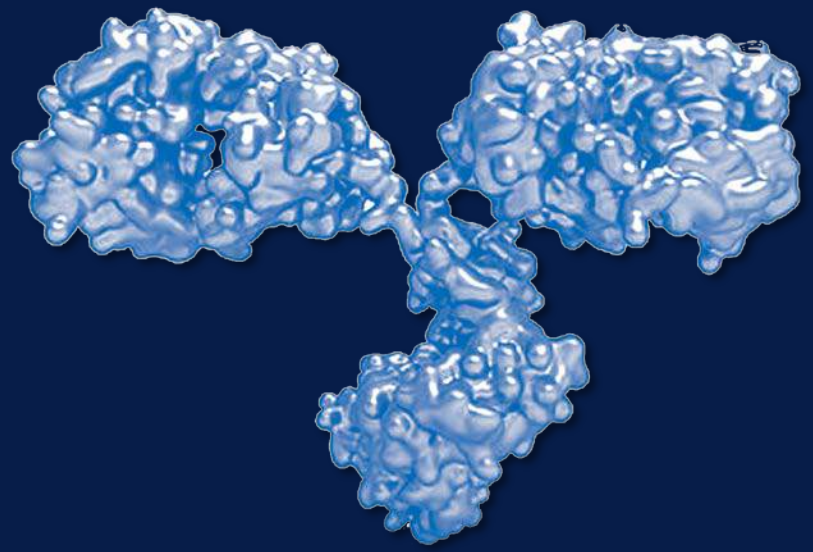
abbvie

INTERCHANGEABILITY AND SUBSTITUTION FOR BIOLOGICAL MEDICINAL PRODUCTS



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Director Médico Latinoamérica

Global Medical Affairs, Biotherapeutics

24 de Febrero, 2015

Definitions and Regulatory Environment

Evidence and Challenges on Interchangeability

Summary

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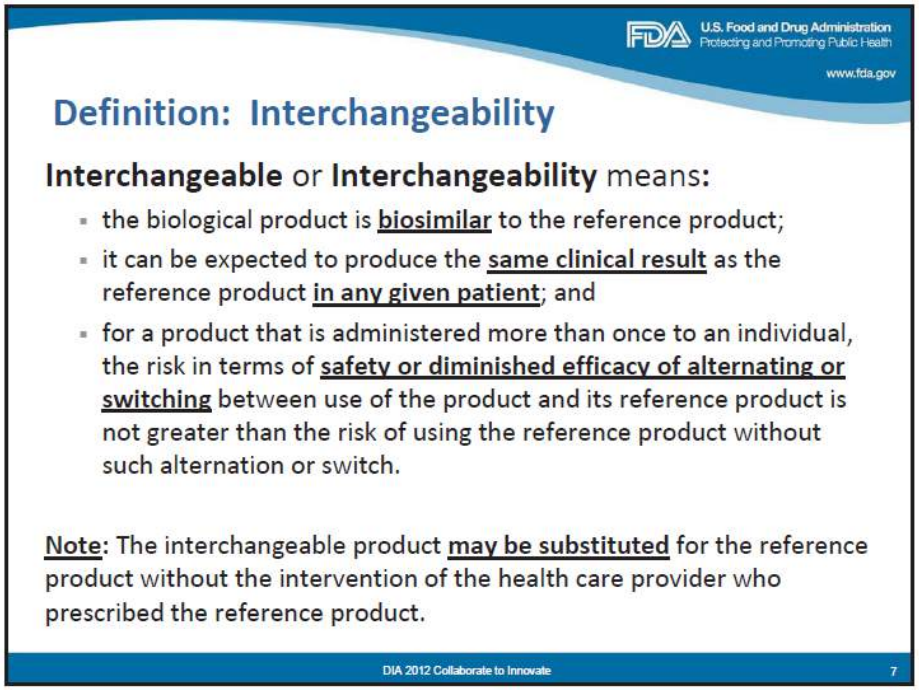
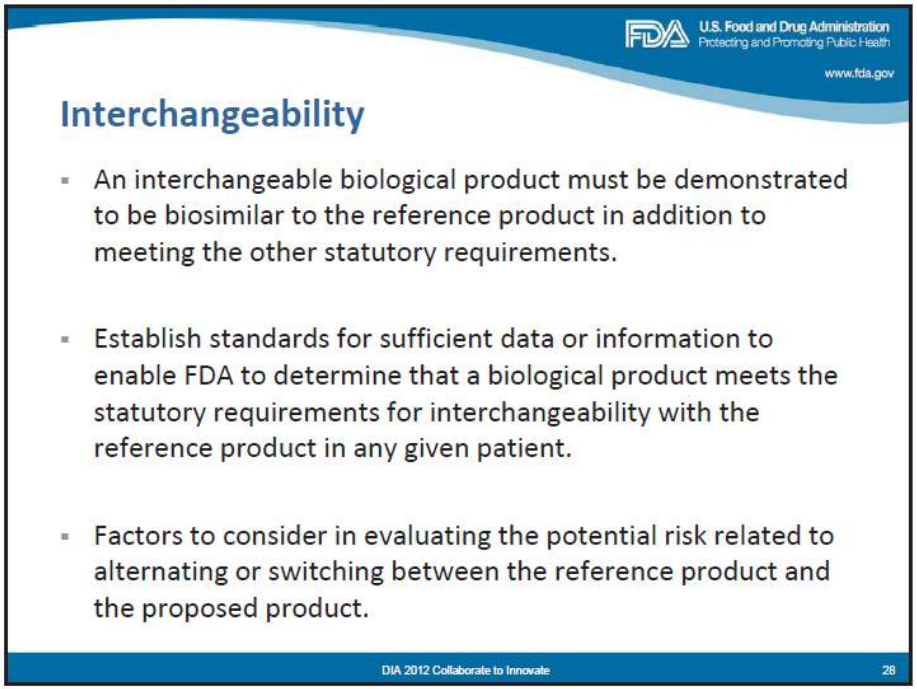
Regulatory Definitions of Interchangeability[1]

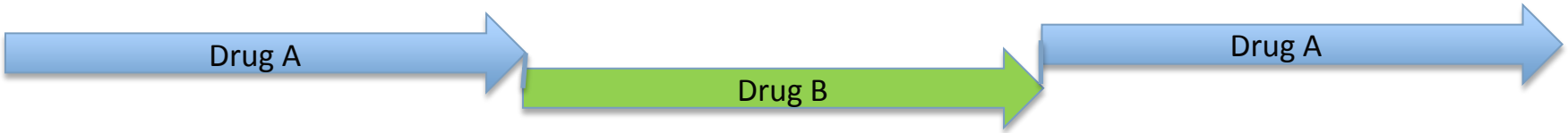




1. Adapted from BPCI Act. Biologics Price Competition and Innovation Act of 2009. Federal Register 2010; H.R. 3590-686-702. http://www.fda.gove; accessed November 5, 2014.

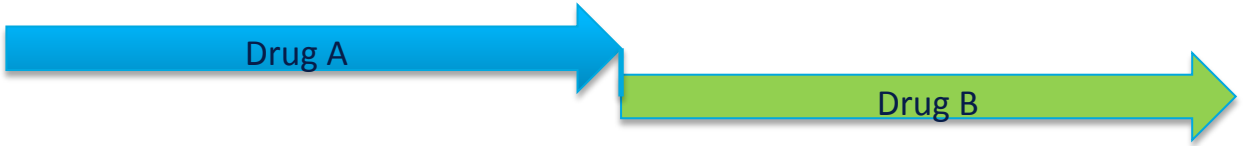
Interchangeability and Medical Switching

- **Substitution** – **Pharmacist Action**
  - When a pharmacist substitutes a certain prescribed product by another equivalent product
  - Qualified as “automatic” or “involuntary” substitution without prescribing physician’s involvement

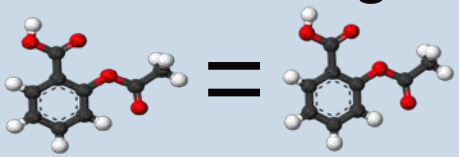
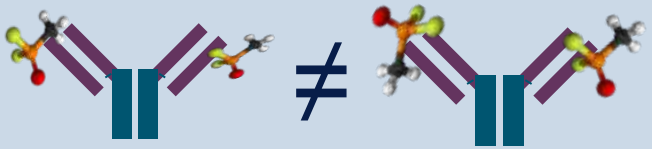


Medical Switching - **Treating Physician Decision**

- When a prescribing physician changes medication, usually because of efficacy or safety issue(s)



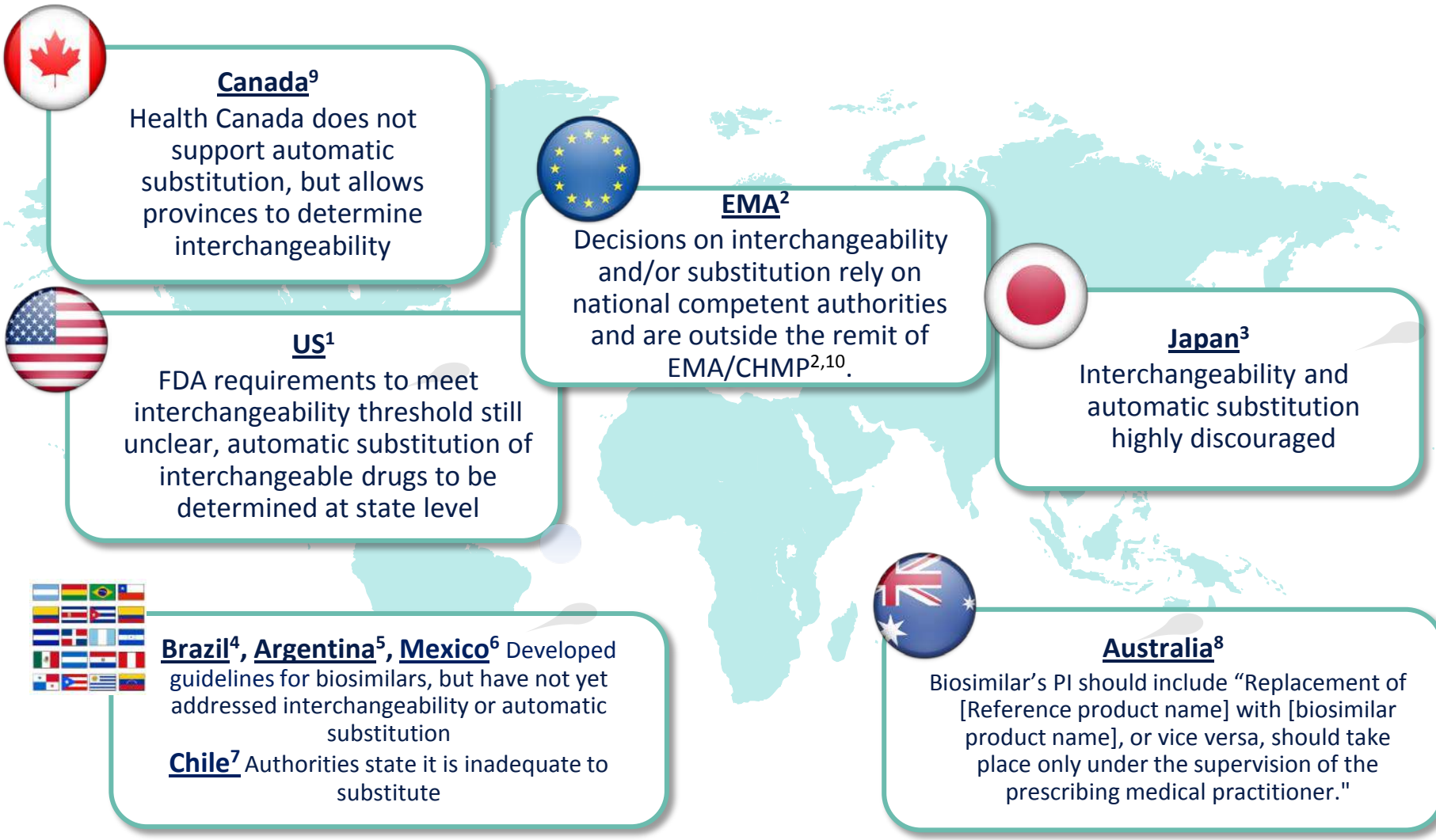
Biosimilars Are Not Generics

Generic Drugs	Biosimilars
	
Produced by using chemical synthesis Less sensitive to production process change and reproducibility easy to establish[1]	Produced by complex biological process in cell lines in specialized production facilities[1] Sensitive to production process changes and reproducibility difficult to establish[1]
Regulatory agencies generally designate the two as **interchangeable*** Depending on local rules, pharmacists may be authorized or even required to substitute a generic for the original without informing the prescribing physician **(automatic substitution)**	Due to their complexity and impurity profiles, interchangeability of biologics or biosimilars could have clinical consequences and repeated switches may increase immunogenicity[2] **Biosimilarity status by a regulator does not imply interchangeability** [3-8]

* EMA still defer to national agencies

1.Sekhon Biosimilars 2011:1 1–112 2. Bradley J Scott, PhD; Agnes Klein, MD,PhD; Jian Wang,MD,PhD: Journal of Clinical Pharmacology June 2014; DOI 10.1002 3.FDA Biosimilar Guidance Webinar, February 15, 2012; 24.EMA, Questions and Answers on biosimilar medicines; European Biopharmaceutical Enterprises (EBE) Survey on Biosimilars, May 2011; 5.MHLW Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products, March 2009 ; 6.FDLI Update, July 2012; 7. Discussion paper on Similar Biological Medicinal Products (SBMPs), Australia PBS; 8.Health Canada Interchangeability and Substitutability of Subsequent Entry Biologics, July 2010

Interchangeability and Substitution Worldwide



Canada[9]
Health Canada does not support automatic substitution, but allows provinces to determine interchangeability

EMA[2]
Decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of EMA/CHMP[2,10].

US[1]
FDA requirements to meet interchangeability threshold still unclear, automatic substitution of interchangeable drugs to be determined at state level

Japan[3]
Interchangeability and automatic substitution highly discouraged

Brazil[4], **Argentina**[5], **Mexico**[6] Developed guidelines for biosimilars, but have not yet addressed interchangeability or automatic substitution

Chile[7] Authorities state it is inadequate to substitute

Australia[8]
Biosimilar's PI should include "Replacement of [Reference product name] with [biosimilar product name], or vice versa, should take place only under the supervision of the prescribing medical practitioner."

1 FDA Biosimilar Guidance Webinar, February 15, 2012; 2: EMA, Questions and Answers on biosimilar medicines; 3: MHLW Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products, March 2009 ; 4: ANVISA: Resolucao RDC N° 55, de 16 de Deem bro de 2010; Diario Oficial da Uniao-Secao 1; N° 241; 5: ANMAT, Disposición N° 7729/2011 (publicado el 21 de Noviembre de 2011); 6: Proyecto de PROY-NOM-257-SSA1-2013; 7.*Norma Técnica Nº 170 Sobre Registro Sanitario de Productos Biotecnológicos Derivados de Técnicas ADN Recombinantes; Diario Oficial de la República de Chile, 6 de Septiembre de 2014*)8: TGA Biosimilar Guidance; 30 July 2013; 9:; Health Canada Interchangeability and Substitutability of Subsequent Entry Biologics, July 2010 http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/01-2010-seb-pbu-qa-qr-eng.php#q15 10. European Commission: What you need to know about biosimilar medicinal products . Consensus Information Paper 2013.

Definitions and Regulatory Environment

Evidence and Challenges on Interchangeability

Summary

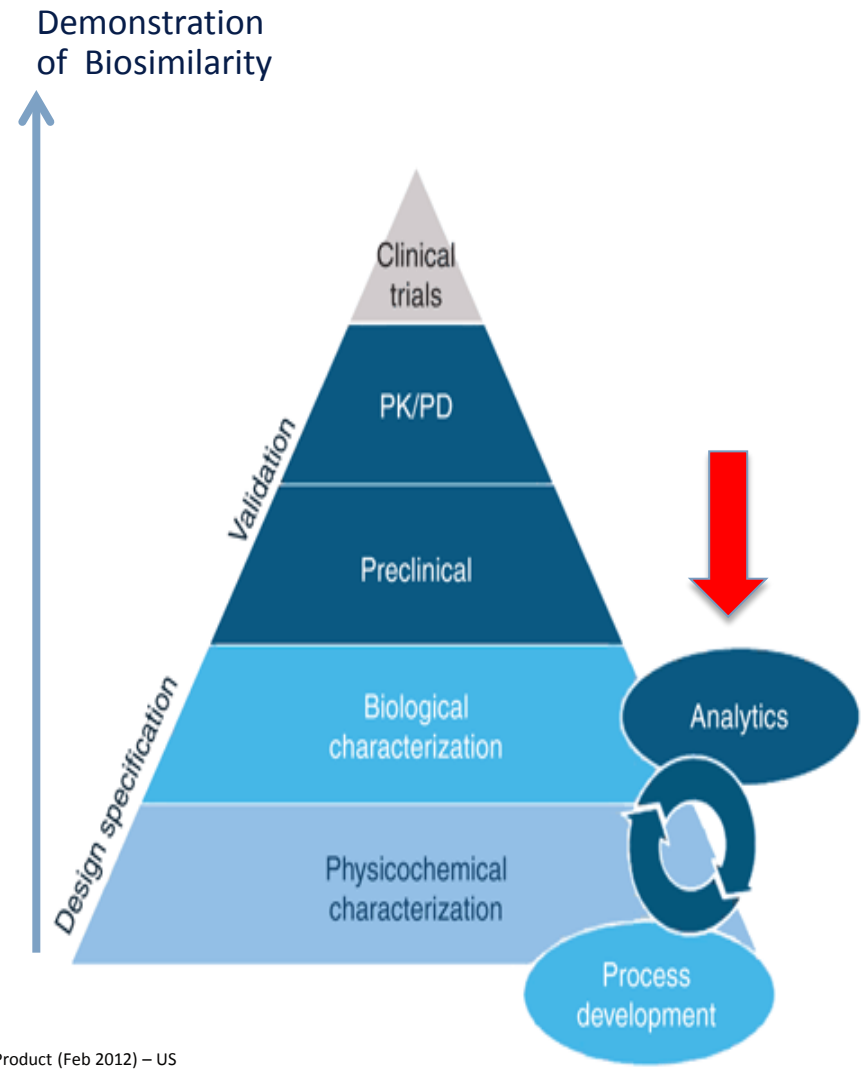
What can be Minimized With Acceptable Risk ?
The «Abbreviated Clinical Pathway»

Assumptions about analytical quality and similarity

- All efforts should be made to identify the **type, nature and extent of any analytical difference** between the two products [1,2,3,4]

Assessment of residual uncertainty

- **The degree of residual uncertainty** that remains at each step of the development process regarding the similarity of the products is determined [1,2,3,4]
- Based on the similarity of quality and pre-clinical data ,**the amount of clinical data needed to show clinical comparability with the RP is defined in a progressive, risk-based approach[1,2,3,4]**



Adapted from 1.FDA Draft Guidances – Quality and 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. Health Canada: Guideline for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) (March 2010) 4. WHO Guidelines on Similar Biotherapeutic Products. http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf

*RP= Reference Product

Development of Biosimilars: Analytics

The biosimilar development starts with definition of the molecular characteristics and quality attributes of the RP*[1,2,3]

Followed by a comparability exercise of the quality and pre-clinical data [1,2,3]

Detection of quality differences

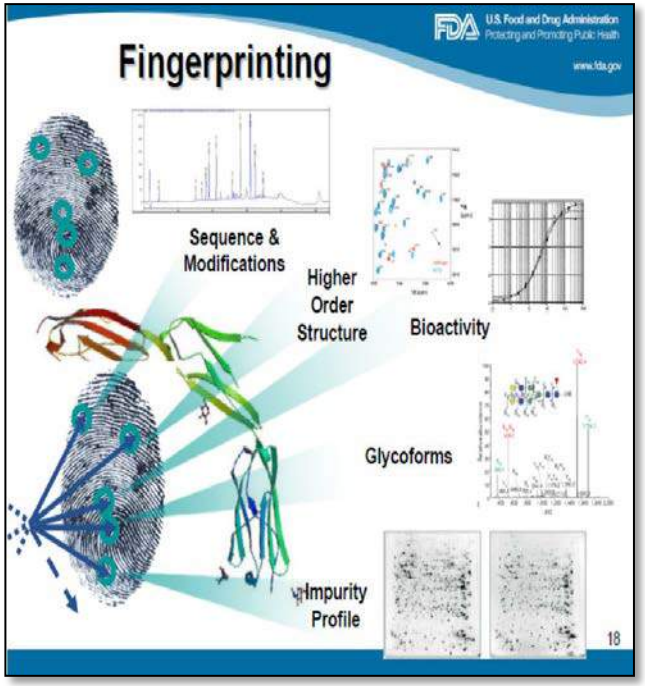
- Quality differences may vary with manufacturing processes and given current analytical limitations, it is possible that some of them cannot be fully defined [4]

*RP= Reference Product

The non-clinical and clinical comparability then provides the confidence that any differences observed at the quality level have no impact on the safety and efficacy of the biosimilar medicinal product when compared to the reference medicinal product .Every biosimilar medicinal product application is assessed on an individual basis. [6]

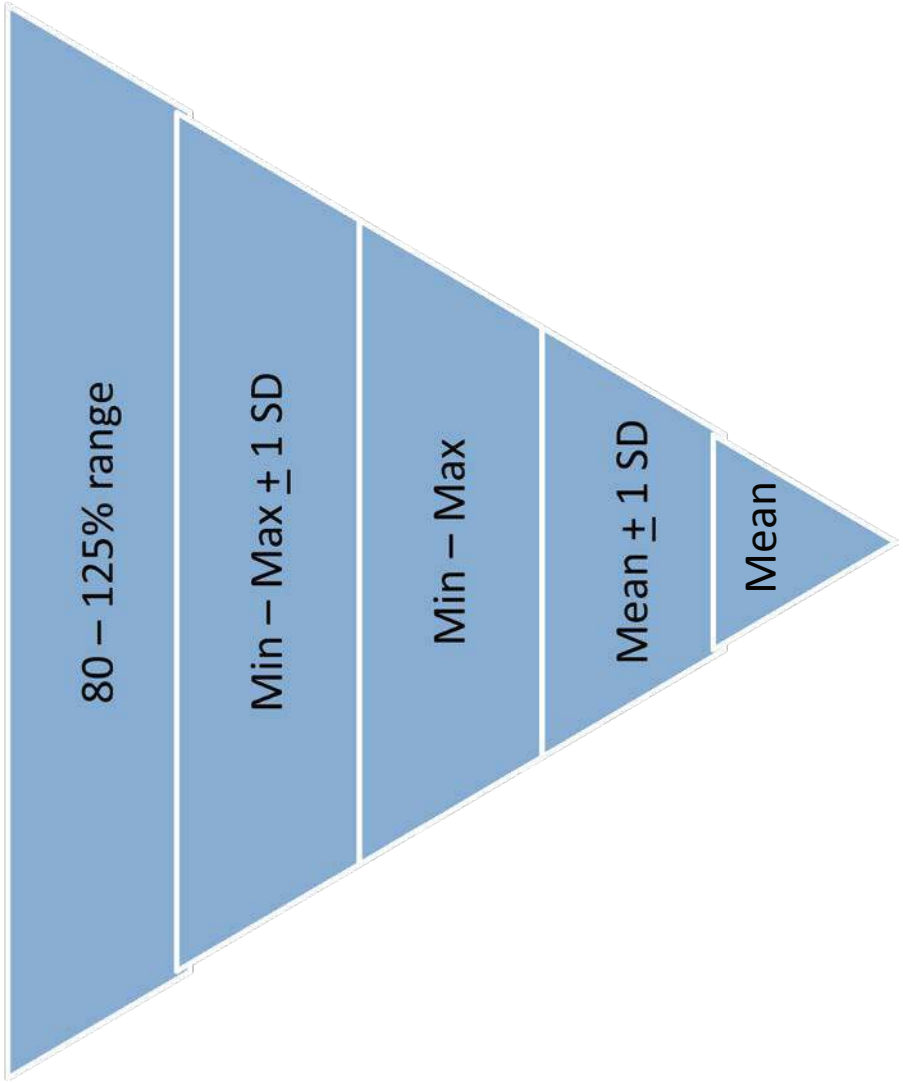
Clinical relevance of quality differences

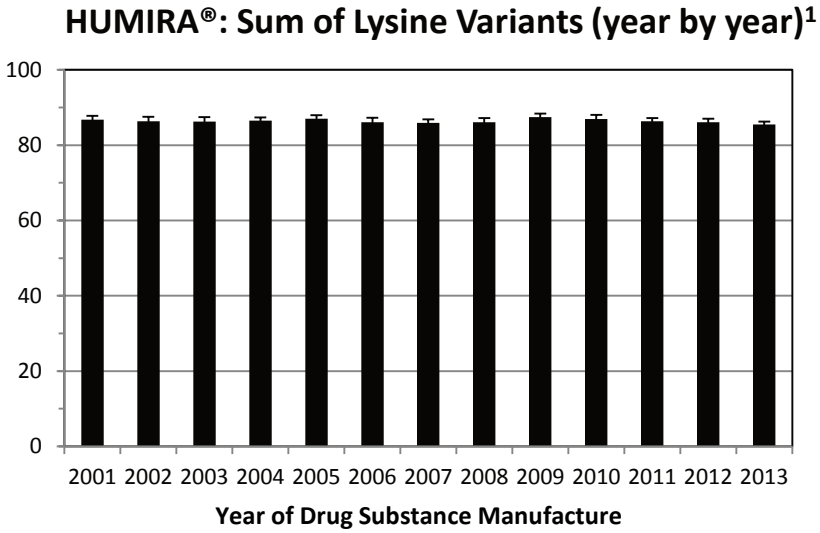
- At the current stage of knowledge it may be difficult to interpret the relevance of minor quality differences when comparing a biosimilar mAb to a reference mAb[5]



1.FDA Draft Guidances – Quality and 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 4.Sekhon BS et al Biosimilars 2011: 1 1-11 5.Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies –Non-clinical and Clinical Issues/EMA/CHMP/BMWP/403543/2010 6. European Commission: What you need to know about biosimilar medicinal products . Consensus Information Paper

Six Degrees of Separation: The Windows of Similarity





1. AbbVie Inc, Data on File

Equivalency Window Perspectives

BioDrugs
DOI 10.1007/s40259-013-0036-3

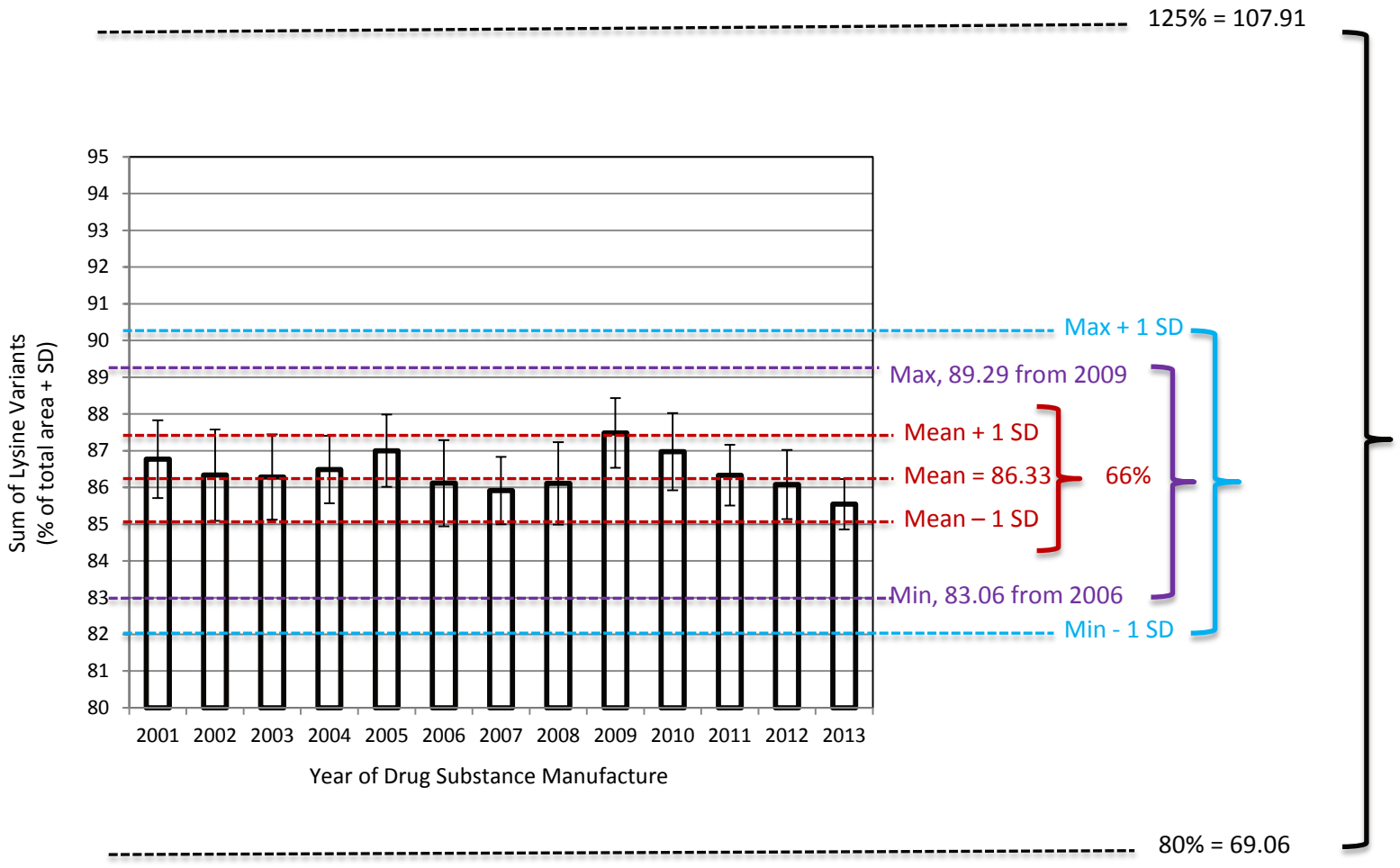
ORIGINAL RESEARCH ARTICLE

Physicochemical and Functional Comparability Between the Proposed Biosimilar Rituximab GP2013 and Originator Rituximab

Jan Visser · Isabel Feuerstein · Thomas Stangler · Timo Schmiederer · Cornelius Fritsch · Martin Schiestl

The results from all potency bioassays were assessed for bioequivalence using the two-sided test procedure (TOST) and applying the usual bioequivalence limits of 0.8–1.25.

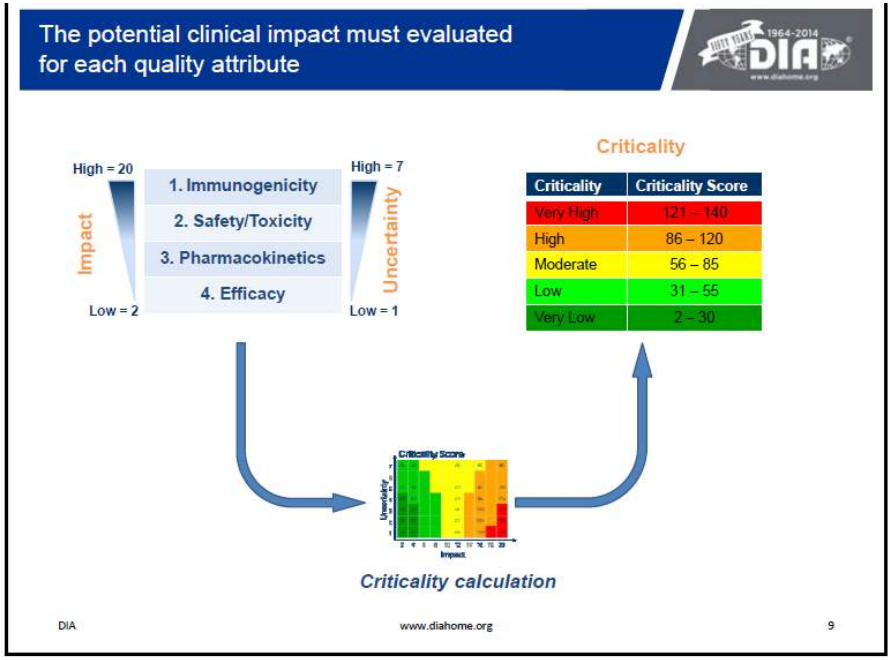
C-terminal Lysines: Equivalency Window Options for HUMIRA®[1]

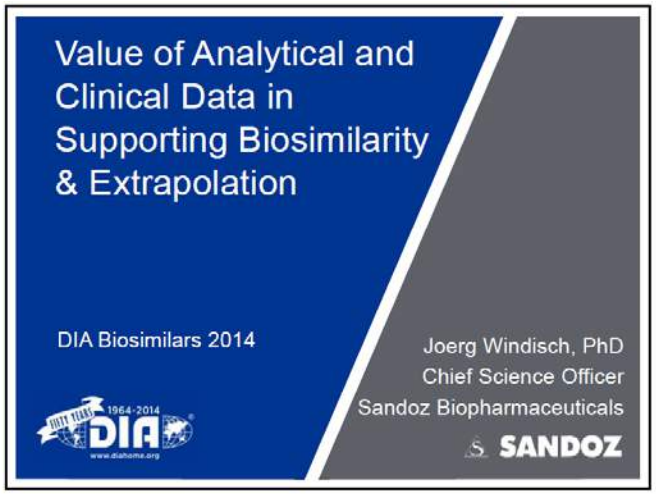


Max = 89.29, 2009; Min = 83.06, 2006; Mean 86.33, SD = 1.09644

1. AbbVie Inc, Data on File

Biosimilarity Index: Equivalency Window Criticality Score[1]





1. **Customized per attribute analyzed (>100's attributes)**
2. **Dictated by the variation in the originator per attribute**
3. **Incorporates distance (from the equivalency window)**
4. **Assesses Impact (known or derived functionality of the attribute)**
5. **Aggregates into an overall index for the biosimilar candidate [quantifies the degree of similarity]**

1. J. Windisch, Sandoz. Value of Analytical and Clinical Data in Supporting Biosimilarity and Extrapolation. DIA Biosimilars 2014, Washington DC.

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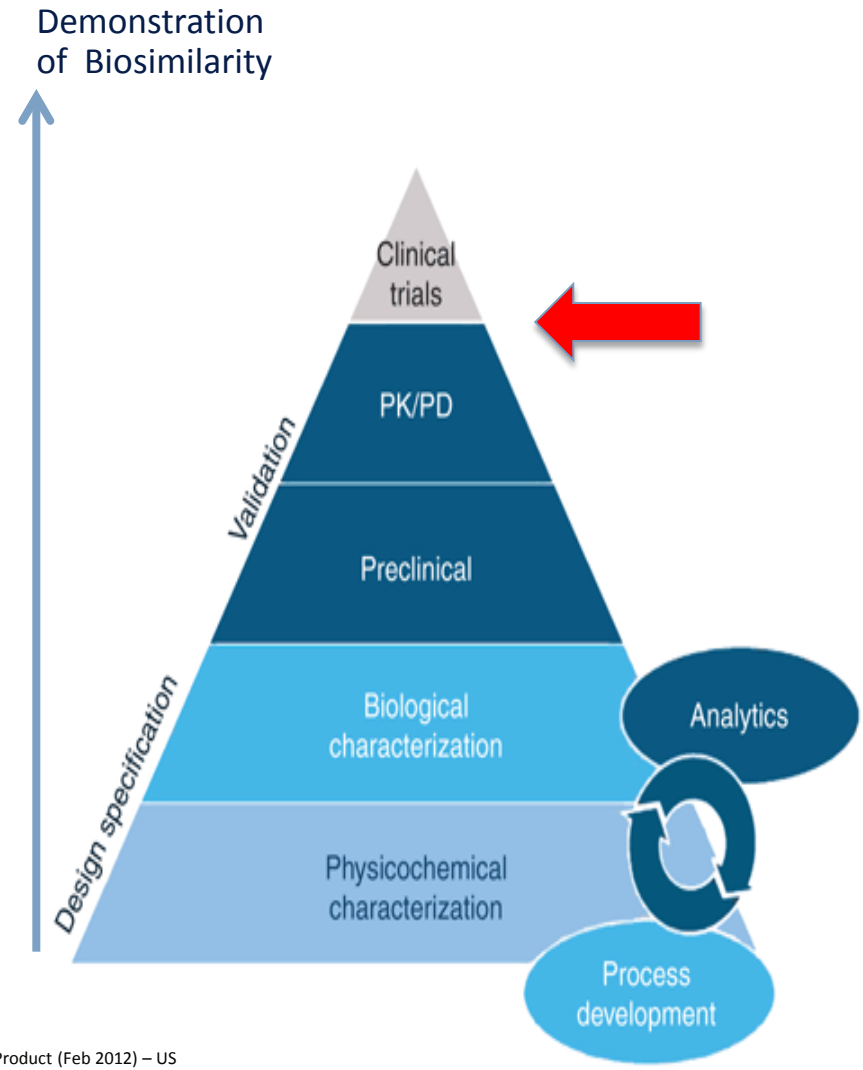

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*RP= Reference Product

Review of Switching Across Innovator and Biosimilar Epoetins, Growth Hormones and G-CSFs

- A review of clinical trials evaluating switching within the classes of erythropoietin, growth hormone or G-CSF was performed[1]
  - 58 clinical trials & 12,039 patients who were switched (total # includes non-switched patients) across innovator products and/or between innovator products and biosimilars
  - 193 post authorization case reports for biosimilars authorized in the EU
- The limited clinical data that specifically studied the effects of switching mostly concluded that patients can be safely switched from one product to the other[1]
- Most clinical trials were not designed to identify switching related adverse events and some studies only followed-up patients after being switched in a single-arm, open label design[1]
- Spontaneous reporting systems may not be well equipped to identify adverse events associated with switching[1]
- In order to understand the real time dynamics of switching and the occurrence of safety events because of switching, more studies are required on the clinical practice of switching[1]

1.Ebbers H ,et al.Expert Opin. Biol. Ther. (2012) 12(11.

Evidence of Switching Across Other Biologics including Monoclonal Antibodies

- Experience of switching across other classes of biologics is limited and mainly restricted to switching across different products of the same class[1]
  - Switching across insulin products has been reported to be safe and effective[2]
  - Most mAb data are related to TNFI[3-5] where switch is mostly motivated by a lack of efficacy or the occurrence of AEs[1]
  - For stabilized Crohn's patients non medical switching from one TNFI to another may lead to more dose increases and more interruption of treatments [6]
- There is very limited evidence for switching from biosimilars of mAbs to their reference product [7]

G-CSF: Granulocyte colony stimulating factors mAb= monoclonal antibody RP = Reference Product TNFI = Tumor Necrosis Factor Inhibitor
AE = Adverse Event

1.Ebbers H ,et al.Expert Opin. Biol. Ther. (2012) 12(11 2. Valensi P ,Int J Clin Pract 2009;63 (3) : 522-3 3.D'Haens GR, Panaccione R, Higgins PD, et al. Am J Gastroenterol 2011;106(2):199-212; quiz 213 29.
4.Ormerod AD. Br J Dermatol 2010 163(4) 667-9 5 .Bombardieri S, Rheumatology ; 46: 1191-1199 6. Van Assche G et al. Gut 2012; 61: 229-234 7.Park W et al. Abstract 29301, presented at ACR 2013, San Diego, 25th-30th October

Interchangeability: Switching Studies

Despite the definition of interchangeability as stated by the FDA, there is no agreement as to the optimal clinical study design that can be used to demonstrate this concept

It is also unclear what population should be included in these studies[1–7]:

1. For chronic diseases, should both **new patients** and **stable treated patients** be studied ?
2. Should switching studies be conducted in the **most sensitive populations ?**
3. Potential additional factors to consider
   - Immunogenicity risk (frequency, severity, anti-drug antibodies)?
   - Safety and efficacy in different indications?
   - Use of extrapolated indication(s)?
   - Subpopulations with distinct efficacy or safety profiles (e.g. pediatric)?

FDA, Food and Drug Administration

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; 5. Declerck P. J. GaBi Journal, Vol.1, Issue 1, 2012, 13-16 ; 6. Mould DR and Greens B- Concepts and Lessons for drug development Biodrugs 2010; 24(1): 23-39.; 7. Ebbers H.C. et al., Expert Opin Biol. Ther. 2012, 12 (11) 1473-1485.

Switching Studies for Biosimilars and Their Reference Product

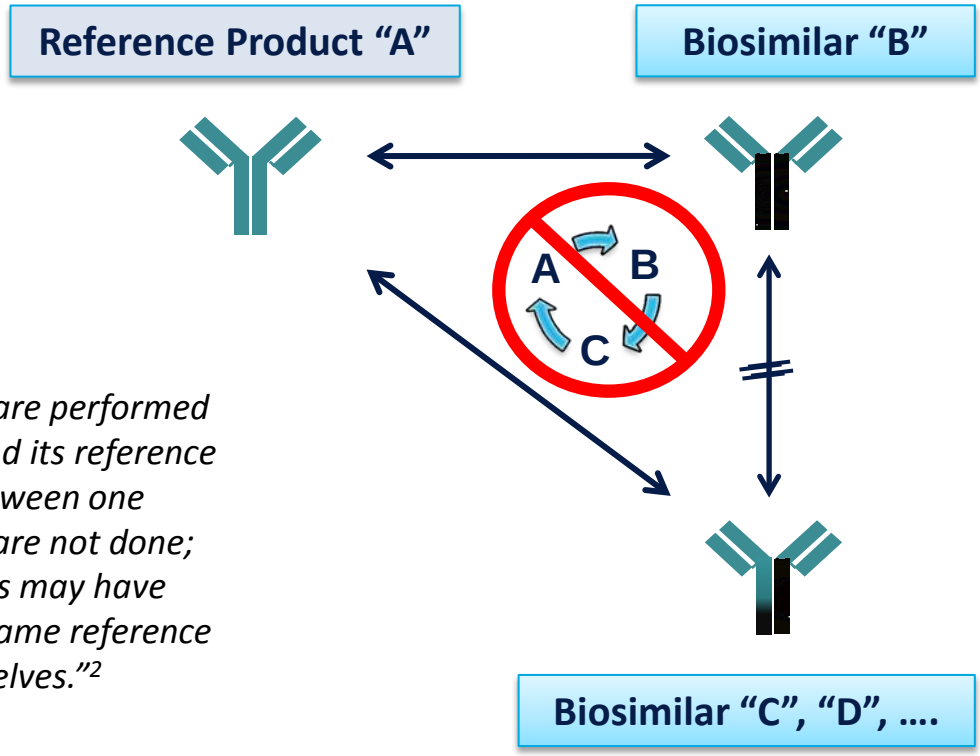
Ethics of Switching Studies

- Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects (Helsinki declaration[1])
  - How to consider a switching study with a null hypothesis that no clinical benefit is expected for (stable) patients while the potential risk is increased?
  - Can access to affordable medications be considered a sufficient benefit for patients included in switching studies?

1. World Medical Association Declaration of Helsinki, JAMA Oct. 2013

How to Consider Switching Between Several Biosimilars ?

A biological product may not be evaluated against more than ONE reference product.[1]
Will interchangeability transitivity be applied in practice? If A=B and A=C, does B=C follow?



"Comparability studies are performed between a biosimilar and its reference product, but studies between one biosimilar and another are not done; two separate biosimilars may have been compared to the same reference but not between themselves."[2]

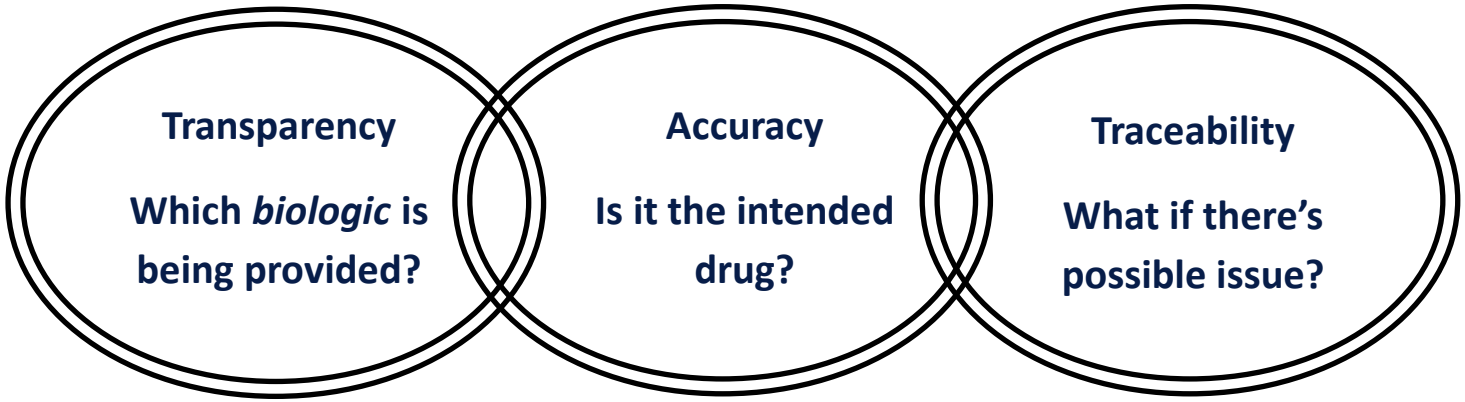
1. Biologics Price Competition and Innovation Act of 2010.
2.WHO 56th Consultation on International Nonproprietary Names for Pharmaceutical Substances; Executive Summary Geneva, 15-17 April 2013

Additional Considerations on Interchangeability and Substitution

Tracking and Traceability

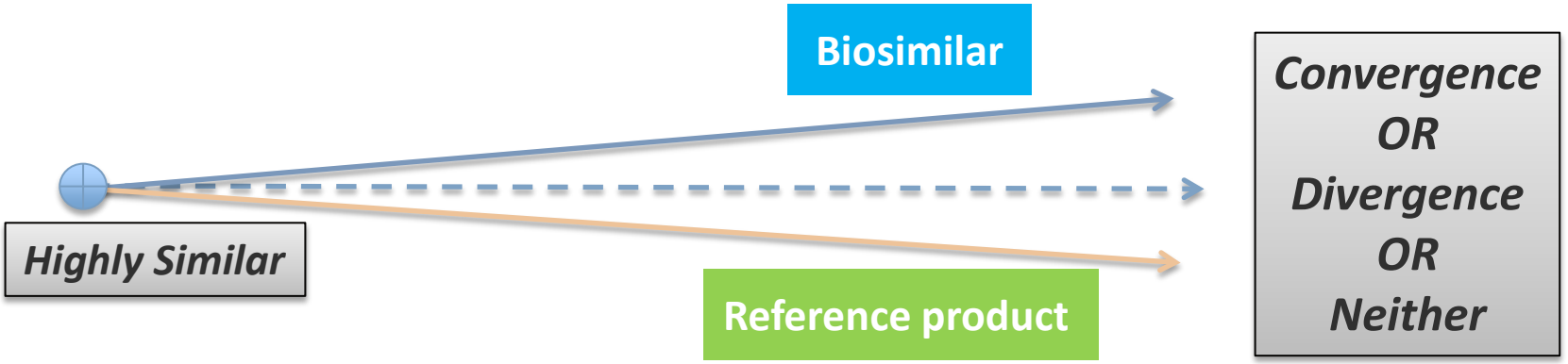
Substitution may complicate effective pharmacovigilance:

- If physicians are not informed, it may subvert the ability to attribute adverse events to the appropriate agent.[1]
- If the onset of the adverse reaction is delayed: Some adverse reactions, including immunogenic reactions such as pure red cell aplasia (PRCA), 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, 20.47

Interchangeability and Independent Product Manufacturing Changes



- Even small changes can have a large impact.[1]

- **Independent changes** made by **different manufacturers** could cause **convergence, divergence or neither in their profiles over time**[2-3]
  - Post-marketing comparative biosimilarity validation not required [4]
  - A reason some regulators do not endorse interchangeability[3,5]

1 .Schneider ,CK Biosimilars in Rheumatology, the wind of change. Ann Rheum Dis 2013 72: 315-318; 2. J. Kay et al. / Biologicals 40 (2012) 517e527; 3. Ramanan S, Grampp G. BioDrugs DOI 10.1007/s40259-014-0088-z;
4. US "Biologics Price Competition and Innovation Act (BPCIA) of 2009; 5. Wang J, Bedford P. GaBI Journal 2014 http://gabi-journal.net/perspective-on-biosimilarity-and-interchangeability-incanada.html

Additional Considerations on Interchangeability and Substitution

Extrapolation:

- Can clinical interchangeability data be extrapolated from one tested indication to another?
- Currently not addressed by authorities or the scientific community

Interchangeability and Devices

- **For self-injectable medications, should new patients be trained after switching?**
- **In order to prevent injection errors, how similar should the delivery devices be?**

FDA Guidance:
Additional considerations apply for a proposed interchangeable product. For example, in reviewing an application for a proposed interchangeable product, FDA may consider whether the **differences from the reference product significantly alter critical design attributes, product performance, or operating principles, or would require additional instruction to healthcare providers or patients**, for patients to be safely alternated or switched between the reference product and one or more interchangeable products without the intervention of the prescribing healthcare provider. **Additional performance data about the delivery device may also be necessary.**[1]

MPA Statement:
Currently, these medical products are injected, which means that they may also be packaged in/supplied with different injection aids and hence are also unsuitable for substitution from this perspective. In addition, the approval of these products is tied into requirements of risk management plans which in many cases include follow up of safety for actual use. This would be hard to achieve if they are substituted for other products in a rolling manner at a pharmacy level. [2]

1. Guidance for Industry Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009
2. Investigation of the possibility to extend the substitution system and of substitution for new prescriptions, Swedish Medical Products Agency . 26 September, 2011

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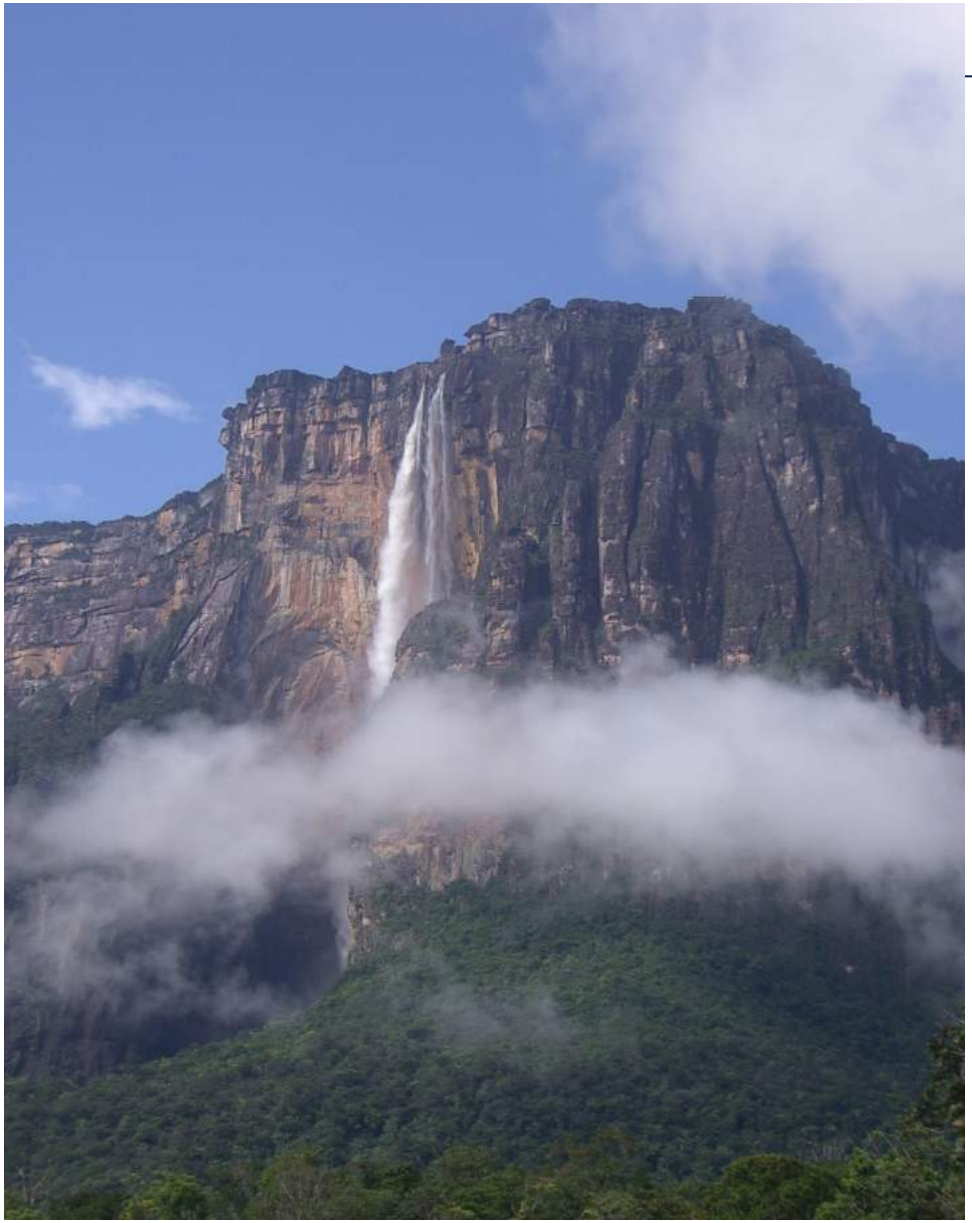
Summary

Conclusion

- Biosimilarity approval by a regulatory agency does not imply interchangeability[1-6]
- Given the limitations of post authorization data, it is currently impossible to conclude an absence of a risk of switching biologics[7,8]
- **Some approaches, including analytics and switching clinical studies efforts are currently ongoing but many challenges remain[9-15]**
- **Important additional considerations including traceability of adverse events, the presence of multiple biosimilars, product divergence over time, extrapolation of interchangeability and the device must be appropriately addressed**
- Some physicians[16] and regulators[17] have recommended that physicians always be involved in making decisions about changing treatment among biosimilars and reference products

1.FDA Biosimilar Guidance Webinar, February 15, 2012; 2. EMA, Questions and Answers on biosimilar medicines; European Biopharmaceutical Enterprises (EBE) Survey on Biosimilars, May 2011; 3. MHLW Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products, March 2009 ; 4 FDLI Update, July 2012; 5.Discussion paper on Similar Biological Medicinal Products (SBMPs), Australia PBS; 6.Health Canada Interchangeability and Substitutability of Subsequent Entry Biologics, July 20102009 7.Ebbers H ,et al.Expert Opin. Biol. Ther. (2012) 12(11. 8.European Commission: What you need to know about biosimilar medicinal products . Consensus Information Paper 2013 9. Declerck P. J. GaBi Journal, Vol.1, Issue 1, 2012, 13-16; 10. Lu Y; Chow SC et al. : Drug Designing 2013, Vol. 2; Issue 3; 2- 6 11. Endrenyi L et al. Statist. Med. 2013,32, 434-441; 12. Chow S-C et al. Statist. Med. 2013,32, 442-448.; 13. den Broeder AA et al, Ann Rheum Dis 2013; 72:e14; 14. Mould DR and Greens 8.- Concepts and Lessons for drug development Biodrugs 2010; 24(1): 23-39 ; 15.Park W et al. Abstract 29301, presented at ACR 2013, San Diego, 25th-30th October16.B Gecse Gut, published on line March 16, 2013 as 10.1136/gutjnl-2012-303824. 17.Scott B et al, The journal of Clinical PharmacologyDOI:I 002/jcph.339



¡Gracias por su Atención!

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