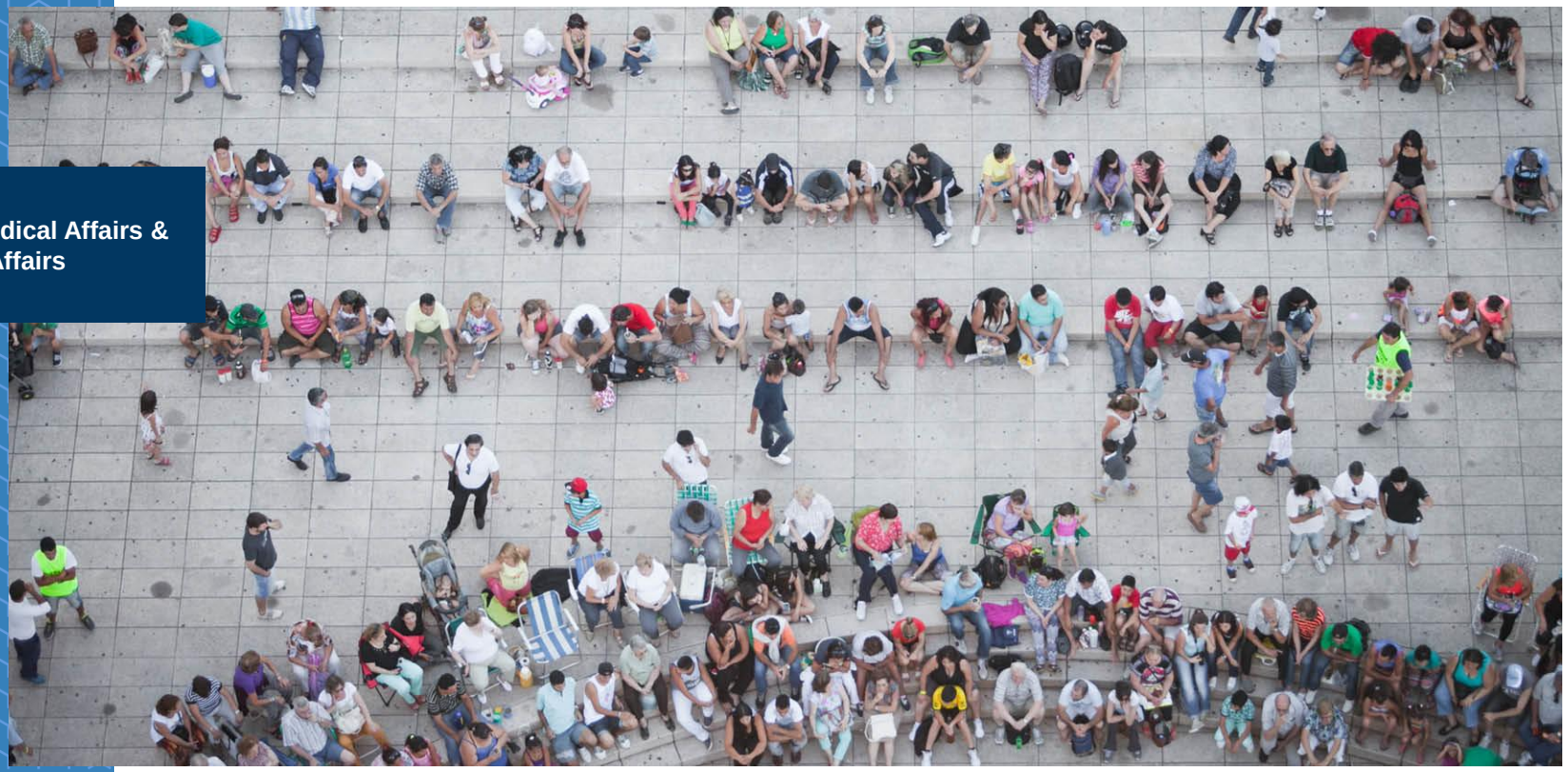
Sandoz Medical Affairs & Scientific Affairs



Sandoz Global Experience with Biosimilars

Hillel P. Cohen PhD and Carlos Sattler MD
Sandoz Inc.
GRx-Biosims 2018 meeting
September 5, 2018

SANDOZ A Novartis Division

Biosimilars improve access for patients:
Price declines accompanied by greater use

Immunology

Anti-TNF	**Price** decline per Therapeutic Day (2016 year before biosimilar entrance)	**Volume** increase per Therapeutic Day (2016 year before biosimilar entrance)
Bulgaria	-23%	190%
Slovakia	-19%	93%
Sweden	-39%	74%
Portugal	-13%	63%
Czech	-13%	59%

Hematology/Oncology and Nephrology

EPO	**Price** decline per Therapeutic Day (2016 year before biosimilar entrance)	**Volume** increase per Therapeutic Day (2016 year before biosimilar entrance)
Poland	-46%	237%
Greece	-51%	196%
Italy	-10%	39%
Czech	-32%	36%
Bulgari	-16%	36%

Hematology/Oncology

C-GSF	**Price** decline per Therapeutic Day (2016 year before biosimilar entrance)	**Volume** increase per Therapeutic Day (2016 year before biosimilar entrance)
Romania	-62%	2542%
Bulgaria	-47%	581%
Slovakia	-61%	509%
Slovenia	-57%	178%
Norway	-31%	164%

Endocrinology

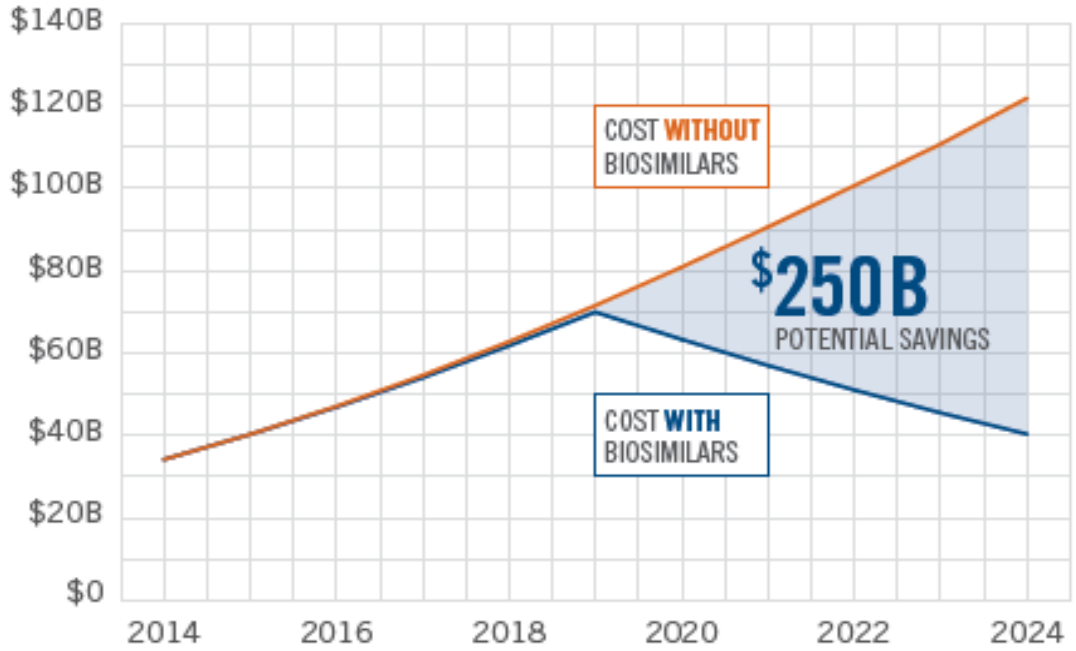
HGH	**Price** decline per Therapeutic Day (2016 year before biosimilar entrance)	**Volume** increase per Therapeutic Day (2016 year before biosimilar entrance)
Romania	-31%	152%
Poland	-42%	82%
United Kingdom	-16%	79%
Finland	-52%	70%
Czech	-25%	68%

TNF, Tumor Necrosis Factor; CSF, Colony Stimulating Factor; EPO, Erythropoietin; HGH, Human Growth Hormone

The Impact of Biosimilar Competition in Europe: https://www.medicinesforeurope.com/wp-content/uploads/2017/05/IMS-Biosimilar-2017_V9.pdf. Accessed 8.27.18

SANDOZ A Novartis Division

$250 billion could be saved in the next decade if these 11 biosimilars are launched in the US



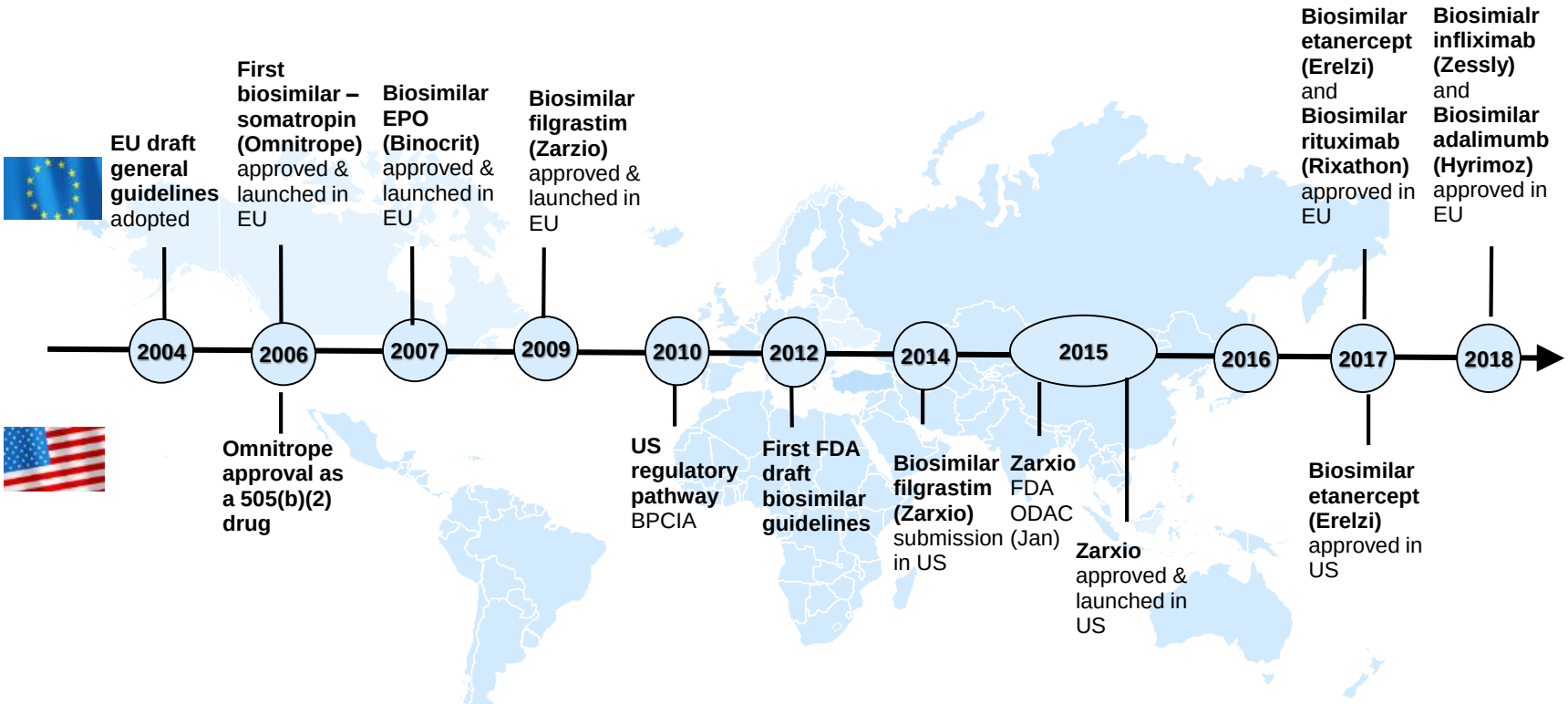
Avastin® *(bevacizumab)*
Epogen® *(epoetin alfa)*
Herceptin® *(trastuzumab)*
Humira® *(adalimumab)*
Intron A® *(interferon alfa-2a)*
Neulasta® *(pegfilgrastim)*
Neupogen® *(filgrastim)*
Pegintron® *(peginterferon alfa-2b)*
Procrit® *(epoetin alfa)*
Remicade® *(infliximab)*
Rituxan® *(rituximab)*

Avastin® is a registered trademark of Genentech Inc.
Epogen® is a registered trademark of Amgen Inc.
Herceptin® is a registered trademark of Genentech Inc.
Humira® is a registered trademark of Abbott Biotechnology LTD
Intron A® is a registered trademark of Merck Sharpe & Dohme
Neulasta® is a registered trademark of Amgen Inc.
Neupogen® is a registered trademark of Amgen Inc.
Pegintron® is a registered trademark of Schering Corporation
Procrit® is a registered trademark of Johnson & Johnson
Remicade® is a registered trademark of Janssen Biotech Inc.
Rituxan® is a registered trademark of Biogen IDEC Inc.

The $250 Billion Potential of Biosimilars: http://lab.express-scripts.com/lab/insights/industry-updates/the-$250-billion-potential-of-biosimilars. Accessed 8.27.18

SANDOZ A Novartis Division

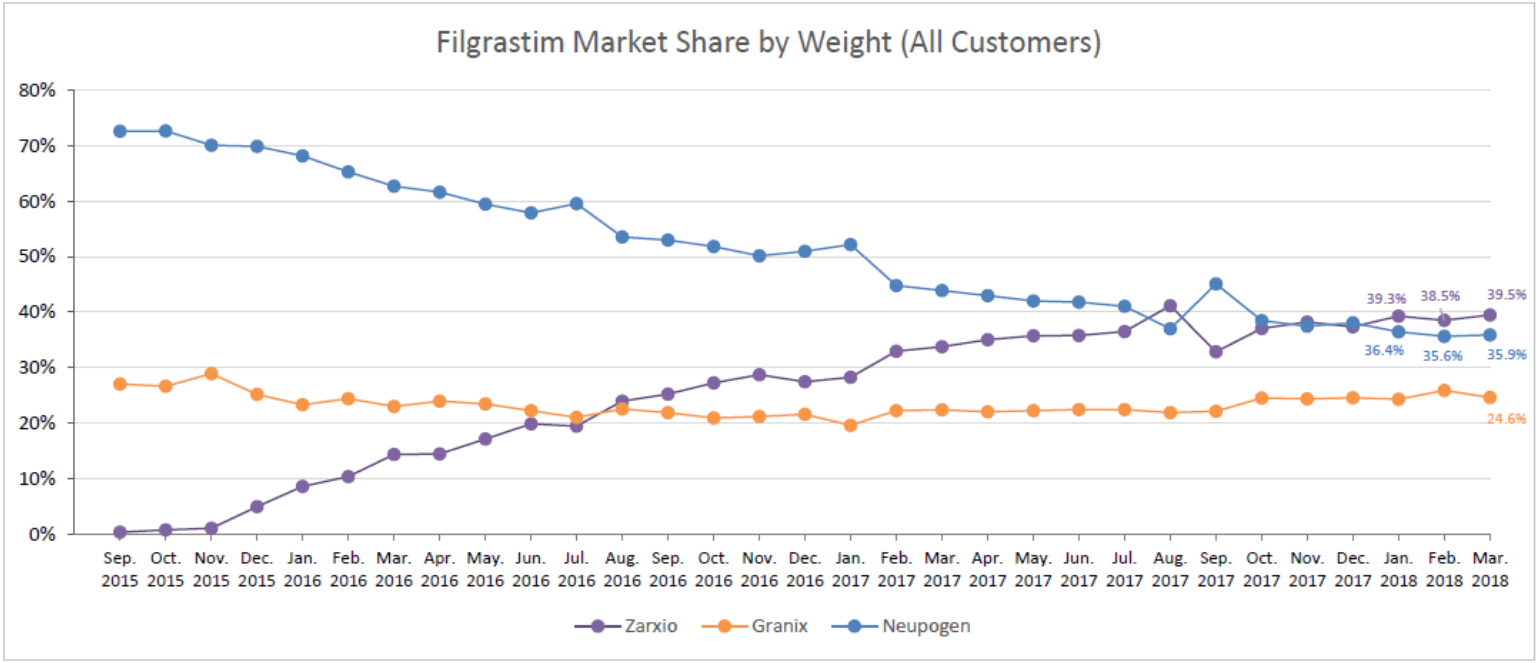
Key regulatory timelines for Sandoz biosimilars (US & EU)



BPCIA = Biologics Price Competition and Innovation Act; CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; ODAC = Oncology Drugs Advisory Committee

CHMP Guideline on similar biological medicinal products, CHMP/437/04, London, 30 October 2005 Accessed May 29. 2018
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000917/human_med_001170.jsp&mid=WC0b01ac058001d124; accessed May 29. 2018
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm; accessed May 29. 2018
http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm291186.htm; accessed May 29. 2018
https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/ucm428779.htm; accessed May 29. 2018
https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm436648.htm; accessed May 29. 2018

Zarxio has surpassed its' reference product to become the #1 short-acting filgrastim in the US



Source: IMS NSP data through March 2018, internal chargeback data and internal analysis

Zarxio® is a registered trademark of Sandoz Inc.
Granix® is a registered trademark of Teva Pharmaceuticals USA, Inc.
Neupogen® is a registered trademark of Amgen Inc.

SANDOZ A Novartis Division

Current status since first marketing authorization of Zarxio

- Global
  - First marketing authorization: EU in Feb 2009[1]
  - Approved in 86 countries [2]
  - Estimated overall patient exposure
    - Over 24.2 million patient-days [2,3]

- US
  - Approval: March 2015
  - Launch: September 2015
  - Estimated overall patient exposure
    - Over 2,100,000 patient-days (US and Canada) [2,3]

1 Authorized as Zarzio (filgrastim)
2. Sandoz global periodic safety update report (PSUR) v12
3. The calculation is based on the sales volumes of filgrastim in million units (MIU) and the defined daily dose (DDD) provided by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo: Patient exposure (patient-days) =Quantity of filgrastim sold (MIU)/Defined Daily Dose (MIU/day)

SANDOZ A Novartis Division

Major global challenges for biosimilar development

- Global comparator
- Manufacturing variability of the reference product during its lifecycle
- Nonproprietary name
- Labeling
- Switching / interchangeability

SANDOZ A Novartis Division

Global comparator

- Currently, reference product must be approved in the jurisdiction for which approval is sought
  - Clinical bridging studies of reference products typically required:

    Even if reference products sourced from different countries are from same originator facility & analytical comparisons do not detect differences
  - Adds time, complexity, cost to develop a biosimilar

- Global comparator concept applicable to both establishing biosimilarity and interchangeability
  - Draft interchangeability specifies US reference product only

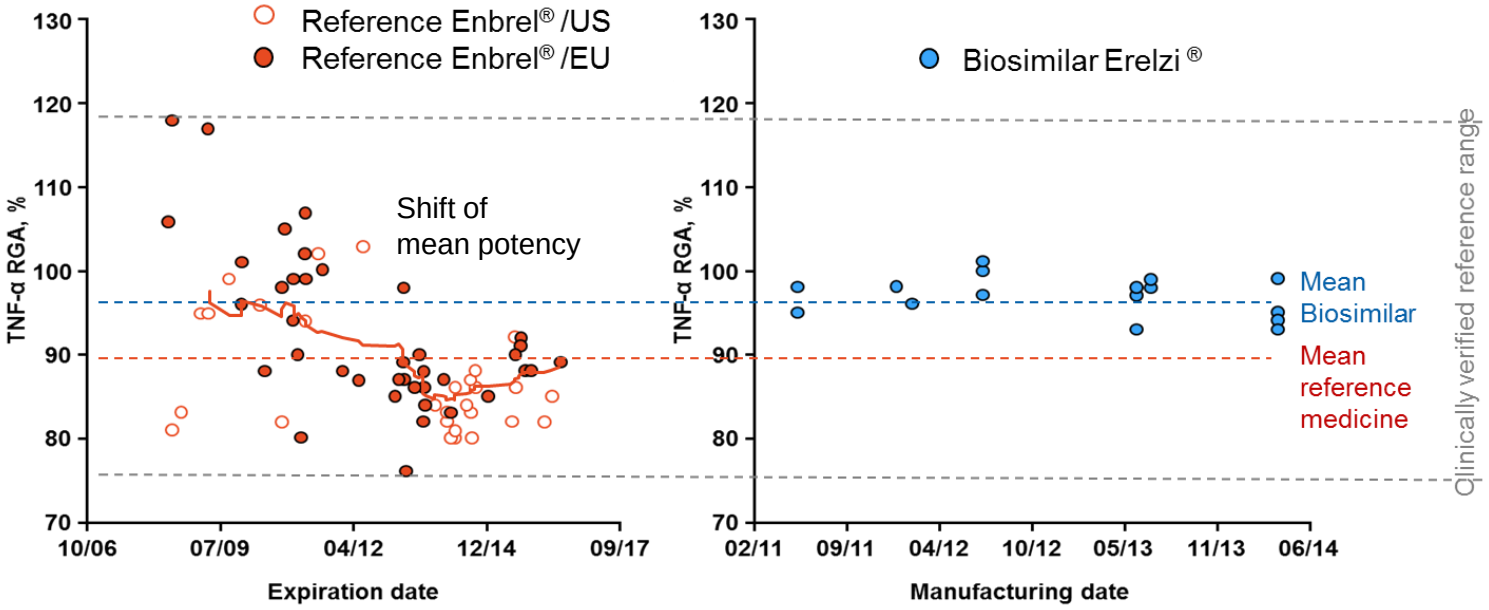
- Concept proposed, but not yet accepted
- Details ...

SANDOZ A Novartis Division

Originator manufacturing variability sets the basis for biosimilarity “Goal Posts”...

...lifecycle of originator products can introduce changes which make these “moving targets”

The mean can change over time – Etanercept reference medicine



The red line indicates the moving mean as calculated by 11 to 21 data points

Lamanna et al., Scientific Reports, 7: 3951, 2017, https://www.nature.com/articles/s41598-017-04320-5 , accessed June 2018

Enbrel® is a registered trademark of Amgen Inc.
Erelzi® is a registered trademark of Sandoz Inc.

SANDOZ A Novartis Division

Differences in global naming

- US: random 4-letter nonproprietary name suffix (only implemented for newly registered products to date)[1]
  - Reference products do not yet have suffixes
  - Will interchangeable products carry a unique suffix or share the same suffix as the reference product?
- Japan (PMDA) add the suffix “BS” (=biosimilar) and digit to INN[2]
- EU: INN only, although all biologics must be prescribed by use of tradename
- Other jurisdictions use INN
  - Health Canada: potentially looking into addition of suffix[3]
  - WHO and the Therapeutic Goods Administration (Australia): expressed their disinterest in using suffixes[4-5]

[1]https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf
[2]https://www.pmda.go.jp/english/review-services/regulatory-info/0003.html
[3]https://safebiologics.org/2018/02/asbm-submits-comments-to-health-canada-on-naming/
[4]https://www.centerforbiosimilars.com/news/who-will-not-proceed-with-biological-qualifiers-for-biosimilars
[5]https://www.centerforbiosimilars.com/news/australian-government-announces-decision-on-biosimilar-naming-conventions

SANDOZ A Novartis Division

Country-specific differences in global labelling of biosimilars

Label based on reference product:

- FDA and EMA don't include biosimilar study results in clinical portion of the label[1,2]

Label that contains data from reference product & biosimilar:

- Health Canada (Canada)[3], TGA (Australia)[4], MedSafe (New Zealand)[5] and ANVISA (Brazil)[6], are some of the countries using a "hybrid" label that includes comparative clinical biosimilarity data

[1]https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf
[2] http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf
[3]https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/product-monograph/product-monograph-template-schedule-biosimilar-biologic-drug.html
[4]https://www.tga.gov.au/publication/biosimilar-medicines-regulation
[5]http://www.medsafe.govt.nz/profs/RIss/Biosimilars.asp
[6]http://portal.anvisa.gov.br/resultado-de-busca?p_p_id=101&p_p_lifecycle=0&p_p_state=maximized&p_p_mode=view&p_p_col_id=column-1&p_p_col_count=1&_101_struts_action=%2Fasset_publisher%2Fview_content&_101_assetEntryId=2868421&_101_type=document

SANDOZ A Novartis Division

Switching: Extensive literature on reference biologic to biosimilar switching reveals no efficacy or safety concerns

- >90 studies with varying designs, endpoints, and products[1-4]
  - Randomized clinical trials + real world use
  - Endpoints: efficacy, SAEs, TSAEs, immunogenicity (ADAs and NABs)
  - Less complex biologics: somatropin, filgrastim, epoetin
  - More complex biologics: infliximab, etanercept, adalimumab, rituximab
- Evaluated in 14 disease states and healthy volunteers[1-4]
- >14,000 patients enrolled in combined studies[1-4]
  - No decline in efficacy
  - No increase in treatment-related events
  - No differences in anti-drug antibodies
  - No neutralizing antibodies detected after switching

ADA=anti-drug antibodies, NAB=neutralizing antibodies, SAE=serious adverse events, TSAEs=treatment-related SAEs

1. Ebbers et al. Expert Opinion Biol Therapy 2012;12:1473-1485
2. Chingcuanco et al. Ann Int Med 2016;165:565-574
3. Moots et al. Curr Rheumatol Rep 2017; 19:37-53
4. Cohen HP et al. Drugs (2018) 78:463-473

SANDOZ A Novartis Division

European regulators‘ perspective on switching

- European regulators have been reviewing, approving and monitoring biosimilars for more 12 years
- Conclusions of a recent publication by European regulators: [1]

  - *“Our conclusion is that a switch between comparable versions of the same active substance **approved in accordance with EU legislation** is not expected to trigger or enhance immunogenicity.“*
  - *“In our opinion, biosimilars licensed in the EU are interchangeable if the patient is clinically monitored, will receive the necessary information, and, if needed, training on the administration of the new products.“*

[1)] **Interchangeability of Biosimilars: A European Perspective**, BioDrugs, DOI 10.1007/s40259-017-0210-0; https://www.ncbi.nlm.nih.gov/pubmed/28120313

SANDOZ A Novartis Division

Interchangeability

In the US:

- Unique to the US as a regulatory concept
- Requires the conduct of a “switching” study
- Interchangeability is an additional data requirement to address the practice of switching back and forth multiple times
- From a quality perspective, interchangeable products are not different from biosimilars

In the EU:

- “Interchangeability” means that a biosimilar can be exchanged for its reference product by a physician

Efforts are being undertaken by some to introduce the US regulatory concept of interchangeability into ROW countries

Data on File: Novartis Position on innovative Biologic Medicines and Biosimilars
Considerations in Demonstrating Interchangeability with a Reference Product – FDA Draft Guidance for Industry - Dr. Christl presentation at DIA 2018 Global Annual meeting

SANDOZ A Novartis Division

Thank you

SANDOZ A Novartis Division