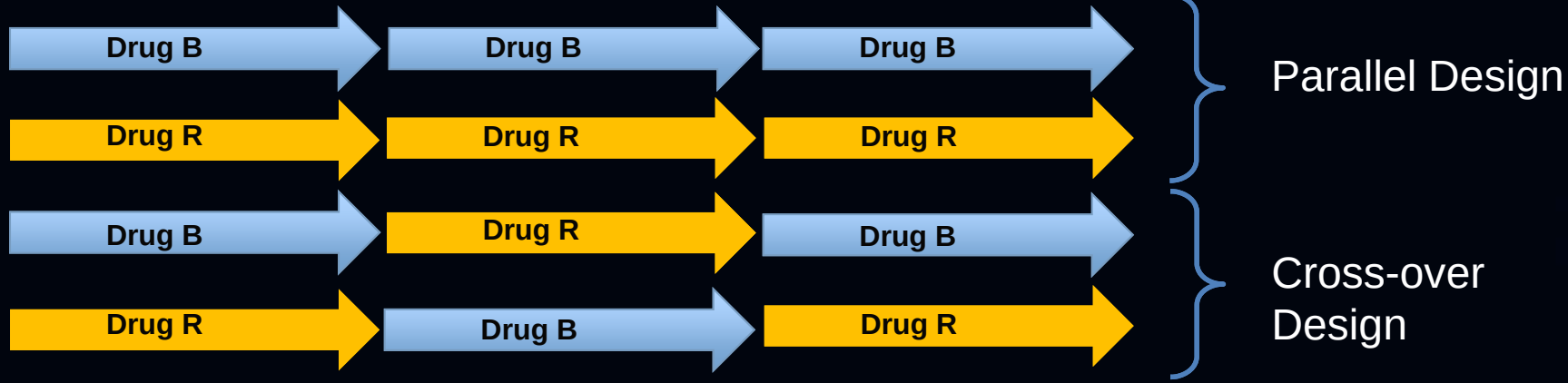
Interchangeability and Substitution:
Switching Studies Some Technical Considerations

Design

Switching studies

1. should be randomized, controlled trials and should not be open labelled.
2. should follow a cross-over and/or parallel design
3. should include multiple switches.
4. Should include appropriate control groups
5. Should include efficacy, safety and immunogenicity assessment

SWITCHING / ALTERNATING

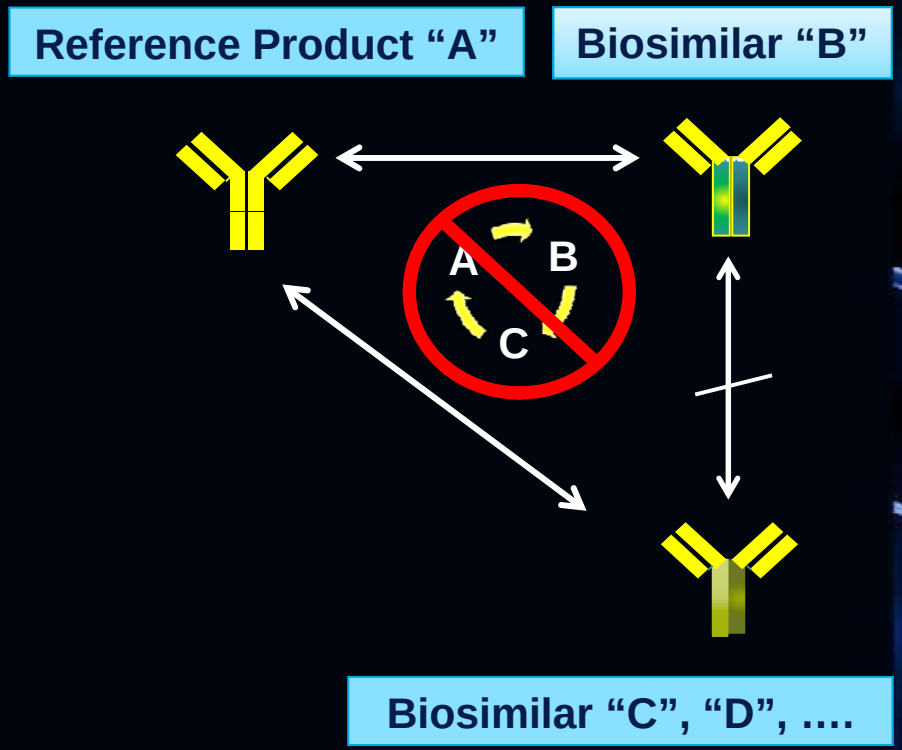


1.Biologics Price Competition and Innovation Act of 2009 (BPCIA) – U.S. Law; 2. Lu Y; Chow SC, *et al. Drug Designing.* 2013, Vol. 2; Issue 3; page 2 to 6; 3. Endrenyi L, *et al. Statist Med*. 2013;32:434-441; 4. Chow S-C, *et al. Statist Med.* 2013;32: 442-448.

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*. Pure Red-Cell Aplasia and Recombinant Erythropoietin. New England Journal of Medicine. 2002;Vol. 346:1584-1585. 3.Wieser C, Rosenkranz AR. *Clin Kidney J*. 2013;0:1-4.

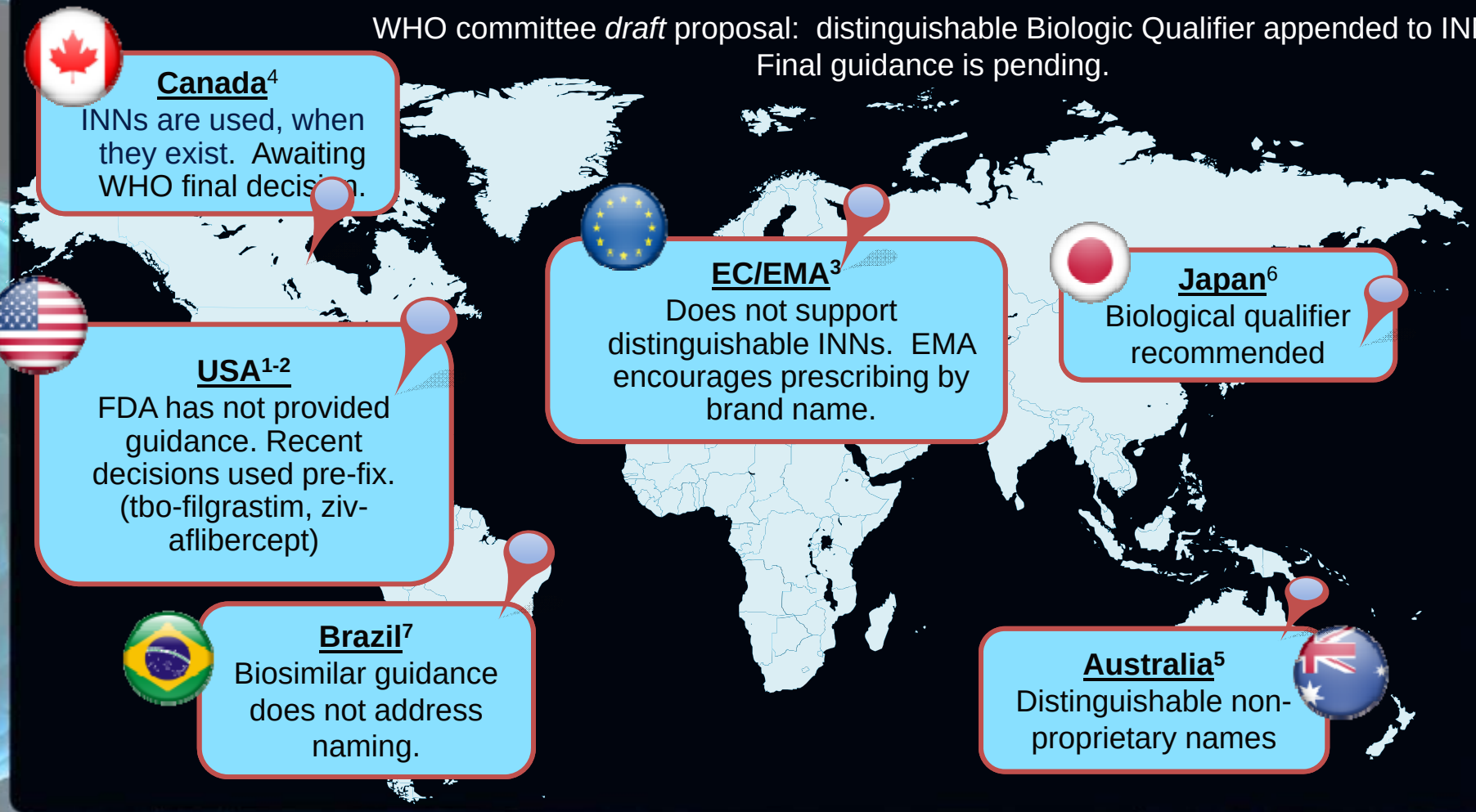
Benefits of Distinguishable Non proprietary names for **Biotherapeutics**

- Enhances effective adverse events reporting[1,2]
  - Promote effective pharmacovigilance by increasing accuracy of adverse event reporting and potential corrective actions[3,4]
- Increases accurate prescribing[3,4]
  - Increase transparency of dispensed product to patients
  - Enhance control of physicians to make prescribing decision
  - Minimize risk of unintentional prescribing
    - Wrong-drug dispensing errors est. 4.8M / year (US)[5]
    - Most common type of pharmacy malpractice claim[6]
  - Minimize risk of inappropriate, involuntary or automatic substitution

1. Zuniga Pharmacoepidemiology and Drug Safety. 2010;19:661-669 2.Casadevall Expert Opin Biol Ther. 2013;13(7):1039-1047 3. Fitzhugh Burrill Report Generics and Biosimilars BIO argues. Feb 2014 4. Gaffney Pharmacogivilance Concerns lead group to call for unique names Regulatory Focus 2012 5. Hicks RW, et. al. (2008) MEDMARX data report. US Pharmacopeia. 6. Gianutsos G. U.S. Pharmacist 2008 ACPE Program No.: 430-000-08-024-H03-P.

Global Positions on Identical vs. Distinguishable Non-Proprietary Names for Biopharmaceuticals

WHO committee *draft* proposal: distinguishable Biologic Qualifier appended to INN. Final guidance is pending.



Canada[4]
INNs are used, when they exist. Awaiting WHO final decision.

USA[1-2]
FDA has not provided guidance. Recent decisions used pre-fix. (tbo-filgrastim, ziv-aflibercept)

Brazil[7]
Biosimilar guidance does not address naming.

EC/EMA[3]
Does not support distinguishable INNs. EMA encourages prescribing by brand name.

Japan[6]
Biological qualifier recommended

Australia[5]
Distinguishable non-proprietary names

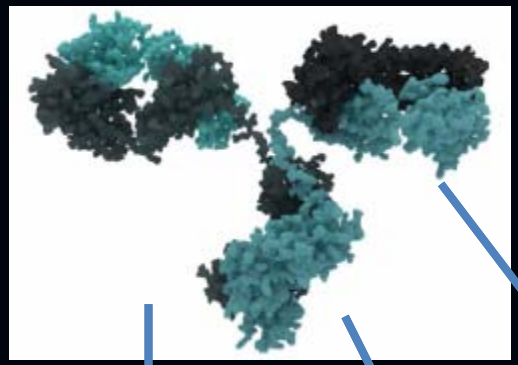
1. Zaltrap US FDA Naming summary: Accessed on: August 1, 2013; 2. FDA. 2012; Week (vol. 18), No 36, September 7; 3. Eu Comm. Pharmaceutical Committee Meeting. 2013; 23 Oct; 4. Health Canada Drug Products Database: Terminology; 5. Australian TGA 17 July, 2013. Evaluation of Biosimilars; 6. WHO 57th Consultation on INNs Geneva Switzerland 2013.

Indication Extrapolation[1,2,3,4]

Reference product has been approved for Indications A, B, C and D

Approval in Indication **A**

2



1 Comparative CMC/quality, safety and efficacy studies of a biosimilar in a single disease or specific patient population (Indication **A**)

3 Extrapolation to other diseases or patient populations?

Indication **B**

Indication **C**

Indication **D**

Adapted from: 1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf 4.EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012)

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Key Factors for Indication Extrapolation
based on EMEA, FDA and WHO Guidelines

- The Mechanism of Action and/or the receptor(s) of the innovator reference product is known and the same across all indications intended for extrapolation[1,2,3,4] or a strong scientific rationale 2 and relevant data[2,3,4] have been provided

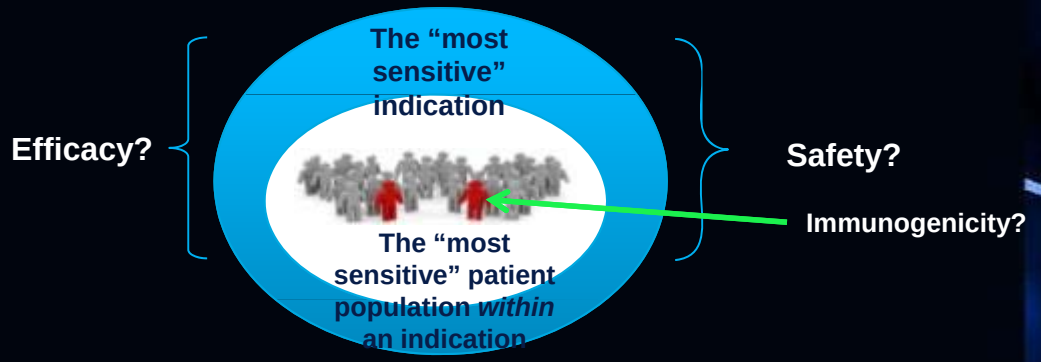
- Equivalence and clinical comparative studies have been performed in the most sensitive indication or, if pertinent, in a well-defined and understood population of the patients most sensitive to detect clinical differences between the biosimilar and the reference medicine[1,2,3,4]
  - The most sensitive indication/population should ideally be the one that shows clinically relevant differences in terms of key efficacy and safety, including immunogenicity, parameters between two products[1]

Adapted from: 1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf 3. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 4.EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012)

Anti-TNFs

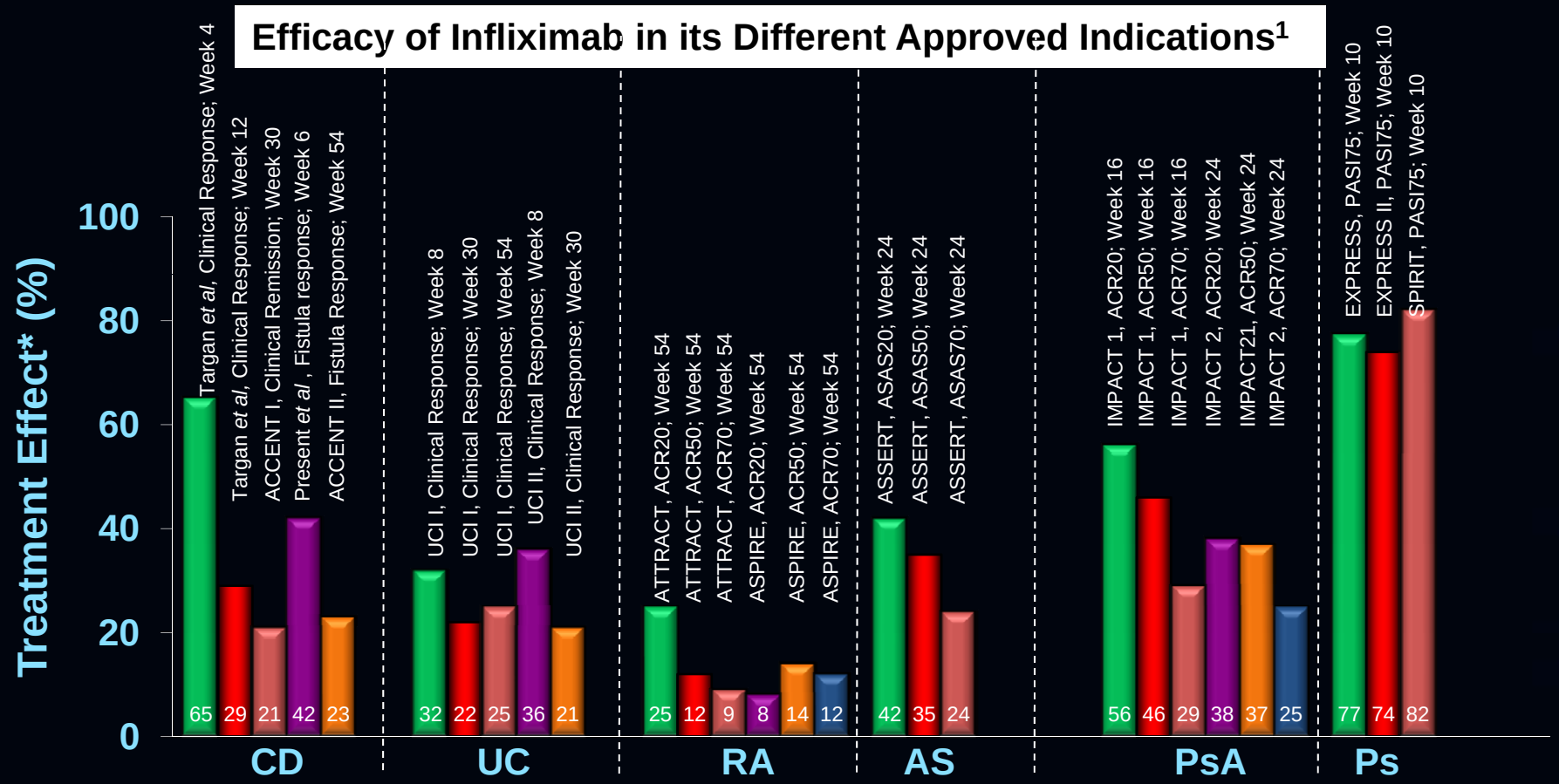
- Anti-TNFs[1,2,3]Multiple (up to 10) approved indications
  - Different patient populations across and within indications
  - The exact downstream effects that are responsible for efficacy of anti-TNF medication in the various disease states are unknown.[10]
  - Efficacy and safety profiles may vary by indication or patient type

Identification of **the most sensitive population** must be considered in terms of:[4,5,6,7]



1 HUMIRA SmPc. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000481/human_med_000822.jsp&mid=WC0b01ac058001d124; accessed 04/0714. 2. ENBREL SmPC. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000262/human_med_000764.jsp&mid=WC0b01ac058001d124; accessed 04/0814. 3. REMICADE SmPC. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000240/human_med_001023.jsp&mid=WC0b01ac058001d124; accessed 04/08/14. 4. Adapted from: FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 5. Adapted from: EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 6. Adapted from: WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf 7. Adapted from: EMA: CHMP Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues (30 May 2012) 8. Miletich J et al. mAbs 3:3, 1-8; May/June 2011. 9. . Peake STC *et al.* Inflamm Bowel Dis 2013; 19: 1546-1555 -10 ,B Gecse Gut, published on line March 16, 2013 as 10.1136/gutjnl-2012-303824.

Which Clinical Model is the Most Sensitive for the Detection of Efficacy Differences?



"If the difference in efficacy between a treatment and placebo is small, it is difficult (i.e., less sensitive) to show a difference between the treatment and another treatment similar to that even if there is"[1]

1. Adapted from: Lee H, The AAPS Journal (published online: 11 October 2013); DOI: 10.1208/s12248-013-9534-y

* Placebo-adjusted difference (i.e. infliximab *minus* placebo) in percentage points

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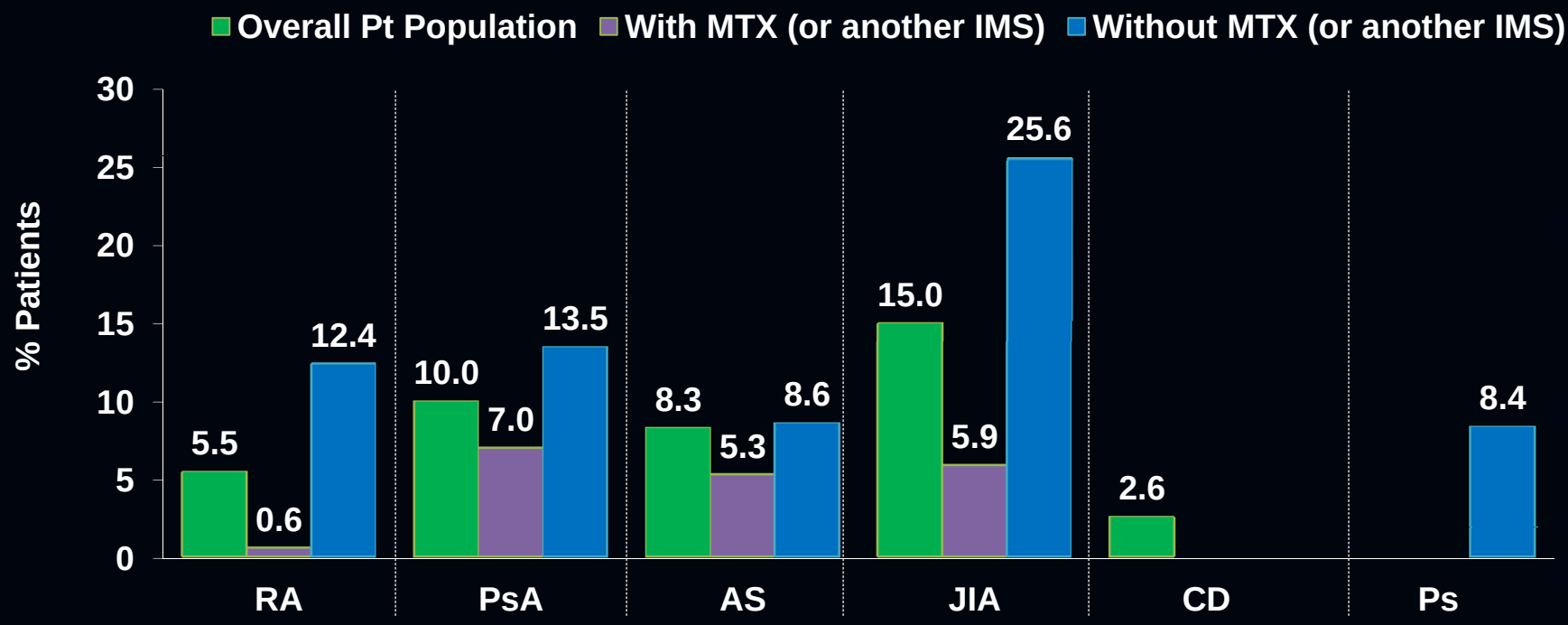
Which is the Most Sensitive Indication and Patient Population? An Adalimumab example

Anti-Drug Antibody Formation Rate in Various Indications[1,*]



RA: rheumatoid arthritis; PsA: psoriatic arthritis; AS: Ankylosing spondylitis; JIA: juvenile idiopathic arthritis; CD: Crohn's Diisease; Ps: Psoriasis; MTX: Methotrexate; *percentages not shown are not available in HUMIRA's US PI

1. FDA HUMIRA Prescribing Information; accessed at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/125057s0110lbl.pdf on 03/31/2014

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Indication Extrapolation and Immunogenicity

Consider the following:

- The most immuno-competent patient population would generally be preferred over immuno-suppressed patients[3]
- **Populations may vary in their response to biologics:**
  - Overall ADA incidence
  - Time course for generation of anti-drug antibodies
  - Route of administration
  - Occurrence of neutralizing antibodies
  - Effects of ADA on PK and PD
  - Potential negative effects of antibodies on safety or efficacy
  - Confounding by concomitant medication (eg, immunosuppressants)

1.FDA Draft Guidances – Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (Feb 2012) – US Guidance 2. EMA: CHMP Guideline On Similar Biological Medicinal Products Containing Biotechnology-derived Proteins As Active Substance: Non-clinical And Clinical Issues (22 February 2006) 3. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics

CT-P13 Infliximab Indications by Type of Approval

Indication	S. Korea 2012	EU 2013	Canada 2014
Rheumatoid Arthritis (RA)	CT*	CT*	CT*
Ankylosing Spondylitis (AS)	CT**	CT**	CT**
Psoriatic Arthritis	E	E	E
Psoriasis	E	E	E
Crohn's Disease (CD)	E	E	-
Pediatric CD	-	E	-
Ulcerative Colitis (UC)	E	E	-
Pediatric UC	-	E	-

CT: Approved with a complete data package including a single phase III* or Phase I** clinical trial. **E:** Extrapolated indication without a phase I or III clinical trial. Dash (**-**): Not approved

These examples are not meant to provide a complete overview of all indication extrapolation decisions for CT-P13. Other juridictions have provided marketing authorization to CT-P13

REMSIMA™ / INFLECTRA™ product information accessed February 24, 2014:

1. S. Korea : http://www.celltrion.com/en/BIO/bio01.asp?menu_num=1
2. EMA: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Summary_for_the_public/human/002576/WC500150872.pdf
3. Canadian Product Monograph; Inflectra www.hc-sc.gc.ca

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The Rheumatology Experience

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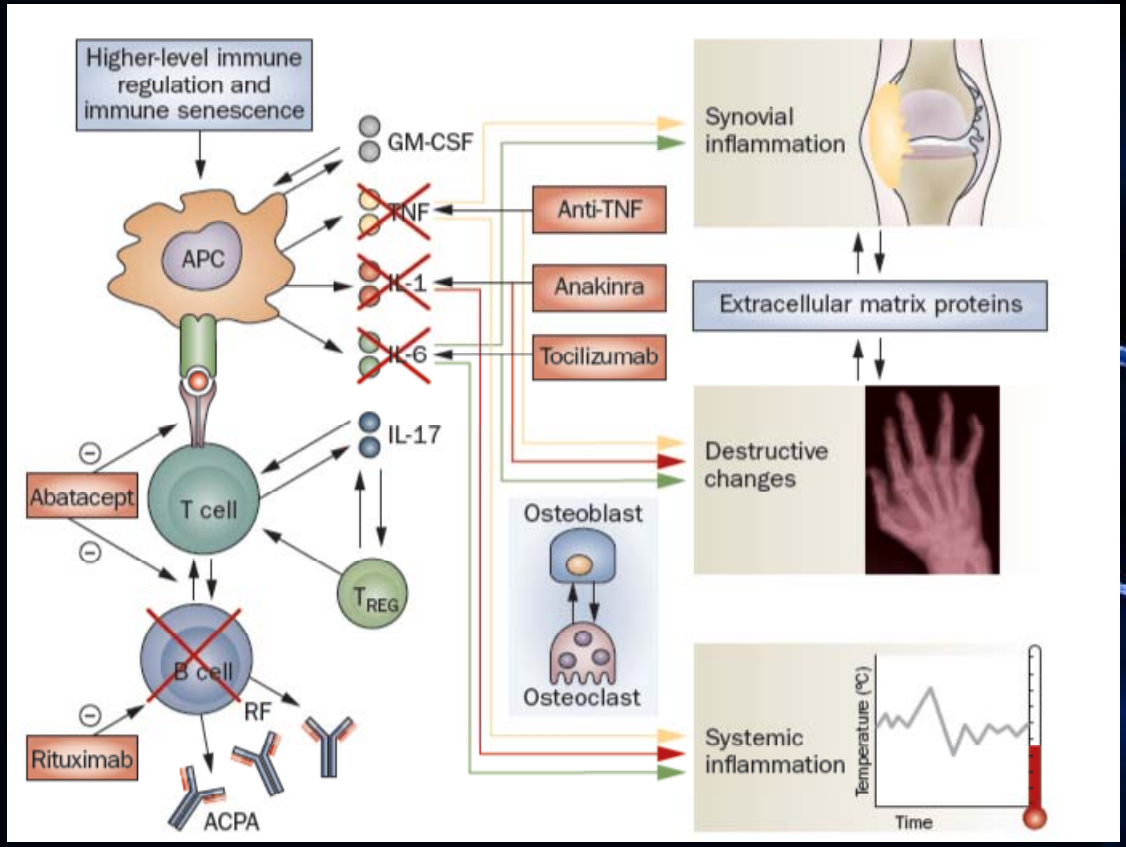
Biologics approved in rheumatic diseases

- TNF inhibitors
  - Infliximab
  - Etanercept
  - Adalimumab
  - Golimumab
  - Certolizumab
- Rituximab (RA)
- Abatacept (RA)
- Tocilizumab (RA)
- Ustekinumab (PsA)
- Belimumab (SLE)
- Anakinra and Canakinumab (AID, Gout)



VanVollenhoven RF.Nat Rheum Rev. 2009

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

Biologics approved in Europe for inflammatory bowel disease

- TNF inhibitors
  - Infliximab (Crohn and UC)
  - Adalimumab (Crohn and UC)
  - Golimumab (UC)
- Vedolizumab (Crohn and UC)

Biologics approved in Europe for Psoriasis

- TNF inhibitors
  - Infliximab
  - Adalimumab
  - Etanercept
- Ustekinumab
- Alefacept (not available in Europe)

Infliximab biosimilar approved in Europe

Studied in Rheumatoid Arthritis and Ankylosing Spondylitis

Not studied: Psoriasis, Crohn, UC, psoriatic arthritis

Has approval for all these indications

The Portuguese Experience

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How things evolved in Portugal?

No formal position on automatic substitution from the government

Decisions are taken on an individual basis by Hospitals

Patients have been engaged into public discussions

The Portuguese Society of Rheumatology has issued a position paper on biosimilars

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;
5. Opposes to extrapolation of indications approved to the originator to completely different diseases and/or age groups without adequate pre-clinical, safety or efficacy data.

INFORMAÇÃO: No formulário das terapêuticas, já podem ser registados os biossimilares do Infliximab.

Registo Nacional de Doentes Reumáticos

Rheumatic Diseases Portuguese Register

Centro: Hospital de Santa Maria

Código de utilizador:

Senha de acesso:

Recuperar dado

OK

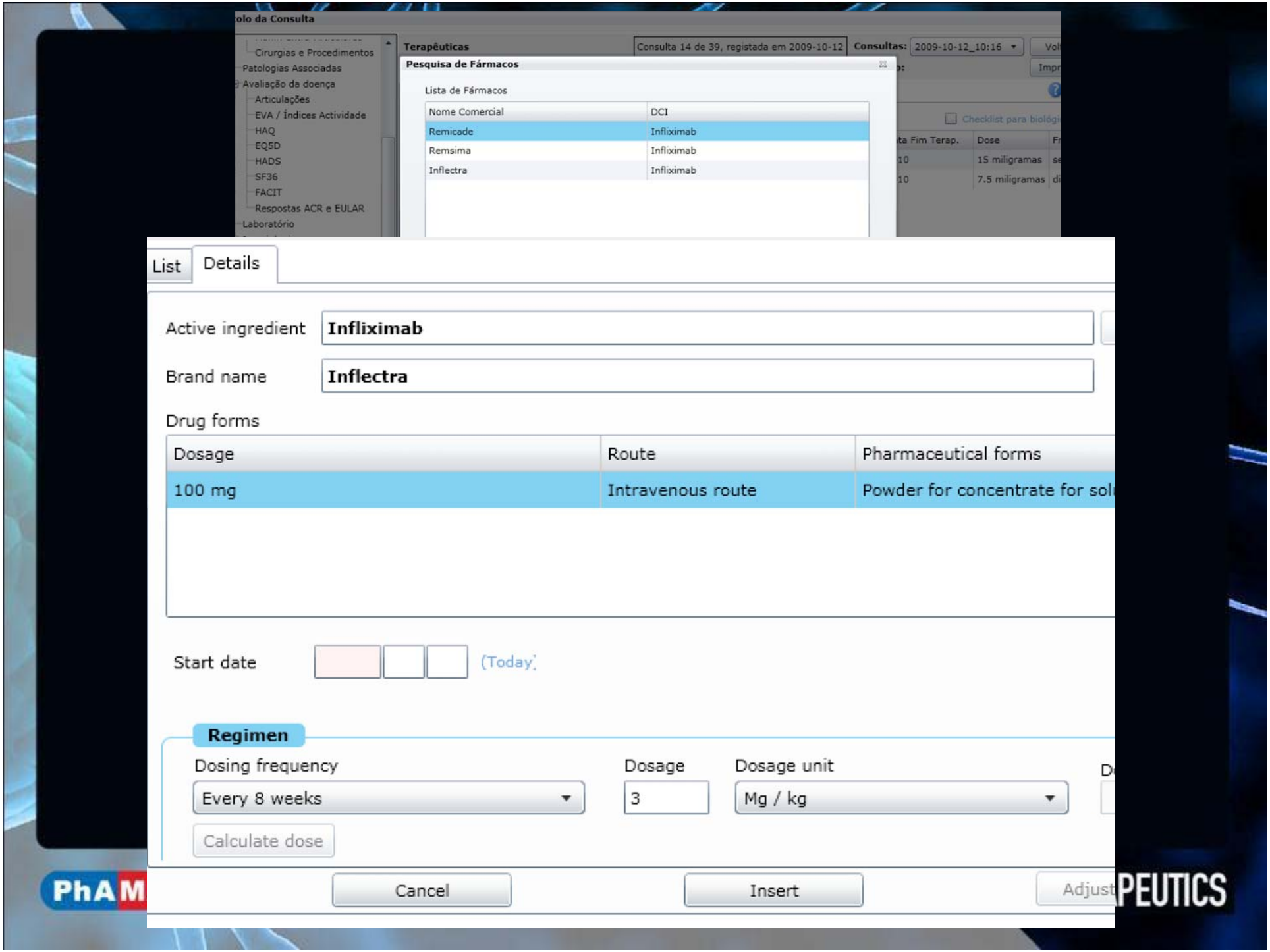
Totais de doentes e consultas registados no

Sociedade Portuguesa d Reumatologi

SEDARE DOLOREM OPUS DIVINUM EST

ELEANORA REGINA

Reuma.pt


olo da Consulta
Cirurgias e Procedimentos
Patologias Associadas
Avaliação da doença
Articulações
EVA / Índices Actividade
HAQ
EQ5D
HADS
SF36
FACIT
Respostas ACR e EULAR
Laboratório
Terapêuticas
Consulta 14 de 39, registada em 2009-10-12
Consultas:
2009-10-12_10:16
Pesquisa de Fármacos
Lista de Fármacos
Nome Comercial
DCI
Remicade
Infliximab
Remsima
Infliximab
Inflectra
Infliximab
Checklist para biológ
ta Fim Terap.
Dose
10
15 miligramas
10
7.5 miligramas
List
Details
Active ingredient
Infliximab
Brand name
Inflectra
Drug forms
Dosage
Route
Pharmaceutical forms
100 mg
Intravenous route
Powder for concentrate for sol
Start date
(Today)
Regimen
Dosing frequency
Every 8 weeks
Dosage
3
Dosage unit
Mg / kg
Calculate dose
Cancel
Insert
Adjust
PhAM
PEUTICS

Paradox: official cost difference between Remicade and Biosimilars is less than 10% in my country

N.º Registo	Substância Activa	Nome do Medicamento	Forma Farmacêutica	Dosagem	Tamanho da Embalagem	CNPEM	PVP Max
5579115	Infliximab	Remsima	Pó para concentrado para solução para perfusão	100 mg	1 unidade(s) - 10 ml	501389	477,88
5571559	Infliximab	Inflectra	Pó para concentrado para solução para perfusão	100 mg	1 unidade(s) - 10 ml	501382	504,40
2972289	Infliximab	Remicade	Pó para concentrado para solução para perfusão	100 mg	1 unidade(s)	500941	530,95

1 Todos Página: 1 Registos por página: 25

¹ O Preço ao Utente é o valor pago pelo Utente do regime geral na farmácia.

² O Preço Pensionistas é o valor pago na farmácia pelos pensionistas do regime especial (Pensionistas cujo rendimento total anual não exceda 14 vezes a

http://www.infarmed.pt/genericos/pesquisamg/pesquisaMG.php

How things evolved in my centre?

Tender system: 40% less expensive in my hospital…

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

My personal opinion

My Personal Perspective

- Use in untreated patients (new patients)
  - Acceptable if the cost is clearly lower and both patient and doctor agree.
- Switch a patient from the original molecule into the biosimilar
  - Automatic substitution not acceptable and against current practice. Switch only justified in the context of clinical trials or observational studies with informed consent from the patient.
- Use in diseases where the biosimilar was not tested in trials
  - Debatable. Depends on the available evidence. Reasonable for the extrapolation from RA and AS into PsA. But how about Crohn and the use in children?

My Personal Perspective

- Pharmacovigilance
  - Identification of the molecule, manufacturer and batch in registries.
- Dialogue between doctors, pharmacists and health managements
  - Try to obtain the best possible benefits of this new reality for the national health system
- The patient has the right to be informed
  - In all possible scenarios the patient has to be informed that he/she is going to be treated with a biosimilar


Obrigado!
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CONGRESS – PUTTING PATIENT FIRST
22 NOVEMBER 2014