Regulatory considerations for biologics and biosimilars

Totality of evidence: Establishing Biosimilarity

Importance of stringent regulation

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- All content is strictly for registered Healthcare Professionals only

Important: Off-label data

- This content is not intended for physicians practicing medicine in the USA
- The information contained herein may refer to the use of the product for indications other than those approved and/or listed in the Prescribing Information or relating to molecules currently undergoing experimental trials
- The issues addressed are not meant to suggest that the product be employed for indications other than those authorised

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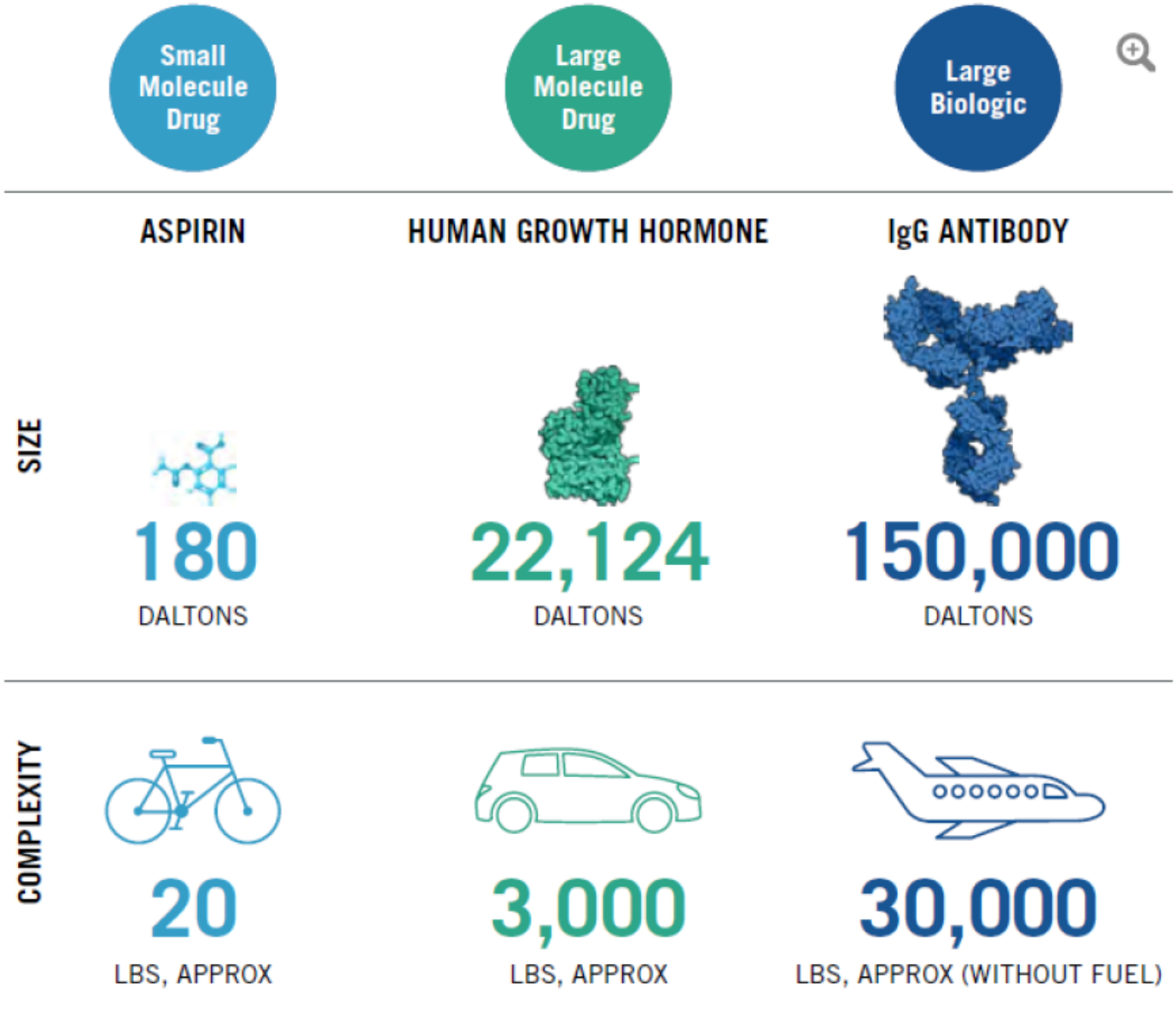
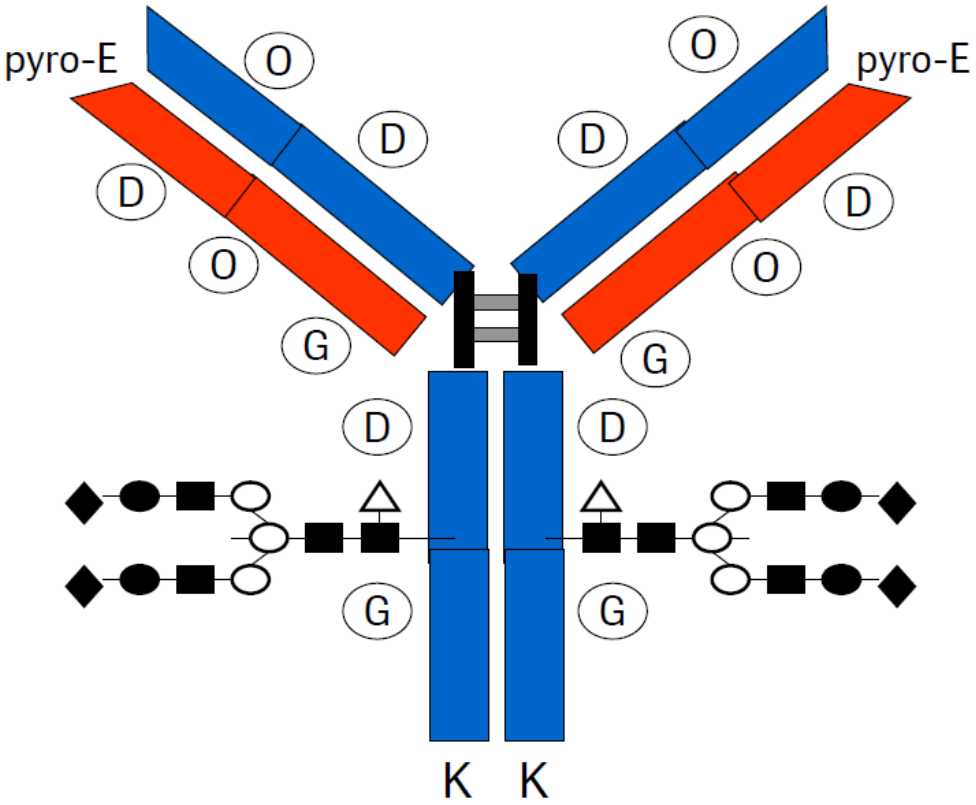
Biologics are very different as compared to synthetic pharmaceuticals



Biological products are highly complex

Generics approval pathways and practices do not apply



- Pyroglutamyl peptides
- Deamidation
- Methionine oxidation
- Glycation
- High mannose,G0,G1,G1,G2
- Sialylation
- C-terminal Lysine

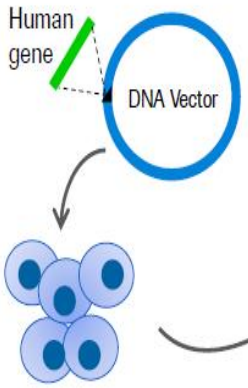
Modifications may result in approximately 10^8 potential variants

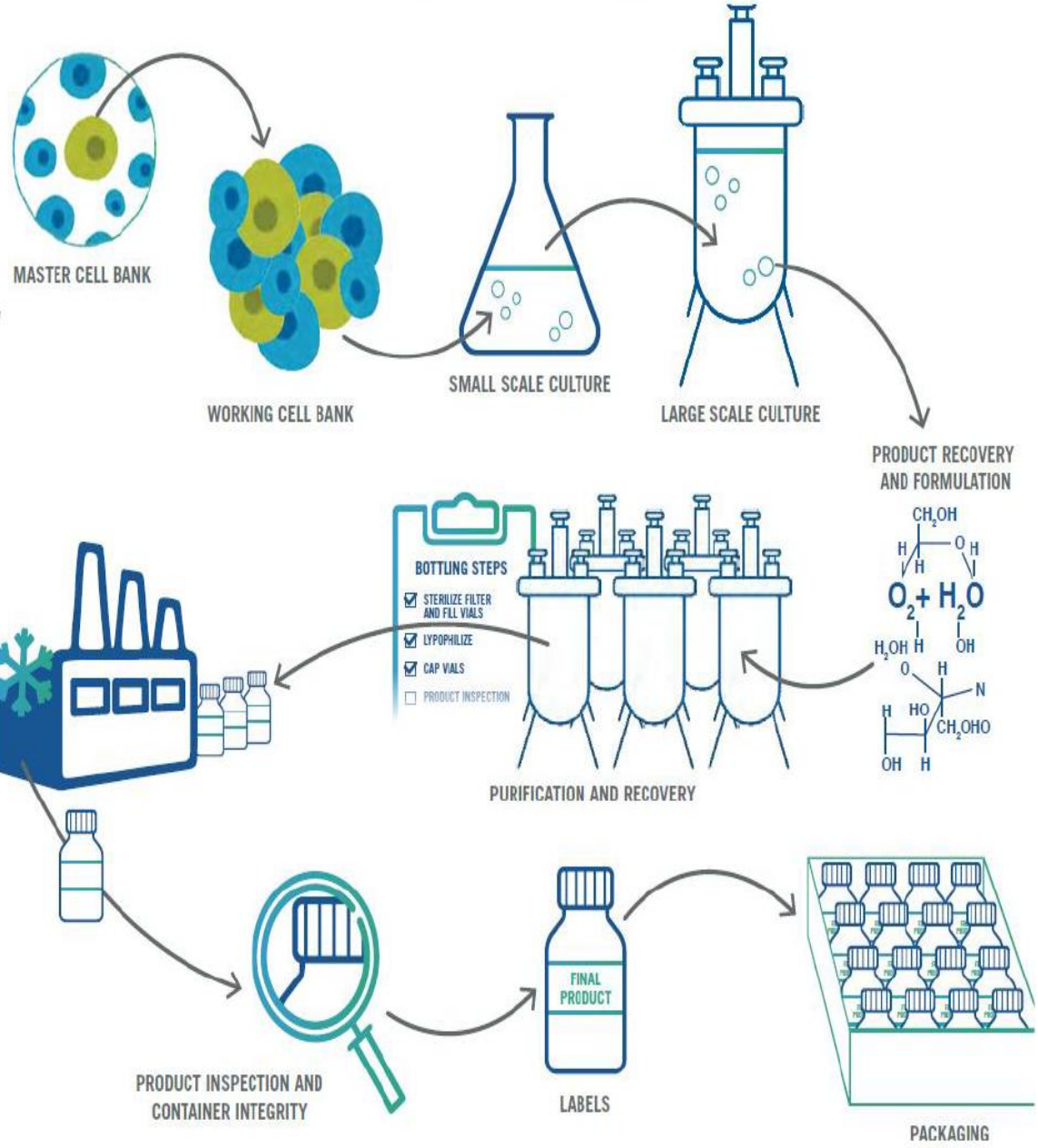
Adapted from: Steven Kozlowski; FDA

Many product attributes are defined by the biologic's complex manufacturing process

CELL LINE DEVELOPMENT

- Cloning of DNA encoding the recombinant mAb
- Introduction of the vector into the host cell
- Selection and cloning of transformants producing the recombinant mAb.





- Each step of the manufacturing process is tailored/optimized
- Small changes in any step may create a structurally different product and potentially affect functional properties
- Biosimilar manufacturers start with a different cell line and must independently develop the manufacturing process

Sekhon and Saluja. Biosimilars. 2011;1(1):1–11.

Biosimilars are Not Generics

Follow-on products of traditional chemical pharmaceuticals are exact chemical copies



Follow-on products of innovator biological pharmaceuticals are only similar ‘copies’



EMA: In support of the European Union's biosimilar framework

"Considering the complexity of biomolecules, the limitations at present in analytical characterization and in clinical trials (like defining sensitive and feasible endpoints to detect differences), it is necessary that the biosimilar concept relies on demonstrating comparability at all three levels (that is, quality, preclinical and clinical to ensure as complete a picture as possible on the features of such complex molecules). A relaxation of these requirements is not justified."

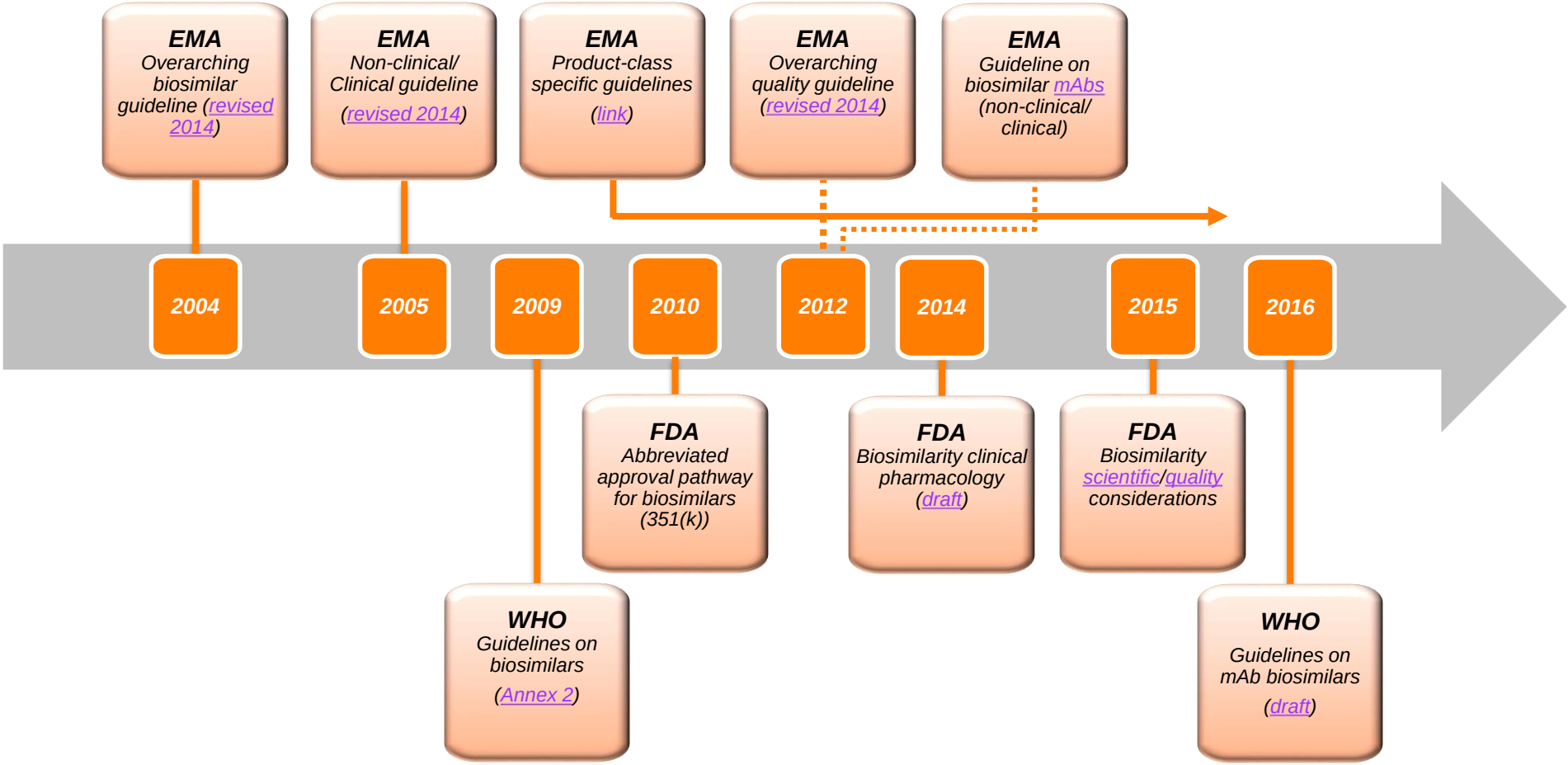
Christian K Schneider1,2, John J Borg3, Falk Ehmann4, Niklas Ekman5, Esa Heinonen5,6, Kowid Ho7, Marcel H Hoefnagel8, Roeland Martijn van der Plas8, Sol Ruiz9, Antonius J van der Stappen8, Robin Thorpe10, Klara Tiitso4, Asterios S Tsiftsoglou11, Camille Vleminckx4, Guenter Waxenecker12, Mats Welin13, Martina Weise14 & Jean-Hugues Trouvin7,15

on behalf of the Working Party on Similar Biological (Biosimilar) Medicinal Products (BMWP) and the Biologicals Working Party (BWP) of the Committee for Medicinal Products for Human Use (CHMP)

NATURE BIOTECHNOLOGY VOLUME 30 NUMBER 8 AUGUST 2012

The complexity of biotherapeutics

The need for specific regulatory frameworks for biosimilars



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EU Biosimilar product overview (Oct 2017)

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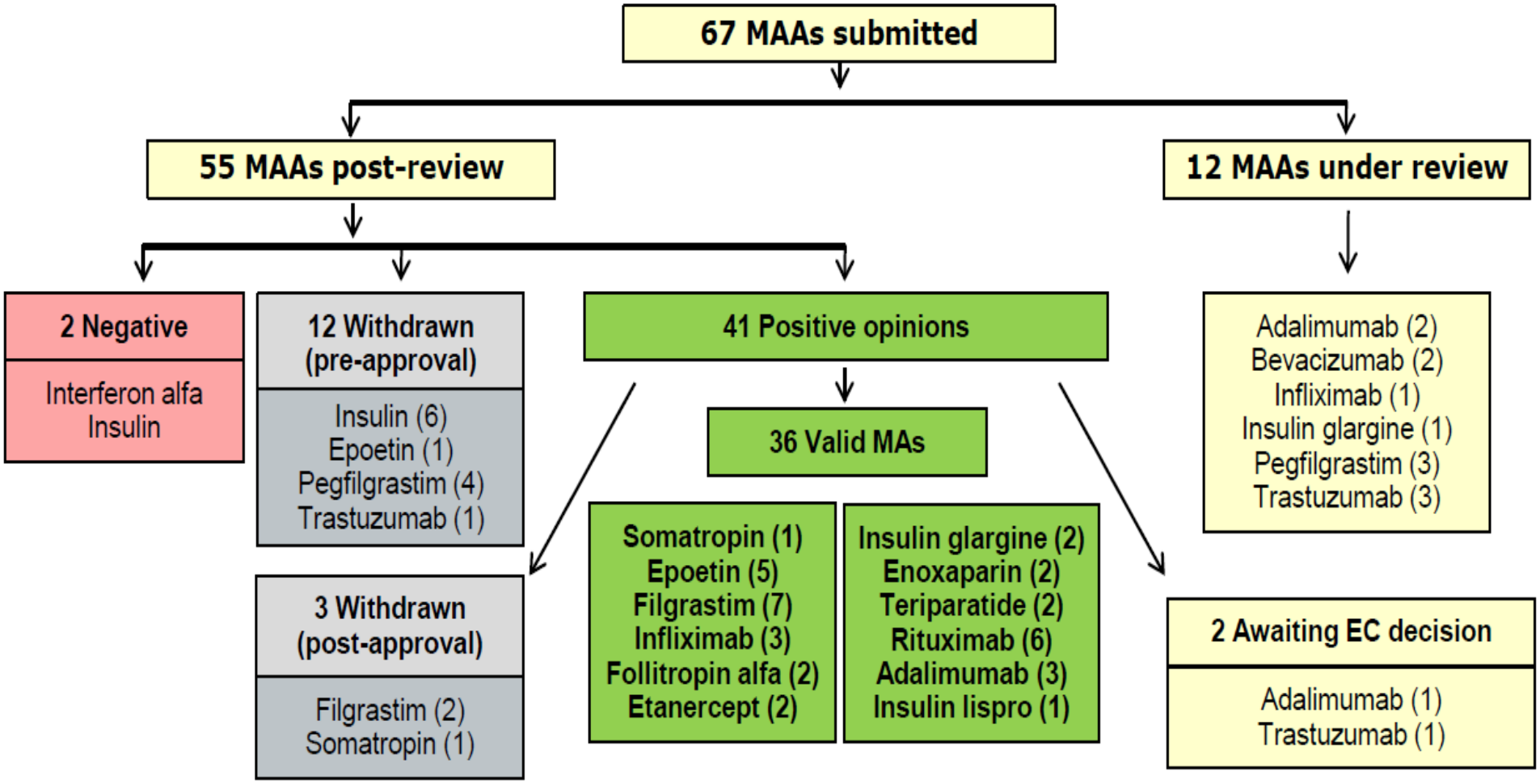
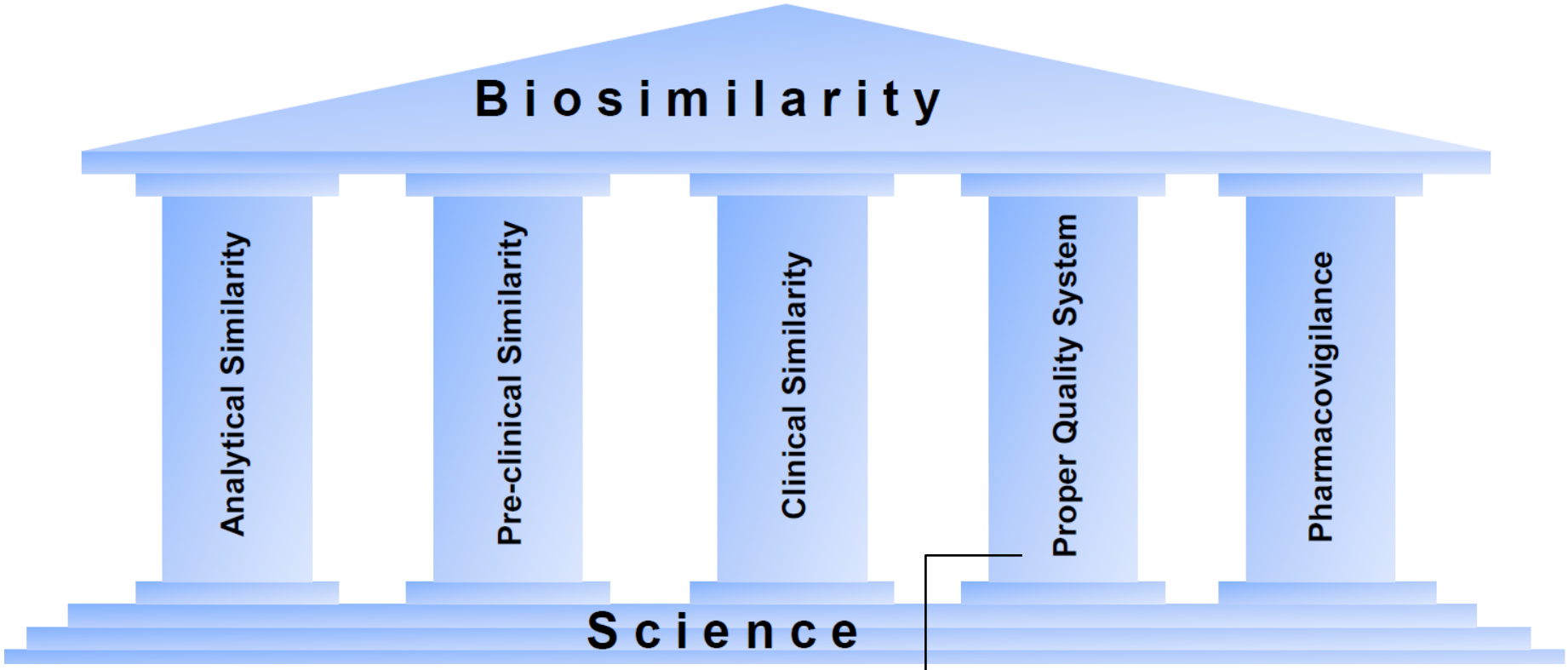


The Basis of Biosimilarity is the «Totality of Evidence» as outlined in all relevant global regulatory guidelines incl. WHO and WHO reference countries



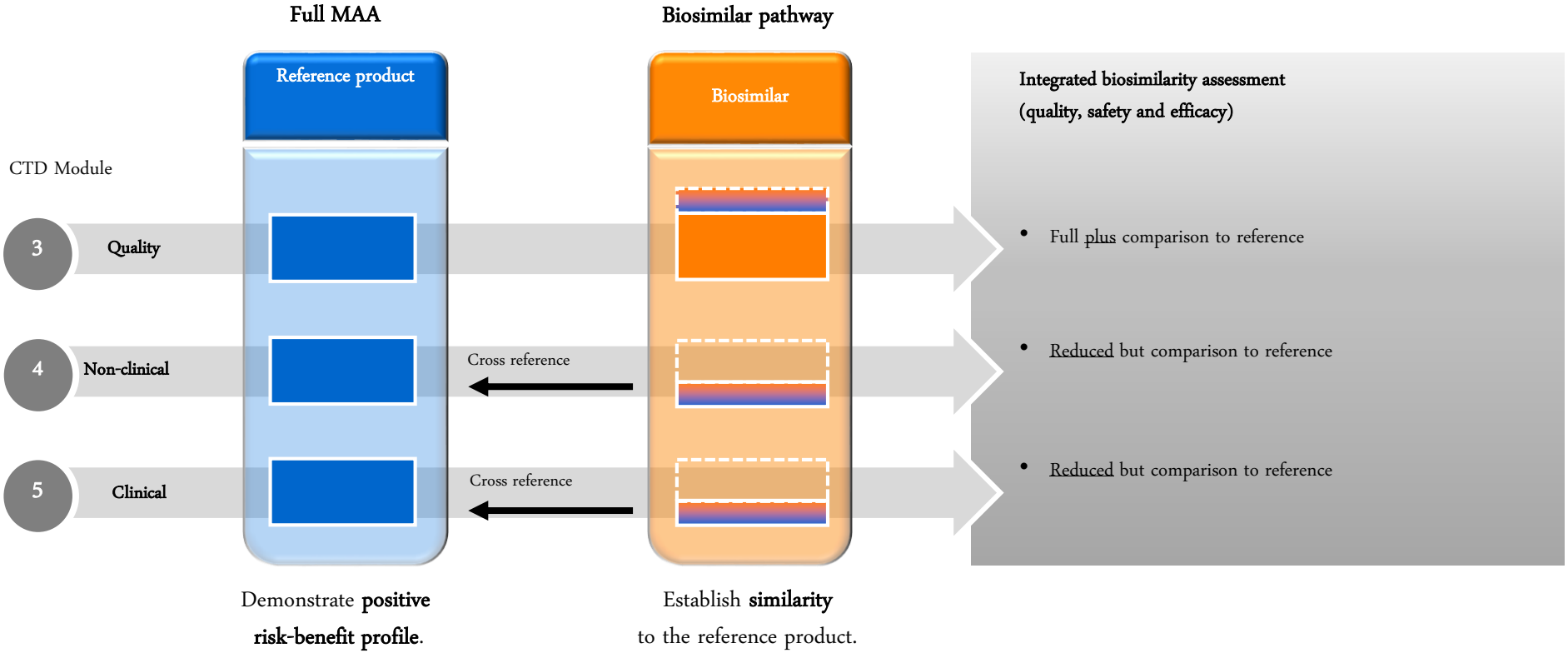
U.S. FOOD & DRUG ADMINISTRATION

"Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B)."

"Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer."

A comprehensive analytical dataset

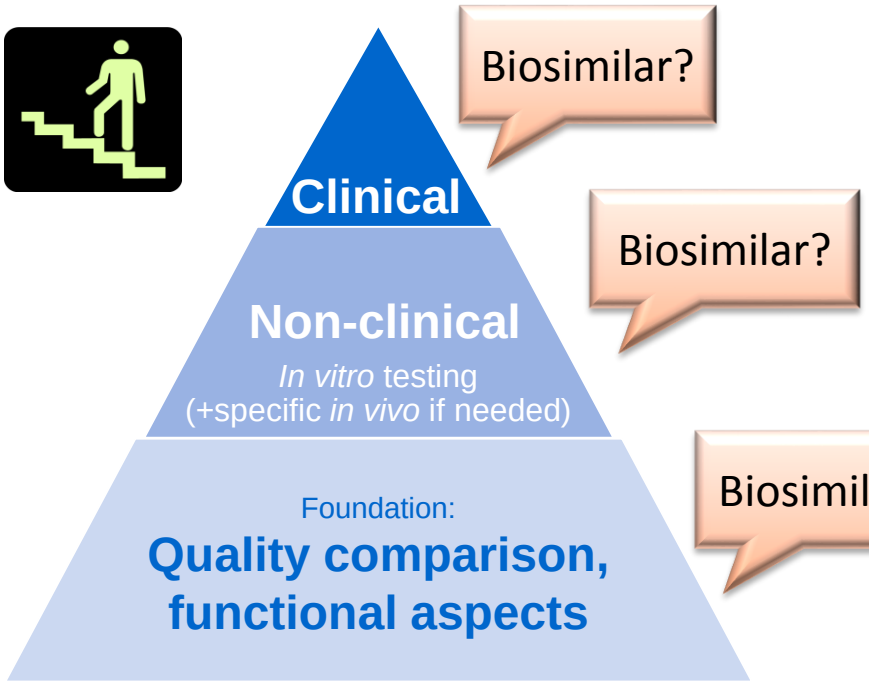
Foundation of the step-wise comparability exercise to establish biosimilarity



Biosimilars follow a different pathway with reduced clinical evidence

Adapted from Peter Richardson, EMA, "How to realise biosimilar's full potential: Regulator's view" DIA EuroMeeting, Vienna, 2014

Development of a biosimilar: A step-wise approach



- Step-wise approach to generate data in support of biosimilarity.
  - *Analytical data (structure and function)*
  - *Non-clinical data*
  - *Clinical data*
- Evaluation of residual uncertainty at each step:
  - *What differences have been observed? Impact?*
  - *What is the residual uncertainty? Studies to address?*
- Clinical development for biosimilars is abbreviated compared to that of innovators and in general consists of:

2. One phase I PK/PD study (n ~ 100)
2. One phase III (n ~ 600 for oncology; ~400 for RA)

Regulatory authorities use the "totality of evidence" to evaluate a product's biosimilarity

FDA. Guidance. Scientific considerations in demonstrating biosimilarity to a reference product. 2015.
EMA. Guideline on similar biological medicinal products. CHMP/437/04 Rev 1.
WHO. Annex 2 – Guidelines on evaluation of similar biotherapeutic products (SBPs). 2009.

Step-wise demonstration of clinical equivalence

(e.g. EMA guideline on monoclonal antibody biosimilars)

PK studies

- Demonstration of PK similarity is usually the initial step of clinical biosimilar mAb development.
- Sensitive, homogenous population required

PD parameters

- PK studies can be combined with PD endpoints, where available.
- In some cases, comparative PD studies can be suitable to provide the pivotal evidence for similar efficacy.

Efficacy studies

- Normally, similar clinical efficacy is demonstrated in adequately powered, randomized, comparative equivalence trial(s).
- Sensitive population and endpoints required.

Purpose: To demonstrate similar clinical efficacy and safety compared to the reference product (not patient benefit *per se*, which has already been shown for the reference product).

Safety parameters

Assessed in all studies; comparable immunogenicity is key for biosimilarity.

EMA. Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (EMA/CHMP/BMWP/403543/2010). 2012.

Considerations for the assessment of clinical data for establishment of biosimilarity

Equivalence

Goal is to demonstrate equivalence to reference product:

→ PK/PD equivalence (AUC ratio equivalence margins: 80–125%)

→ Comparable safety, efficacy and immunogenicity

Sensitivity

Clinical studies should be performed in a sensitive setting (most sensitive study populations and endpoints) to be able to detect product-related difference.

Extrapolation

Clinical trials may not be needed in all indications if extrapolation is scientifically justified:

→ Study was done in most sensitive population

→ Same mode of action in extrapolated indication

Concept of Sensitivity

- **Sensitive populations** are in general homogeneous populations
  Examples:
  - Populations **homogeneous with respect to prognostic baseline characteristic**
  - Presence of many **co-morbities can influence sensitivity** of safety comparison
  - Presence of **chemotherapy may reduce sensitivity** to detect immunogenicity difference
- **Sensitive endpoints** are endpoints that can differentiate with a high likelihood effective from less effective treatments
  - Sensitive endpoints in general provide a **large Δ (i.e. treatment effect difference)** e.g. Δ response rate difference of 20%
  - Sensitive endpoints in general are **(strongly) correlated with clinical outcome** e.g. pCR with event-free survival and overall survival in HER2+ early breast cancer

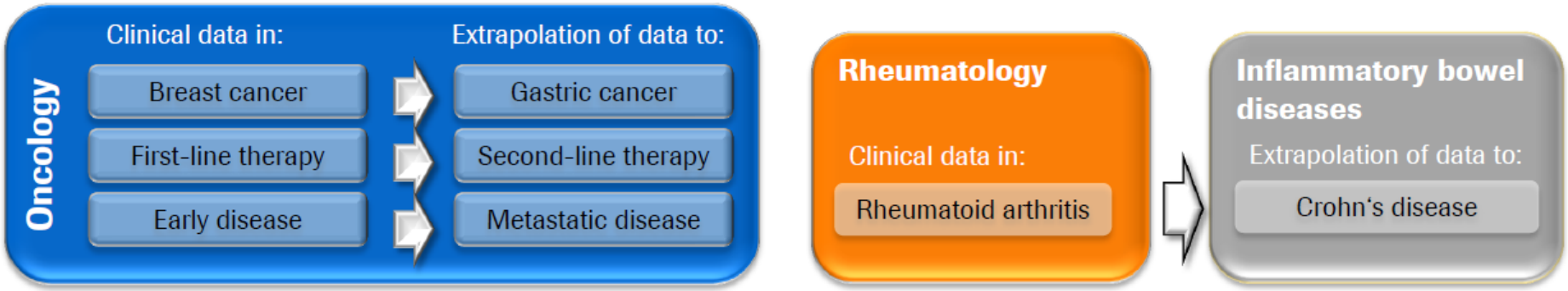
Extrapolation = Building a Bridge

What is extrapolation?

Definition of extrapolation:

- The decision whether to extend the efficacy and safety data from an indication (a medical condition, disorder or disease) for which the biosimilar has been clinically tested to other conditions for which the branded product is approved, is known as “extrapolation”.

Examples of extrapolation (within the same therapeutic area or to a different one):



European Commission. What you need to know about biosimilar medicinal products. December 2014 (accessed 15 Aug 2016).

Comparison of regulatory guidelines for extrapolation of indications

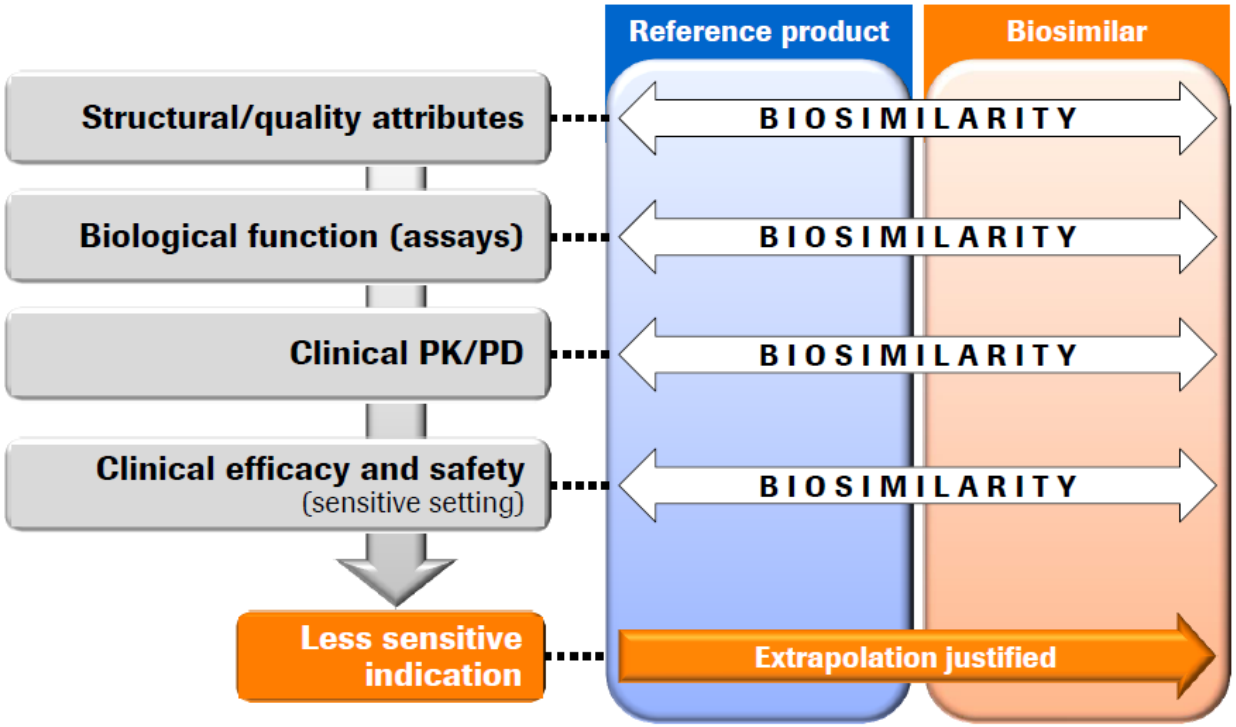
EMA and FDA

	EMA	FDA
General	• Extrapolation is possible based on the overall evidence of comparability provided from the comparability exercise and with adequate justification • The studied indication should be sensitive for differences in all relevant aspects of safety/efficacy	• Extrapolation should be based on sufficient scientific justification • Efficacy and safety should be tested in most sensitive indication to detect clinically meaningful differences in safety (including immunogenicity) and efficacy
Aspects of scientific justification	• Additional data are required e.g., if the biologic interacts with several receptors that may have a different impact in different indications. or if the biologic has more than one active site. • Extrapolation of immunogenicity from the studied indication/route of administration to other uses of the reference product should be justified.	Scientific justification should address (in each condition/for different populations) e.g.: • Mechanism(s) of action, including target/receptor(s), binding, dose/concentration response, molecular pathways, site(s) of action • The PK and biodistribution • Immunogenicity; differences in expected toxicities in each condition and patient population

Whether extrapolation to other indications is acceptable (or not) is decided on a case-by-case basis

EMA. Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues (EMEA/CHMP/BMWP/42832/2005 Rev1). 2014.
EMA. Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies (EMA/CHMP/BMWP/403543/2010). 2012.
FDA. Guidance on Scientific Considerations for Demonstrating Biosimilarity to a Reference Product. 2015.

Extrapolation is based on totality of evidence, not only on clinical data



E.g. infliximab biosimilar:

- Clinical studies performed in
  - Rheumatoid arthritis
  - Ankylosing spondylitis
- Extrapolated to
  - Psoriatic arthritis
  - Crohn's disease
  - Ulcerative colitis
  - Plaque psoriasis

The initial (2015/16) indication approval matrix of Remsima® did indicate that there is no global view on “highly similar”

	Rheumatology										Inflammatory Bowel Disease (IBD)							
	RA		AS		Ps		PsA		BD		aUC		aCD		pCD		pUC	
	O	B	O	B	O	B	O	B	O	B	O	B	O	B	O	B	O	B
South Korea	√	√	√	√	√	√	√	√	x	x	√	√	√	√	√	x	√	x
Europe	√	√	√	√	√	√	√	√	x	x	√	√	√	√	√	√	√	√
Canada	√	√	√	√	√	√	√	√	x	x	√	x	√	x	√	x	√	x
Japan	√	√	√	x	√	x	x	x	√	x	√	√	√	√	x	x	x	x
Turkey	√	√	√	√	√	√	√	√	x	x	√	√	√	√	√	√	√	√
US*	√	√	√	√	√	√	√	√	x	x	√	√	√	√	√	√	√	x
Brazil	√	√	√	√	√	√	√	√	x	x	√	√	√	√	√	√	√	√
Australia	√	√	√	√	√	√	√	√	x	x	√	√	√	√	√	√	√	√

For Japan Remsima has not been approved for Ankylosing Spondylitis (AS), Behcet’s disease (BD) or Psoriasis (Ps) (Remicade is approved in Japan in RA, UC, CD, AS, BD and Ps). This is due to extended patent/Data Exclusivity of the originator in Japan

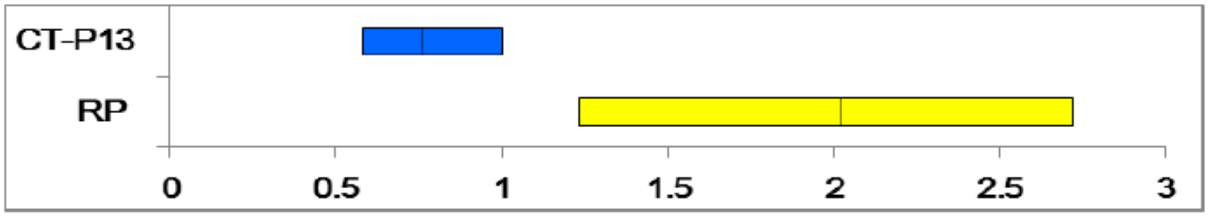
The analysis of the Infliximab Biosimilar Remsima® EPAR and the communication of regulators indicated relevant differences with the reference product

Glycosylation - similar / differences

- Asn300 - only site of N-glycosylation G0F and G1F.
  No O-Glycans, no new glycans
- higher levels of G1FNeuGc and G2FNeuGc
- monosaccharide molar ratios content of neutral and amino sugars.
  NeuGc levels.
- afucosylated glycans levels, Man5 and G0

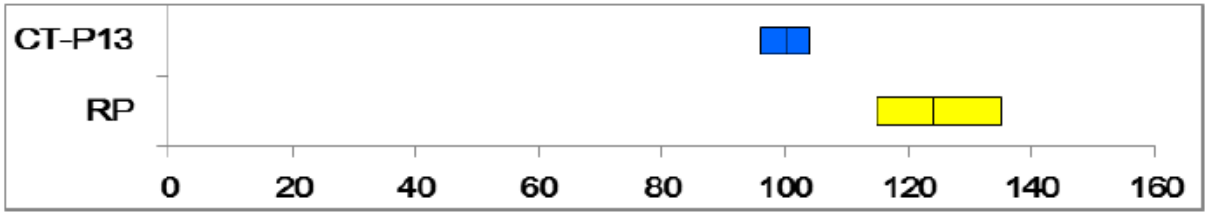
Adopted from Margarida Menezes Ferreira - PDA QbD MAB 9/2014

Of particular importance are differences in afucosylated Glycans of Remsima as compared to the Reference Product

Attributes (Analytical method)	Result
Ratio of G0 (Oligosaccharide, (%))	

Lower G0 translated to lower binding to FcγRIIIa binding

Ratio of FcγRIIIa binding (Relative binding, (%))



Data presented by Celltrion during CASSS CMC Strategy Forum Brazil, 2015

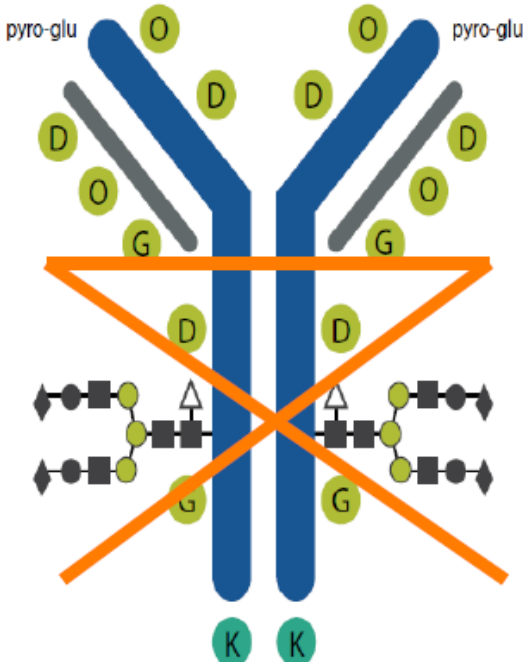
EMA Overall Conclusions and Approval of Remsima® expressed one view on «highly similar»…

On 27 June 2013, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Inflectra, 100 mg powder for concentrate for solution for infusion intended for the **treatment of rheumatoid arthritis, adult Crohn's disease, paediatric Crohn's disease, ulcerative colitis, paediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.**

Summary of opinion EMA/CHMP/364710/2013
Committee for Medicinal Products for Human Use (CHMP)

…while Health Canada's Summary Basis of Decision did express a different view…

- **Celltrion did not receive extrapolation to IBD and Crohn's because:**
  - Observed differences in afucosylation species of Remicade/Inflectra as compared to Remicade
  - The potential impact that this difference has on the FcγRIII receptor and induction of ADCC; ADCC could not be ruled out
    - Cell-based assays were not conclusive/difficult to exclude different ADCC activities as a critical factor
  - Pathophysiological differences exist between Rheumatic disease and the IBDs
  - Cetrolizumab pegol (another anti-TNF), lacks ability to induce ADCC is only marginal efficacy in Crohn's



Switching between the Reference Product and it's Biosimilars will be a Scenario in clinical Practice…

Treatment-naïve patients

Biosimilar is prescribed to treatment-naïve patients.

No clinically meaningful differences are expected, since approved biosimilars have undergone therapeutic equivalence evaluations in treatment-naïve patients.

Treatment-experienced patients

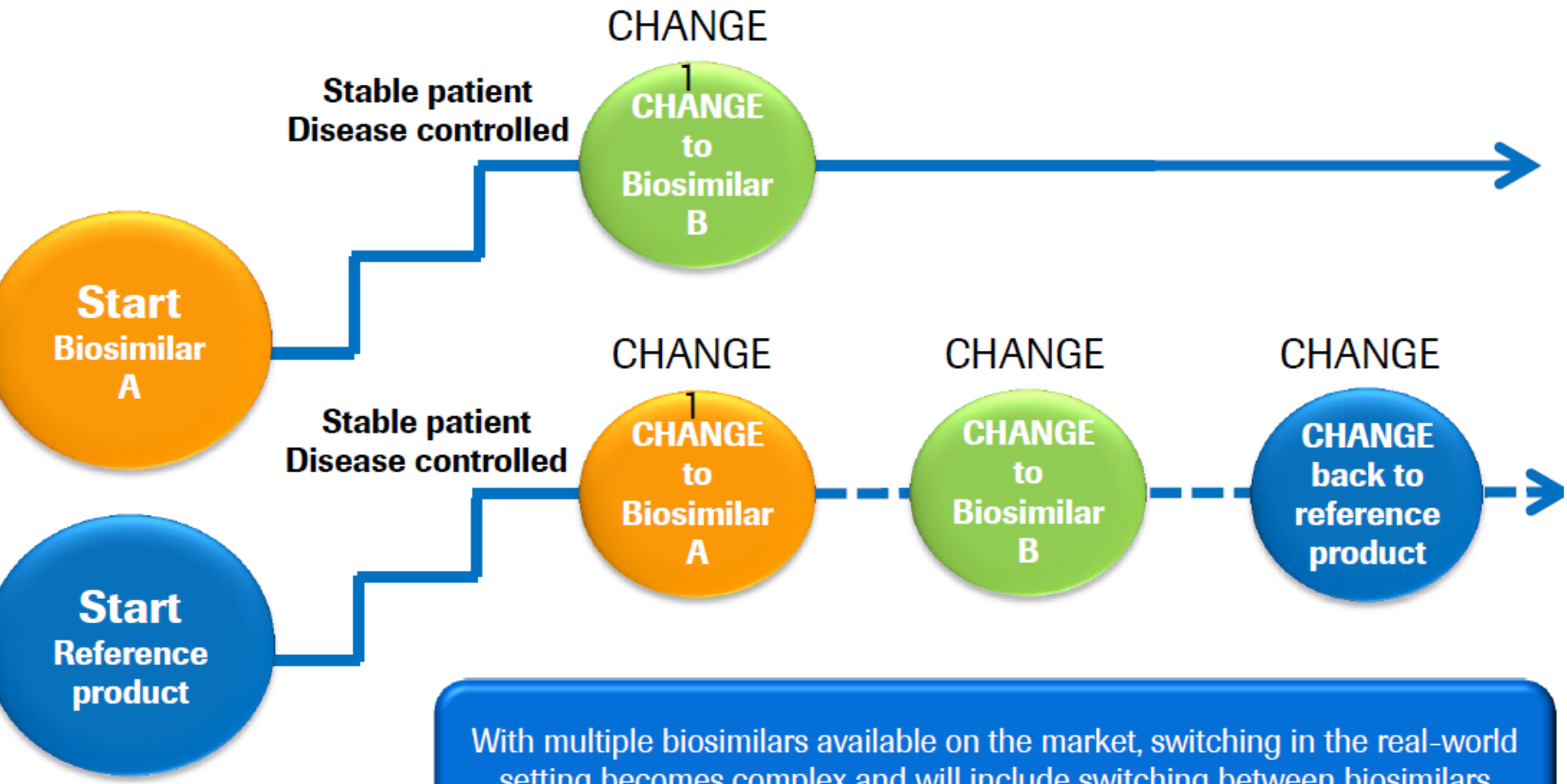
Switching a patient to a biosimilar when he or she is already on a treatment program with the reference product or vice versa

Will require additional clinical evidence going beyond the biosimilarity assessment otherwise the consequences of switching are unknown.

Some countries allow prescription of biosimilars to treatment-naïve patients, but restrict switching of treatment-experienced patients to the biosimilar.

Renwick et al. Lancet Oncol. 2016 Jan;17(1):e31-8. FDA: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, April 2015

…but even but even more complex scenarios might be possible with more and more biosimilars approvals



With multiple biosimilars available on the market, switching in the real-world setting becomes complex and will include switching between biosimilars which may have not been directly compared with each other in clinical studies.

Renwick et al. Lancet Oncol. 2016 Jan;17(1):e31-8. European Commission: What you need to know about biosimilar medicinal products (2014). EBE, EFPIA and IFPMA position paper: "Considerations for physicians on switching decisions regarding biosimilars" 2017,

The FDA's view on Interchangeability/Substitution

U.S. Food and Drug Administration
Protecting and Promoting Public Health

www.fda.gov

Interchangeability

Interchangeable or Interchangeability means that:

- the biological product is biosimilar to the reference product;
- it can be expected to produce the same clinical result as the reference product in any given patient; and
- for a product administered more than once, the safety and reduced efficacy risks of alternating or switching are not greater than with use of the reference product without alternating or switching.

- **Note:** The interchangeable product may be substituted for the reference product without the authorization of the health care prescriber.

Health Canada's view on Interchangeability/Substitution

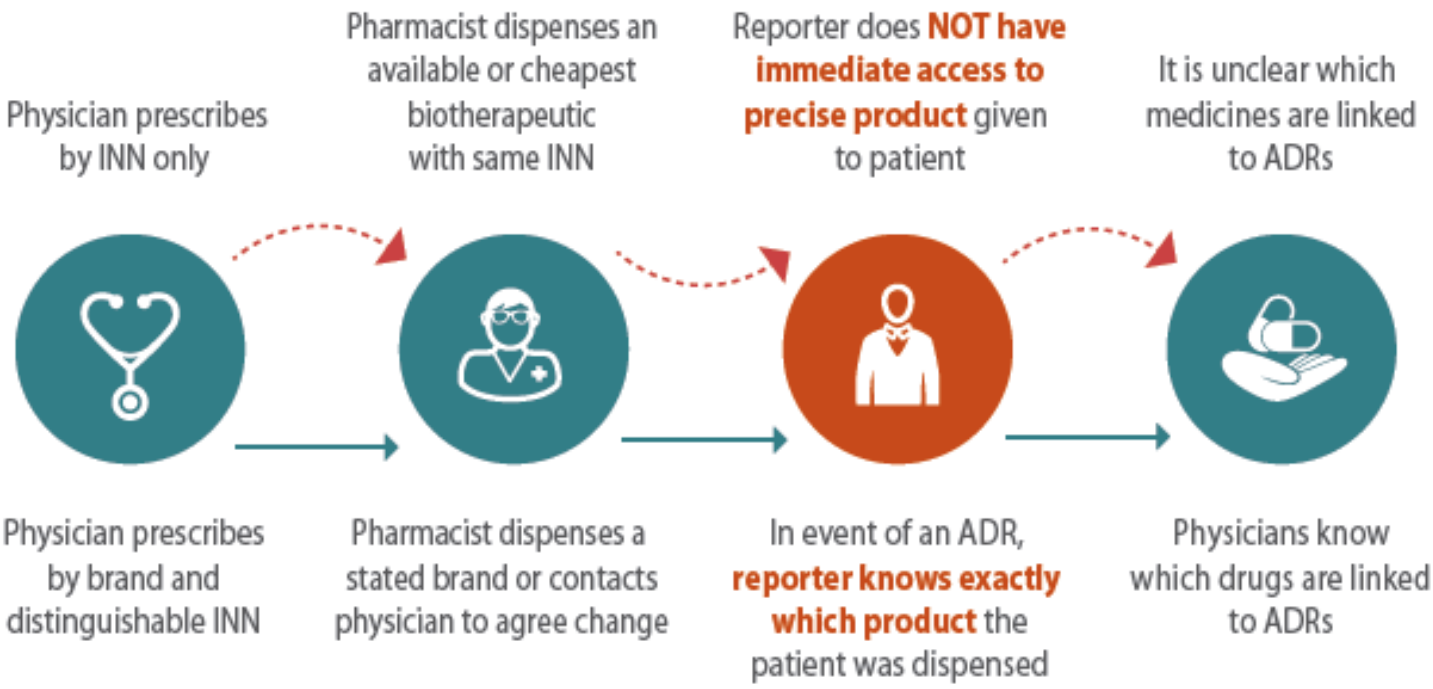
- SEBs (Second Entry Biologics) are not "generic" biologics. Authorisation of an **SEB is not a declaration of pharmaceutical or therapeutic equivalence to the reference drug.**
- **Specialized clinical studies can be used to support therapeutic interchangeablility**, however these studies are not usually done and their relevance may be not long-lasting. Over time, as sponsors of the SEB and the reference biologic make their own independent **manufacturing changes, differences could be introduced that affect the drug products. For this reason Health Canada does not support automatic substitution of a SEB for its reference biologic** drug and recommends that the physicians make only well informed decisions regarding therapeutic interchange

Biosimilar Traceability

Key to enable pharmacovigilance assessments

IN A MULTISOURCE ENVIRONMENT, DISTINGUISHABLE NAMES ENSURE TRACEABILITY

If ADR occurs, INN only



If ADR occurs, Brand and INN

Prescribing by brand name and distinguishable International Nonproprietary Name (INN) allows physicians rapid access to the precise product dispensed when reporting ADRs

Source: Amgen

Traceability: **Unique product identification** is key

IFPMA – Pharmacy-mediated Interchangeability Position

The paper defines **five key principles** under which substitution at the pharmacy level may be acceptable:

- The SBP has received a **formal interchangeability designation by a "competent" authority**
- is **approvable for all indications** of the RBP and approved for all accessible ones
- **"clinically relevant" evidence is available** that switching or alternating between the SBP and RBP would not impact safety or efficacy
- **legal frameworks** have been established to **permitting** the prescribing **physician the 'right-to-refuse'**
- the jurisdiction has established a **robust pharmacovigilance system incl. unique product identification**


IFPMA Policy Position

Pharmacy-mediated Interchangeability for Similar Biotherapeutic Products (SBPs)

The first global position paper on "Interchangeability" industry wide aligned

US FDA's approval as of December 2017

Drug Name	Approval Date
Zarxio (Filgrastim-sndz)	March 2015
Inflectra (Infliximab-dyyb)	April 2016
Erelzi (Etanercept-szzs)	August 2016
Amjevita (Adalimumab-atta)	September 2016
Renflexis (Infliximab-abda)	May 2017
Cyltezo (Adalimumab-adbm)	August 2017
Mvasi (Bevacizumab-awwb)	September 2017
Ogivri (Trastuzumab-dkst)	December 2017
Ixifi (Infliximab-qbtx)	December 2017

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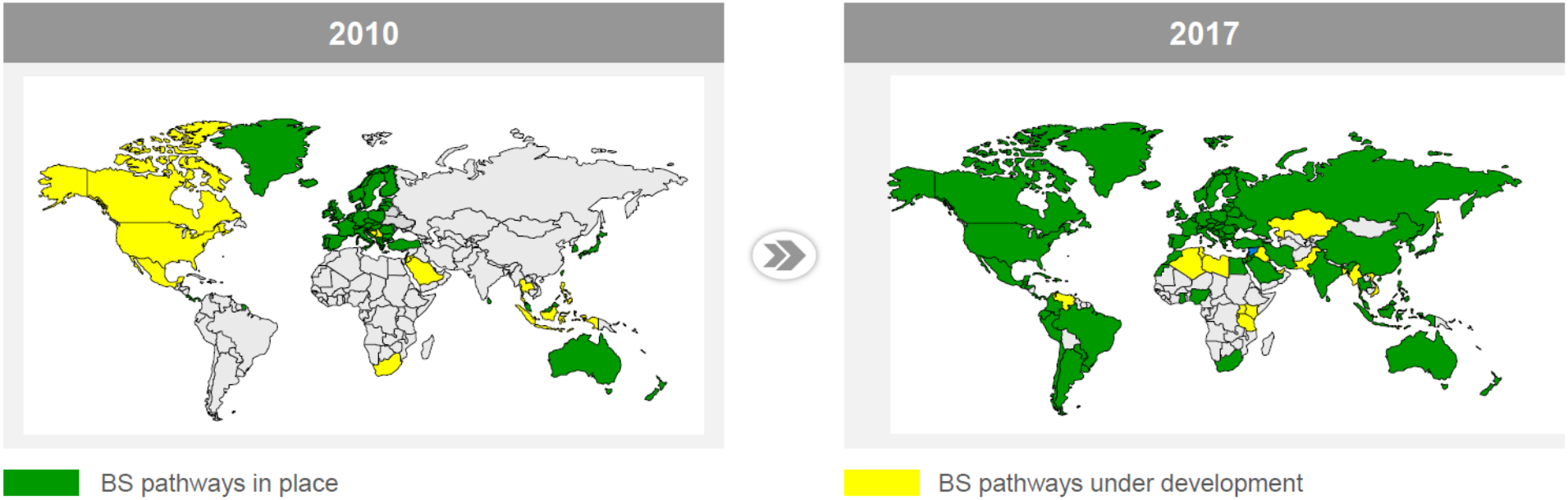
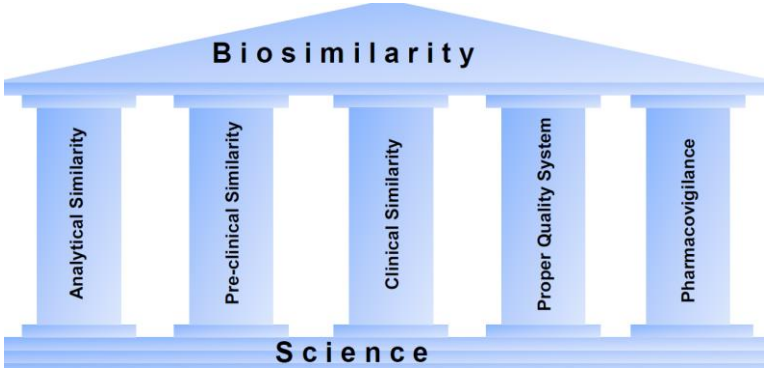
Establishment of Similar Biotherapeutic Product (SBP) Guideline has increased – driven by WHO efforts



Concluding Remarks

- Patients deserve the best available treatment for better outcomes and cure.
- Biosimilars: valid treatment option when approved accordingly to properly implemented standards (5 pillars).
- Uninformed or enforced switching of patients should be avoided through proper procurement strategies and the respective management of formularies
- Automatic substitution: should not be an acceptable practice.
- Interchangeability, remains challenging even when backed by clinical data
- Switching decisions by the treating physician should be based on the patient situation and on the availability of data from robust similarity and switching relevant assessments
- A risk management plan, including immunogenicity testing and post-authorization pharmacovigilance is necessary to ensure proper evaluation of biosimilars.
- HCPs should use uniquely identifiable names when prescribing biotherapeutic medicines. A robust and safe use of biotherapeutics medicines is the responsibility of all in the healthcare community.



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Totality of evidence – Polling questions

Integrated biosimilarity assessment

Question 1

What is the correct order for the generation of data in support of biosimilarity?

a) Non-clinical data → Analytical data → Clinical data

b) Non-clinical data → Clinical data → Analytical data

c) Analytical data → Non-clinical data → Clinical data

Question 1

What is the correct order for the generation of data in support of biosimilarity?

a) Non-clinical data → Analytical data → Clinical data

b) Non-clinical data → Clinical data → Analytical data

c) Analytical data → Non-clinical data → Clinical data

Question 2

When would a biosimilar product require an independent full Market Authorisation Application (MAA)?

a) When there are **no differences** in potency assays between the biosimilar candidate and reference product.

b) When there are **minor differences** in potency between the biosimilar candidate and reference product.

c) When there are **minor differences** in the charge profile between the biosimilar candidate and reference product.

d) When there are **minor differences** in the charge profile **that are not** understood between the biosimilar candidate and reference product.

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Question 3

The goal of the biosimilar clinical development programme is to establish _____ to a reference product.

a) superiority

b) equivalence

c) non-inferiority

Question 3

The goal of the biosimilar clinical development programme is to establish _____ to a reference product.

a) superiority

b) equivalence

c) non-inferiority

Question 4

Extrapolation of a biosimilar to other indications may be possible if:

a) The study was performed in a sensitive population and the mode of action is the same in the extrapolated indication(s).

b) The mode of action is the same in the extrapolated indication(s).

c) The study was performed in a heterogeneous population.

d) The study was performed in a heterogeneous population and the mode of action is the same in the extrapolated indication(s).

Question 4

Extrapolation of a biosimilar to other indications may be possible if:

a) The study was performed in a sensitive population and the mode of action is the same in the extrapolated indication(s).

b) The mode of action is the same in the extrapolated indication(s).

c) The study was performed in a heterogeneous population.

d) The study was performed in a heterogeneous population and the mode of action is the same in the extrapolated indication(s).

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