Biossimilares: A importância da Produção no Brasil e a Incorporação de Novas Tecnologias.

Valderilio Feijó Azevedo, MD,PhD

Coordenador da Comissão de Biotecnologia da SBR

Coordenador do Forum Permanente Latino Americano de Biossimilares

CÂMARA DOS DEPUTADOS

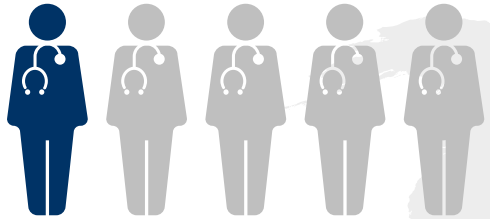
COMISSÃO ESPECIAL DESTINADA A ACOMPANHAR AS AÇÕES DE COMBATE AO CÂNCER NO BRASIL

27/04/2022

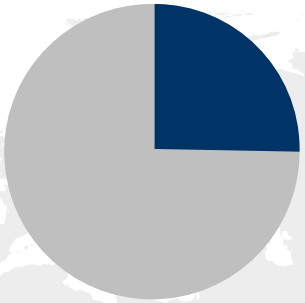
Conflitos de Interesse

- Adjunct Professor and Head of rheumatology Unit at the Federal University of Paraná, Brazil
- Executive Board of Americas Health Foundation. Washington DC
- Advisory Board of Alliance For Safe Biologics Medicines, Washington DC
- General Coordinator of Latin American Forum on Biosimilars – FLAB
- General Coordinator of Biotechnology Commitee of the Brazilian Society of Rheumatology
- R & D Director for new biopharmaceutical product development at Edumed biotech
- Principal Investigator – has recevied Clinical investigational fees from Pfizer, Roche, Janssen, Bristol, Abbott, Medimmune, Boehringer, GSK, UCB, Sanofi
- Financial support to participate in meetings and give national and international conferences to Pfizer, Roche, Sandoz, MSD, BMS, Merck Serono, Lilly, Celltrion, Amgem,Janssen and Novartis

Acesso a medicamentos biológicos é limitado em todo o Mundo



19-24% dos dermatologistas em países da UE e do Canadá acreditam que o custo dos biológicos era uma importante barreira no tratamento da psoríase[3]

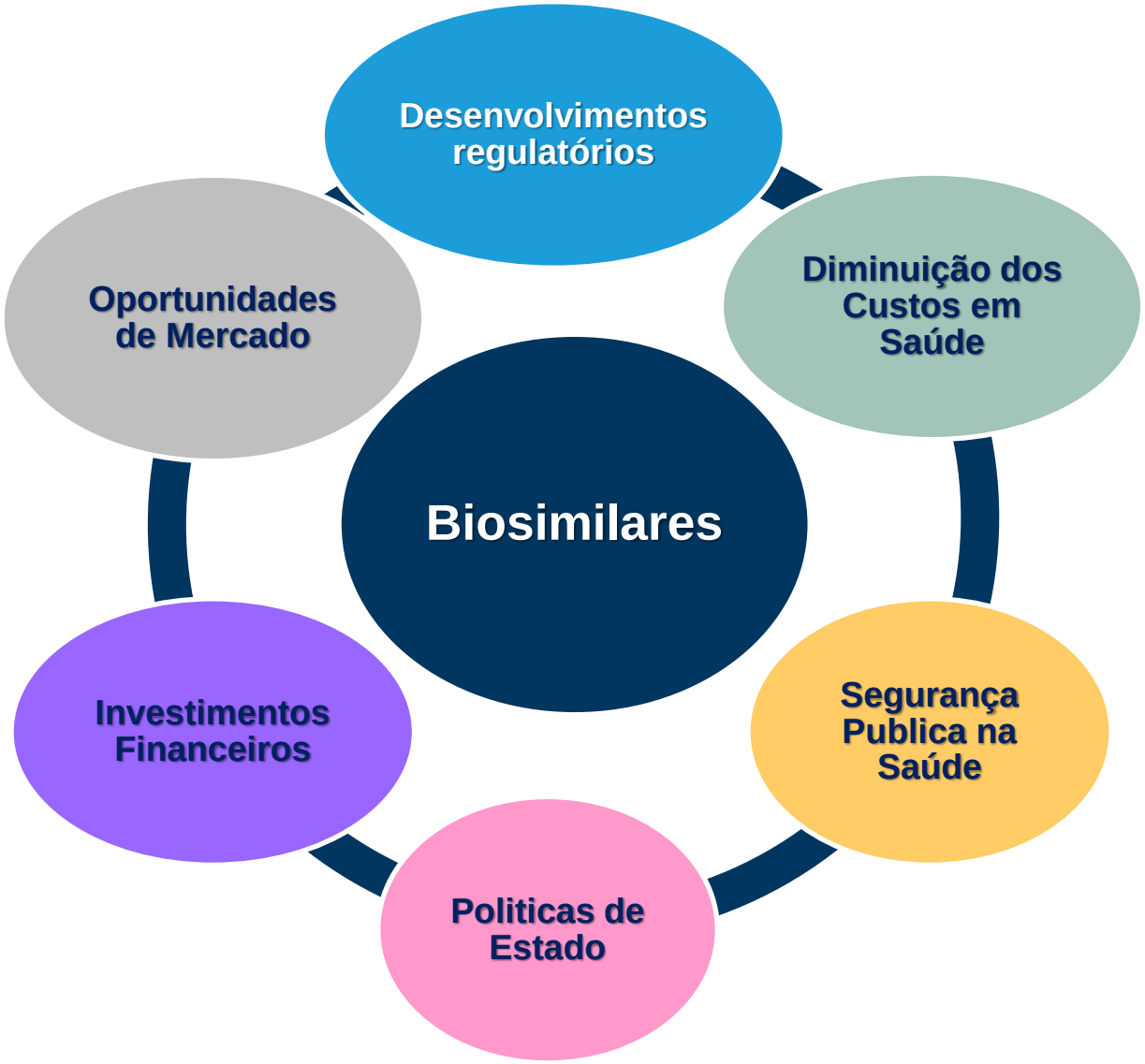


Quase ¼ dos 46 países da UE não garantem acesso a biológicos para o tratamento da artrite reumatoide[1]

Entre ~10-30% dos pacientes na França, Alemanha e Reino Unido recebem biológicos para o tratamento da artrite reumatoide[2]

1. Putrik P, et al. Ann Rheum Dis 2014;73:198–206; 2. Miltenburger C, et al. Barriers to RA treatment access across Europe (2009). Available from http://www.comparatorreports.se/RA%20Barrier%20Report_FINAL_050110.pdf [Accessed 2016 March 30]; 3. Nast A, et al. Arch Dermatol Res 2013;305:899–907.

Biosimilares



Azevedo V F Biosimilars: Uma revolução nas medicações? Correio Braziliense.

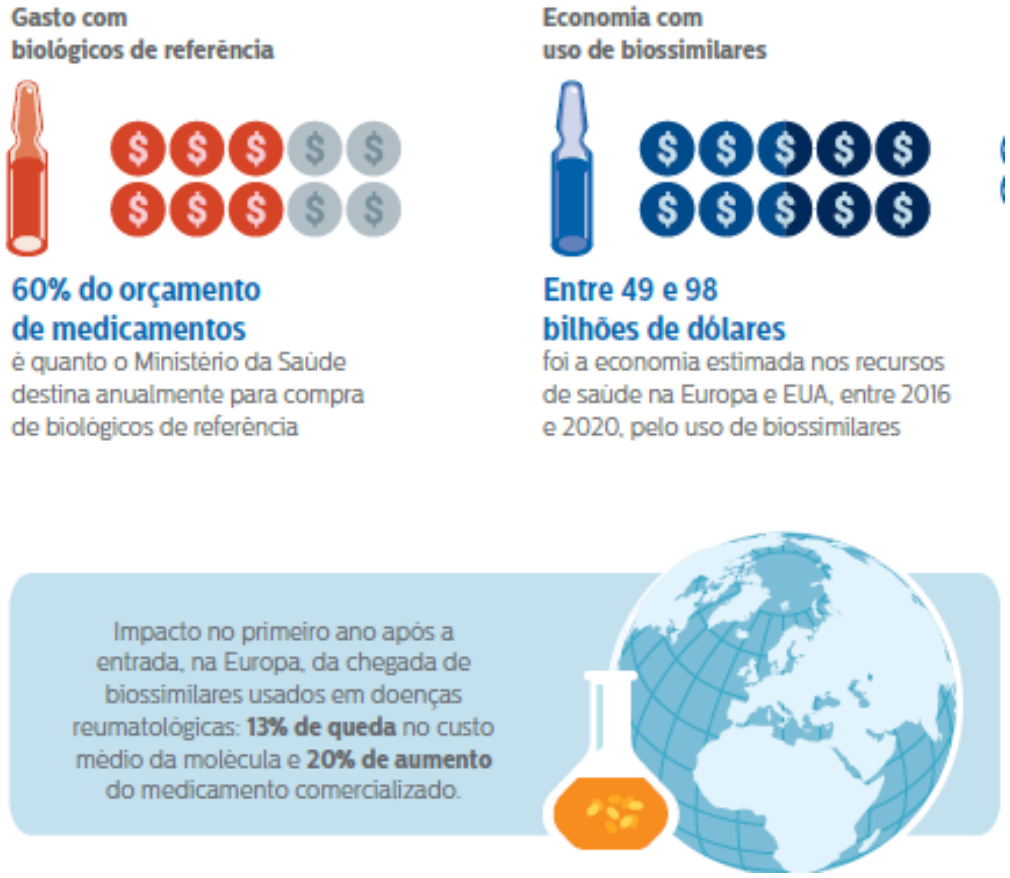
Medicamentos biológicos consomem recursos para a saúde

Dados do IPEA (Instituto de Pesquisa Econômica Aplicada):

60% dos gastos públicos no Brasil com medicamentos são destinados aos biológicos.

Porém, em quantidade de medicamentos, este montante representa o equivalente a apenas **12%**

Impacto na economia



IMS Institute for Healthcare Informatics: Delivering on the Potential of Biosimilar Medicines report. IMS Institute Report. March 2016

Atributos que potencialmente afetam o desenvolvimento de políticas para biossimilares em cinco países latino americanos

Attribute	Brazil	Argentina	Chile	Mexico	Venezuela
Market size (population)	Large (205M)	Mid-sized (42M)	Small (17M)	Large (115M)	Mid-sized (28M)
Interaction with international thought leaders	High	High	Medium	High	Medium
Local production capabilities	Yes	Yes	Yes	Yes	No
Safety issues with biosimilars in the past	Yes (hematology product(s))	No	Yes (Wosullin)	Yes (Kikuzubam)	No
Expected differences in regulatory requirements based on complexity of molecule	Yes	N/A	Yes	Yes	Yes
Regulatory pathway specific for biosimilars	Yes	Yes	No	Yes	No
Year of biosimilar regulatory pathway	2010	2005 / 2011	≥2012	2012	None

Azevedo VF, et al. *Value in Health Regional Issues* 2012;1:228–34.

Drug Revolution?

Are We Prepared to Prescribe Biosimilars?

EDITORIAL

RBR

Are we prepared to prescribe biosimilars?

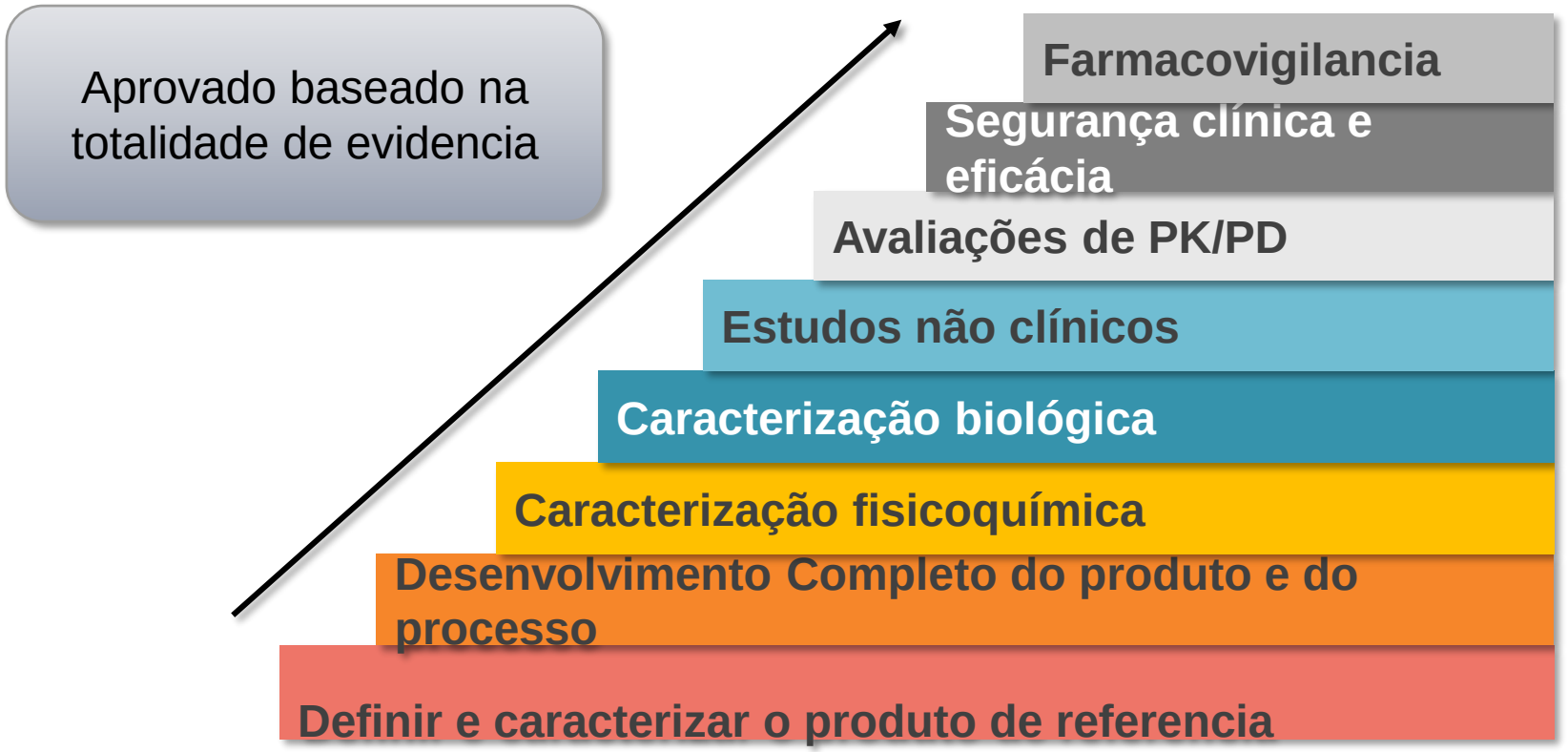
Biodrugs are recombinant proteins used in the treatment of several diseases. Monoclonal autoantibodies and fusion proteins currently being used in the treatment of autoimmune diseases are examples of biodrugs. Contrary to synthetic molecules, with simpler structures and low molecular weight, which are obtained exclusively by chemical methods, biodrugs are very heterogeneous, more unstable compounds, with tridimensional structure and high molecular weight (100 to 1,000 times larger than synthetic molecules), obtained through complex methodologies that include from the initial production in genetically modified living cell organisms (bacteria, fungus, or mammal cells) to processing using fermentation and purification methods, among others.[1-4] It is well-known that the development of these molecules in the decade of 1980 revolutionized the way physicians treated their patients, especially those with diseases

the substitution among biologicals (especially among innovative molecules and biosimilars) can have clinical consequences and even generate public health problems.[7] This does not mean that biosimilars are not safe, considering that, as a rule, they are subject to an approval process, which require substantial additional data in relation to those required for generics by the regulating authorities.

The international nomenclature (International Nonproprietary Name – INN) currently used for synthetic molecules, which is based on well-defined and easily characterized molecular differences, does not seem appropriate for the use intended to the nomenclature of molecules obtained by biotechnological methods, as the different available methods of structure analysis are not sensitive when applied for the characterization of biomolecules. It would be time to rethink a new specific and independent nomenclature for biomolecules.[8,9]

Azevedo VF. Bras J Rheumatol 2010;50(3):221–24.

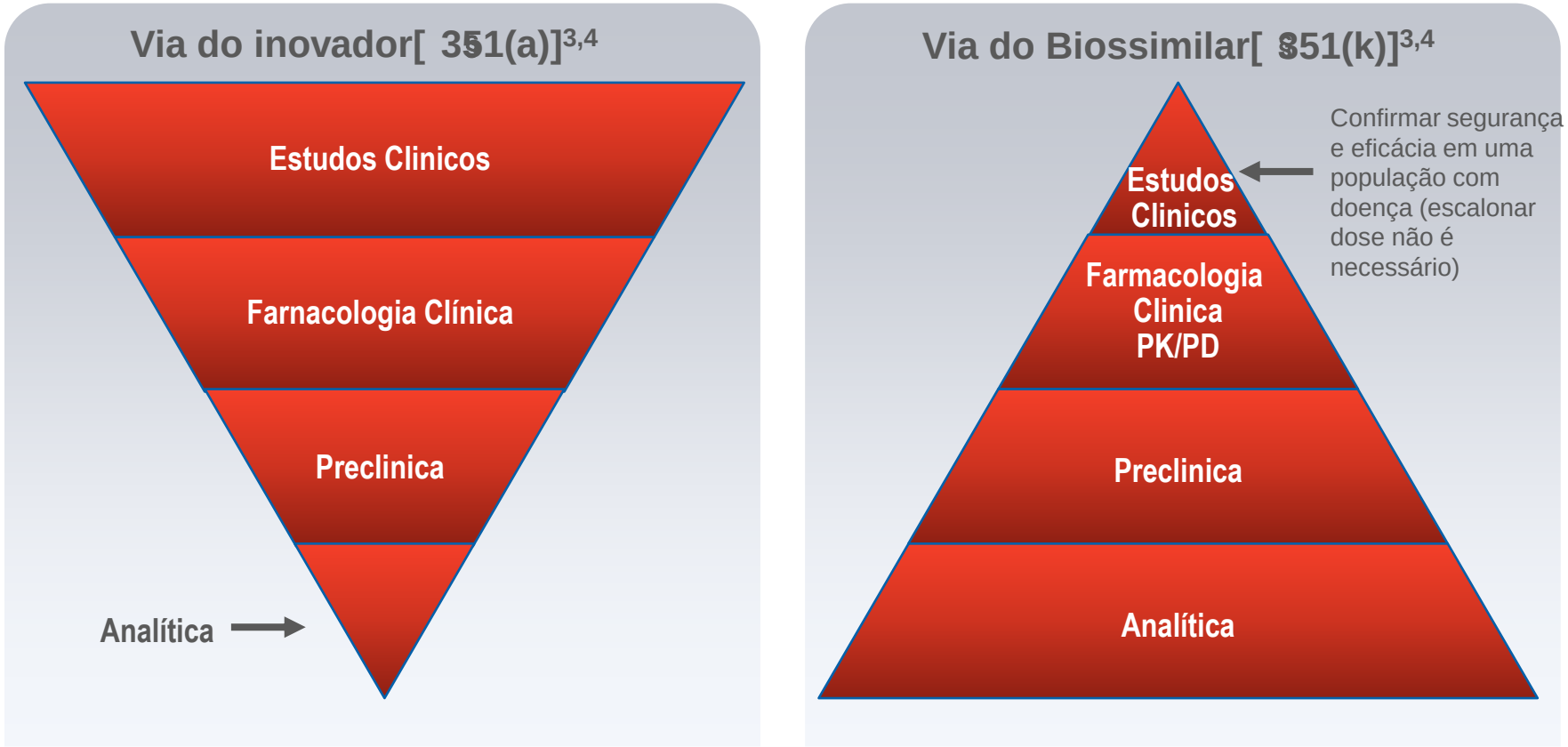
Rigorosos padrões regulatórios[1,2]



1. Committee for Medicinal Products for Human Use. European Medicines Agency. *Guideline on Similar Biological Medicinal Products.* http://www.ema.europa. eu/docs/en_GB/document_library/Scientific_guide line/2009/09/WC500003517.pdf. Accessed December 9, 2014.
2. US Food and Drug Administration. *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.* http://www.fda. gov/downloads/Drugs/GuidanceComplianceRegulator yInformation/Guidances/UCM291128.pdf. Accessed December 9, 2014.

Via de biossimilares representa um paradigma em relação ao padrão de registro de um inovador

O Objetivo do programa de desenvolvimento de um Biossimilar é estabelecer biossimilaridade baseada na Totalidade de Evidencia. Não é reestabelecer o benefício do inovador.[1,2]



PD = farmacocinética.

1. Schneider CK, et al. *Nat Biotechnol.* 2012;30:1179-1185. 2. Koslowski S, et al. *N Engl J Med*. 2011;365:385-388. 3. MacDonald J. Presented at: APEC: Biotherapeutics Workshop; September 2013. 4. McCamish M. Presented at: EMA Workshop on Biosimilars; October 2013; London, UK.

GaBiJournal
Generics and Biosimilars Initiative Journal

REVIEW ARTICLE

Recommendations for the regulation of biosimilars and their implementation in Latin America

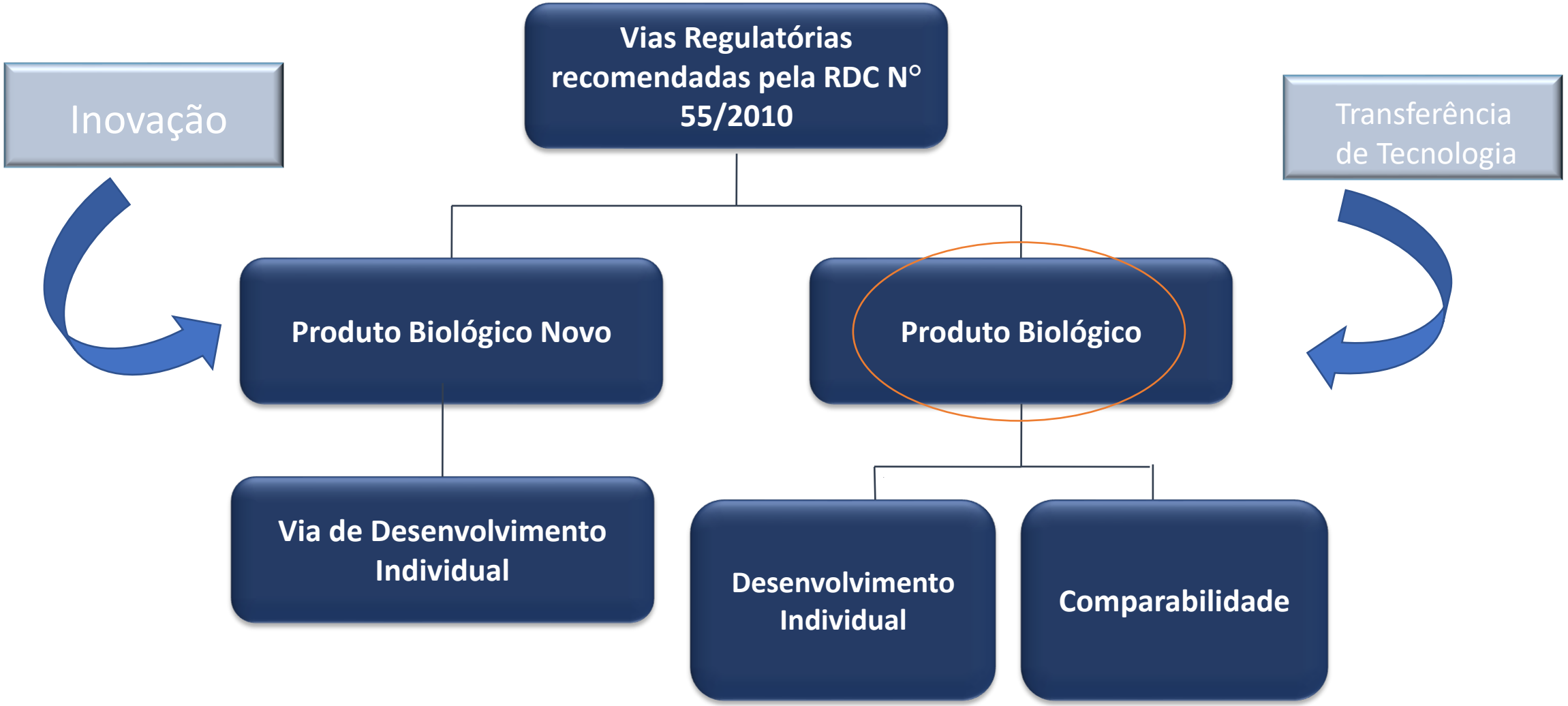
Valderilio Feijó Azevedo, MD, PhD; Eduardo Mysler, MD; Alexis Aceituno Álvarez, PharmD, PhD; Juana Hughes, MSc; Francisco Javier Flores-Murrieta, PhD, FCP; Eva Maria Ruiz de Castilla, MS, MAA, PhD

With the emergence of biosimilars as a new class of biotherapeutic agents, the use of these products in Latin America has become a focus of attention. To aid policymakers and regulatory authorities, a group of experts on biosimilars developed a series of recommendations for the regulation of biosimilars and their implementation in the region. Although most of the Latin American countries have adopted, in general, the WHO recommendations; there are some of them whose regulations differ from WHO. Unfortunately, the pace at which the region moves toward reaching its potential of having safe and effective biosimilars has been slow. Countries in the region must enhance their efforts to improve pharmacovigilance to include training more regulatory staff, more public and professional awareness on the importance of reporting adverse events and better systems to capture and analyze data. Regulatory authorities should also establish a process whereby the traceability of an adverse event to a biosimilar can be determined. Products previously approved as 'intended copy' drugs should be evaluated according to regulations specific to biosimilars. It cannot be assumed that a previously approved biopharmaceutical is actually a biosimilar, regardless of current clinical experience. Latin America is no exception to the slower-than-expected pace of developing regulations on biosimilars. The panel's perspectives on the current status led to six major recommendations in order to enhance the safe use of biosimilars in the region.

Azevedo VF, et al. *GaBi Journal* 2014 June 17

Registro Sanitário

RDC n°55/2010



CONTRIBUIÇÃO DA PRODUÇÃO LOCAL DE BIOMEDICAMENTOS

Proteção dos interesses da Administração Pública e da sociedade, ao buscar a economicidade com qualidade

Promoção de condições estruturais para aumentar a capacidade produtiva e de inovação do país, contribuindo para redução do déficit comercial do CEIS e visando a sustentabilidade tecnológica e econômica do SUS a curto, médio e longo prazos

Desenvolvimento da rede de Produção Pública no país e seu papel estratégico para o SUS

Quem decide a intercambialidade?

Tipos possíveis de troca

- Troca unidirecional – transição unidirecional
- Troca transicional reversa – troca reversa
- Multiplas trocas-
- Troca cruzada- transição cruzada.
- Trocas de biossimilares intraclasse.

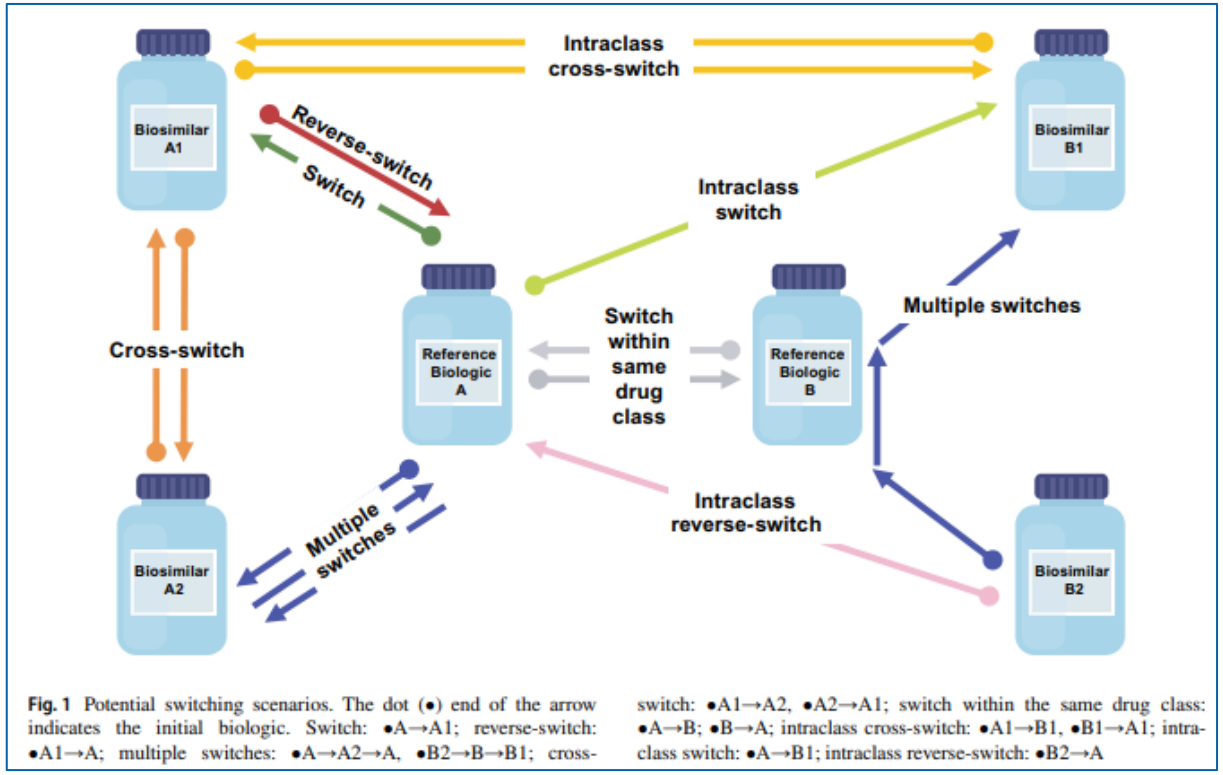


Fig. 1 Potential switching scenarios. The dot (•) end of the arrow indicates the initial biologic. Switch: •A→A1; reverse-switch: •A1→A; multiple switches: •A→A2→A, •B2→B→B1; cross-switch: •A1→A2, •A2→A1; switch within the same drug class: •A→B; •B→A; intraclass cross-switch: •A1→B1, •B1→A1; intraclass switch: •A→B1; intraclass reverse-switch: •B2→A

Adaptado de:
Mysler E, Azevedo VF, Danese S et al. *Drugs.* 2021 Nov;81(16):1859-1879

Considerações para pacientes para trocas

Ainda são preocupações?Em que contexto?

1. Perda de eficácia depois da troca
2. Falha secundária devido a ADAs
3. Outras reações infusionais (RSI, EA infusionais, etc.)
4. Perfil de infecções diferentes do PR
5. Qualquer diferença detectada no perfil de segurança de biossimilares comparados ao do PR

ADA, anti-drug antibody; AE, adverse event; ISR, injection-site reaction.

- Ten Years of biosimilars in Europe: development and Evolution of the regulatory pathways .Schiestl M. et al. Drug Des Devel Ther. 2017
- Biologicals and biosimilars: safety issues in Europe. Portela MDCC, et al. Expert Opin Biol Ther. 2017

Conclusões

- Com a aprovação de mais biossimilares acessiveis no mercado, a decisão de trocas do tratamento de um paciente em uso de um produto de referencia para um biosimilar ou de um paciente em uso de um biosimilar para outro surge como potencial prática e opção clínica.
- Dados cientificos preclinicos sustentam a evidencia de biossimilaridade, com a maior parte das evidencias estabelecidas por meio analitico, não clinico e graus variaveis de dados de farmacologia clinica comparativa antes dos estudos de componentes clínicos.
- Na ausencia de dados de estudos clinicos comparativos entre biossimilares de um mesmo produto de referencia, evidencias preliminares do mundo real garantem uma avaliação no contexto de cada paciente e circusntancias especificas de pagadores e os principios cientificos apoiam a utilidade de biossimilares.
- Atualmente, há uma falta de recomendações clínicas voltadas para o conceito de cross-switching, e tais recomendações podem desempenhar um papel educacional criando uma ponte de passage no hiato de conhecimentos e hesitação clinica na troca entre biossimilares, no sentido de facilitar a segurança e efetivo tratamento de pacientes.

Sackman J, Kuchenreuther M. The bullish outlook for biosimilars. BioPharm International; 2015. p. 38–41.

Dutta B, Huys I, Vulto AG, Simoens S. Identifying key benefits in European off-patent biologics and biosimilar markets: it is not only about price! BioDrugs. 2020;34:159–70.

Blauvelt A, Lacour JP, Fowler JF, Jr., Weinberg JM, Gospodinov D, Schuck E, et al. Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: impact of multiple switches. Br J Dermatol. 2018 Sep;179(3):623–31.

Mysler E, Azevedo V F, Danese S, Drugs 2021