



PRAHEALTHSCIENCES

THE FUTURE OF CLINICAL DEVELOPMENT



# Challenges in demonstrating biosimilarity and interchangeability of biosimilar products

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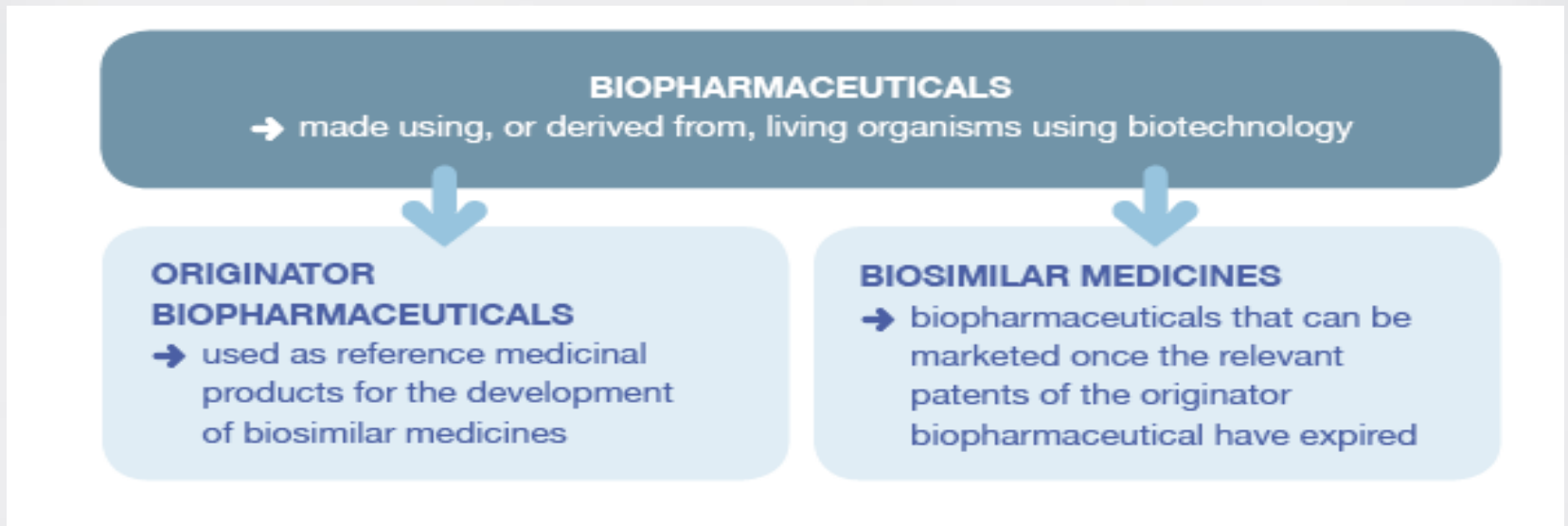


## Topics

- What is a Biosimilar and Why?
- Demonstrating Similarity
  - Quality attributes
  - Non-clinical animal
  - PK/PD Bioequivalence
  - Phase III equivalence; Efficacy and Safety comparability
- Interchangeability
  - Acceptance of interchangeability
  - Demonstrating interchangeability – Is it possible?



# What are Biosimilars?



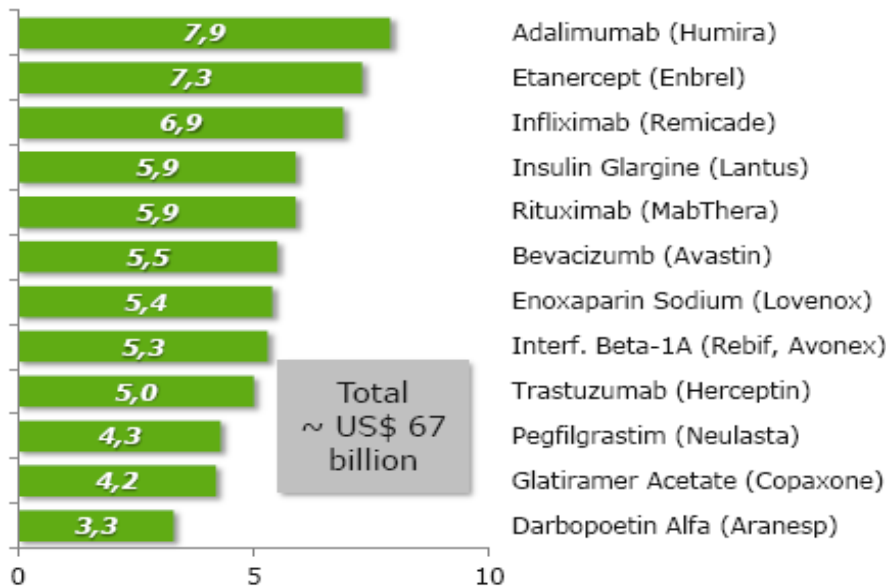


# Patent Cliff

Twelve compounds will present a US\$ 67 billion opportunity

All these products will lose patent protection by 2020, but Enbrel whose US patent has been extended until 2028

Global Sales (MAT 12/2011), US\$, Billion



EU expiry date	US expiry date
2018	2016
2015	2028 (extended)
2014	2018
2014	2014
2013	2016
2010	2017
2012	Expired
2015	2015
2014	2019
2017	2015
2015	2014
2016	2016

Not considered existing biosimilars such as Epoetin Alfa expired in EU, but still patent protected in US

Source: IMS MIDAS, 12/2011, IMS Patent focus

Biosimilars: about to leap? • EGA Symposium, London - 19-20 April, 2012

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## The Potential value of biosimilars

- Biologic therapies are a key driver of increased drug cost
- To maximise health gain from a limited budget, then spend on those interventions that produce the most health gain per pound/dollar
- Cost reductions would be the significant driver to the increased use of targeted biologic cancer drugs in many countries
- Significantly more patients will be treated as biologics costs fall
- EU- savings between 11.8 -33.4 Billion between 2007-2020\*

*\*(Haustein et al GaBI 2012,1(3-4) 120-6)*



## Global Biosimilar Concept

- Generic approach is not appropriate
- Step-wise comparability approach
- *Global* similarity in all aspects:
  - Quality
  - Efficacy
  - Safety
- Case by case approach
- Pharmacovigilance is critical



# Demonstrating Similarity





# Principles of establishing biosimilarity

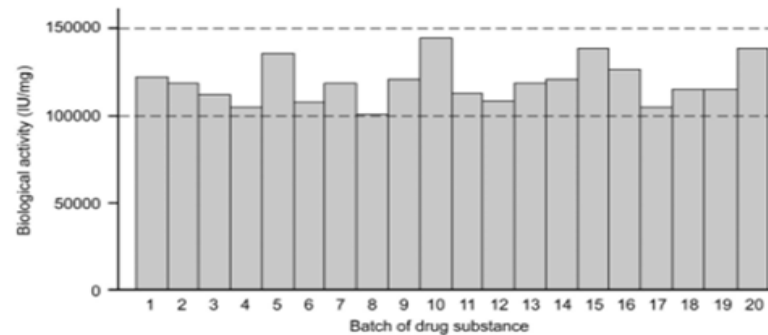
“The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the reference product by the best possible means, ensuring that the previously proven safety and efficacy of the reference medicinal product also applies to the biosimilar.”



# Similarity

## “Similar but not identical”

- „Non-identity“ is a normal principle in biotechnology.
- No batch of any biological is „identical“ to the others



- The „art“ is to demonstrate that the biosimilar is as close as possible to its reference product in all relevant functional and structural aspects, within current technical and scientific limitations (inherent variability)

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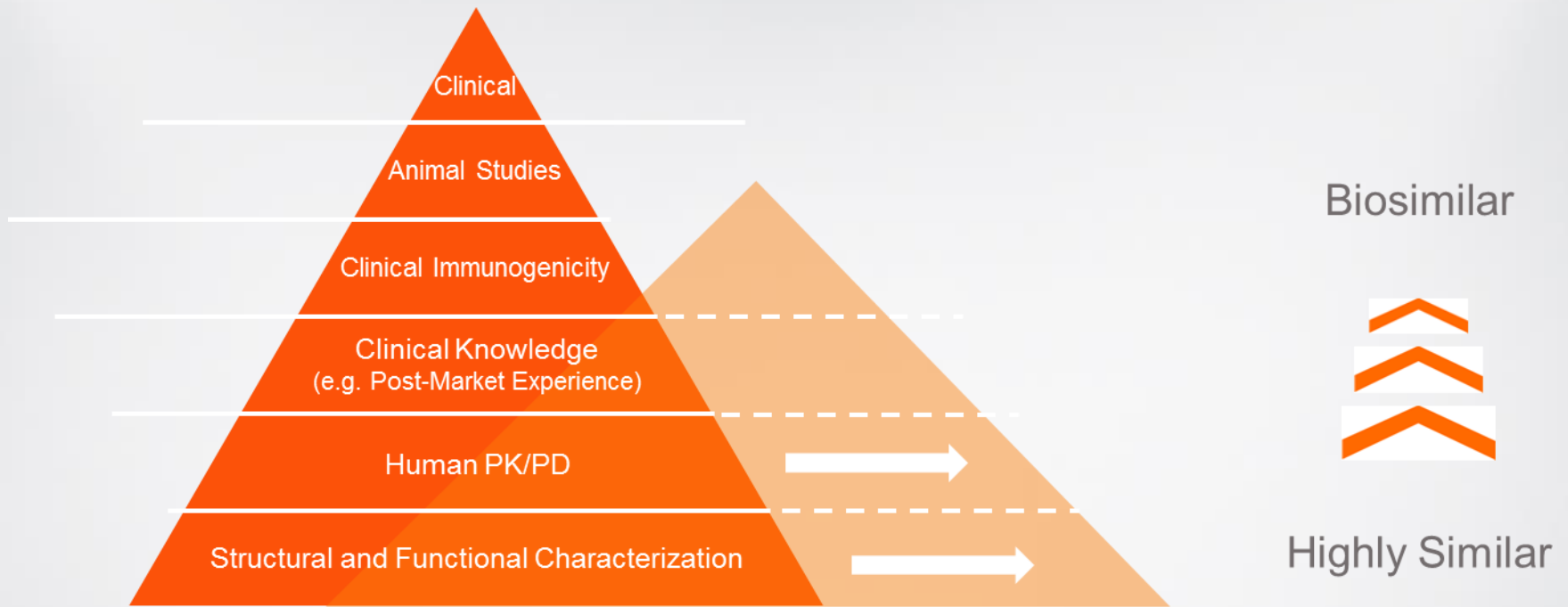


## Demonstrating “similarity”

- Quality attributes
- Non-clinical animal
- PK/PD Bioequivalence
- Phase III equivalence; Efficacy and Safety comparability



# Comprehensive Biosimilarity Exercise



R.E. Sherman, FDA Biosimilar Guidance Webinar, February 15, 2012



# Similarity of Quality Attributes

## EMA

- Quality Target Product Profile (QTPP)
- The “goal posts” for each critical quality attribute need to be established

## FDA

- *Fingerprint-like analysis algorithm*

*“Such a strategy can further quantify the overall similarity between two products and may provide a basis for a more selective and targeted approach to subsequent animal and/or clinical studies.”*



## Similarity non-clinical animal comparability

- Case by Case approach
- EU applies the principles of the 3Rs (replacement, refinement, reduction)
- US and others require more studies



## Similarity clinical “bioequivalence”

- General principle: A test product is considered to be bioequivalent to a reference product if the 90% confidence interval of the geometric mean ratio of AUC and Cmax between the test and reference fall within 80-125%.
- Not applicable to the assessment of biosimilarity between highly variable biological (intra-subject variability greater than 30% C.V.)
- High variability → large Phase I studies 150-300 HVs



# Demonstrating Biosimilarity- Clinical phase III

**Sensitive homogenous population**

**Assay sensitivity/ Similarity**





# Sensitive Homogeneous Population and Endpoints

- Sensitive Homogeneous Population
  - *In principle, the most sensitive model and study conditions (pharmacodynamic or clinical) should be used in a homogeneous patient population*
- Selection of Endpoints
  - The most sensitive clinical endpoint that is able to detect product-related differences

Study design, study population and/or endpoints may be different to those used to establish therapeutic benefit of the reference product



## Determination of margins-Effect size

- An appropriate equivalence margin that is adequate to detect clinically meaningful differences in effectiveness and safety
- The smaller the equivalence margin → the narrower the confidence interval → larger the sample size.
- The choice of margin and its justification are usually supported by statistical estimation based on historical data of the reference product and by comparison of prior study design



## Assay Sensitivity- ICH E10

As for all clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be ensured (EMA/CHMP/BMWP/42832/2005)

- Determining that historical evidence of sensitivity to drug effects exists. **Without this determination, demonstration of efficacy from a showing of non-inferiority is not possible and should not be attempted.**
- Designing a trial. Important details of the trial design, e.g., study population, concomitant therapy, endpoints, run-in periods, **should adhere closely to the design of the trials used to determine that historical evidence of sensitivity to drug effects exists**
- Setting a margin. An acceptable non-inferiority margin should be defined, taking into account the historical data and relevant clinical and statistical considerations
- Conducting the trial. The trial conduct should also adhere closely to that of the historical trials and should be of high quality



# Equivalence OR Non-Inferiority



## Non-Clinical and Clinical

- In general, an equivalence design should be used
- The use of a non-inferiority design may be acceptable if justified on the basis of a strong scientific rationale and taking into consideration:
  - The characteristics of the reference product, e.g. safety profile/tolerability, dose range, dose-response relationship.
- A non-inferiority trial may only be accepted where the possibility of increased efficacy can be excluded on scientific and mechanistic grounds
- However, as in equivalence trials assay sensitivity has to be considered



# Interchangeability

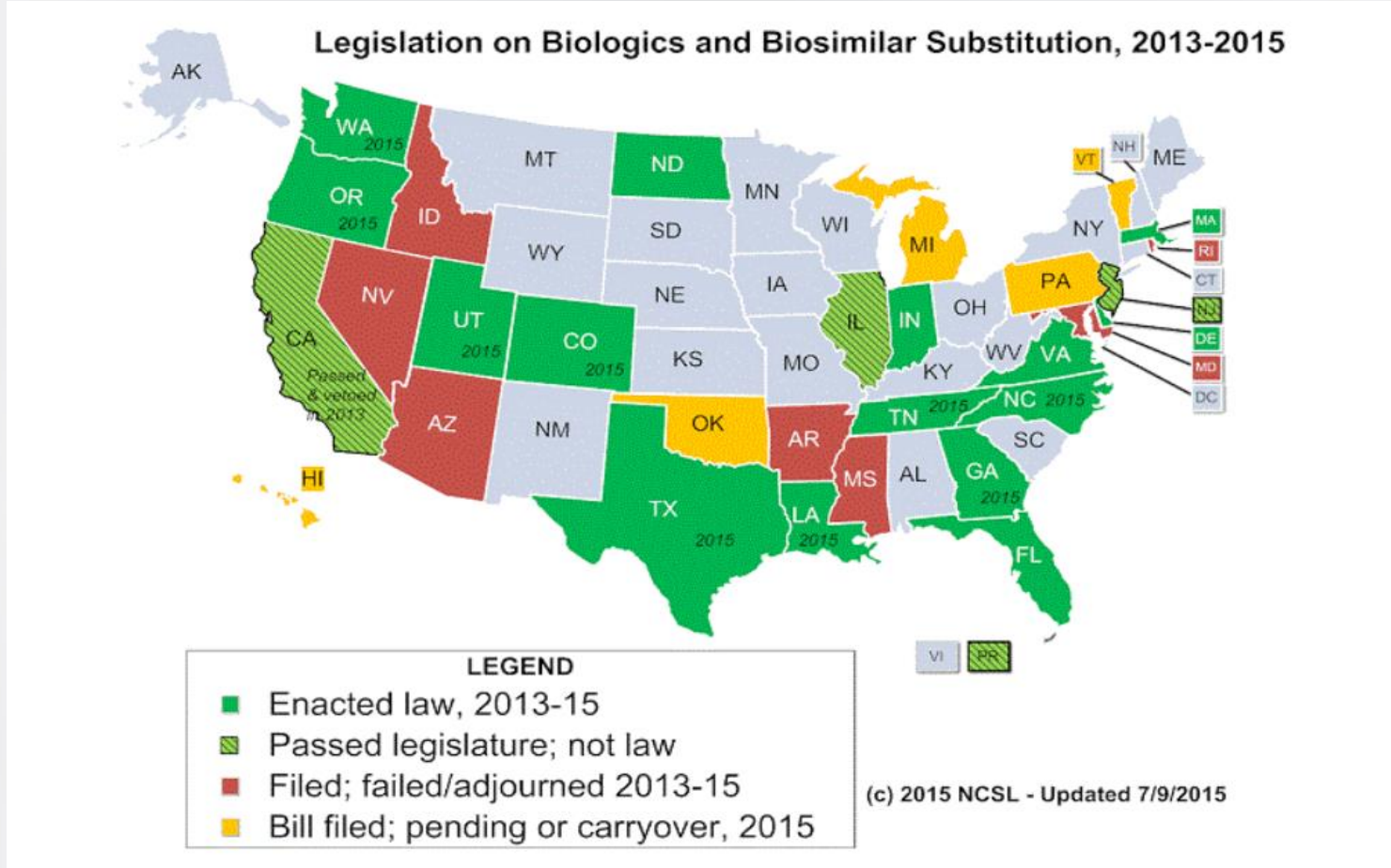


## Demonstrating interchangeability- US

- Under the 2010 *Biosimilar Price Competition and Innovation (BCPI) Act*—passed with the *Patient Protection and Affordable Care Act (PPACA)*—FDA is required to release a definition for interchangeable products
- Drug company would have to show that nothing happens to the patient if you switch them back and forth between the two products. But how the company would show that to regulators remains wide open



# United States



<http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx>





- EU: biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products however decisions on the interchangeability or substitution of biosimilars and originator biologicals are not made by EMA but at the national level
- Health Canada : biosimilar products are not interchangeable;  
**Canadian provinces could still pay for SEB**
- South Africa does not allow biosimilars to be interchangeable with their reference product and automatic substitution cannot apply to biosimilars
- Japan's approach is similar, but also points out that substitution of a biosimilar with its reference or innovator product should be avoided throughout treatment
- Emerging countries: differing views mostly driven by cost



# Paper on EBE Biologics Policy Survey

- Law against substitution
- Law allows substitution at treatment initiation
- Guideline prohibits substitution
- No specific regulation/ no specific guideline/ insufficient information
- No law/ guidance but substitution happening



Survey of EBE indicates that nearly all jurisdictions have policies in place that reflect the different nature of biological medicines. However, policies and their implementation vary among different jurisdictions

<http://gabi-journal.net/what-pricing-and-reimbursement-policies-to-use-for-off-patent-biologics-results-from-the-ebe-2014-biological-medicines-policy-survey.html>



## Recently announced positions of 2 authorities

- Australia Therapeutic Goods Administration (TGA) has approved Eli Lilly's biosimilar insulin glargine
- TGA also said it will consider marking the biosimilars equivalent, **'a' flagging, meaning substitutable at pharmacy level**
- Substitution **will not be applied to SBMPs [similar biological medicinal products, biosimilars]** at this time unless TGA issued statement supportive of 'a' flagging is available'
- And in fact it has even rejected 'a' flagging in the case of the filgrastim biosimilar, Nivestim before.
- The Finnish Medicines Agency, announced on 22 May 2015 that **biosimilars licensed in the EU are interchangeable**
- The Fimea however, **does not recommend automatic substitution** at the pharmacy level.
- The agency specifically recommends that **biosimilars are interchangeable** with their reference products **only under the supervision of a healthcare professional.**



Demonstrating  
Interchangeability.  
Is it possible?



## Study design challenges-

What to measure, who to measure and for how long?

- Endpoints
- Duration of evaluation
- Response margin
- Each indication?
- A question that remains is, if a product is deemed interchangeable with the reference product, does this automatically also mean that a product is interchangeable with other (interchangeable) biosimilars?



# Interchangeability key cog in biosimilar debate!

## Biosimilar Interchangeability Problems Pose Complex Challenge for Regulators

“The big elephant in the room is interchangeability, and whether we’re going to consider a biologic product more like a New Molecular Entity (NME)—a new product that has a similar function but is a completely different drug in how we prescribe it—or if we going to be able to see biosimilars as interchangeable.”



# Guidelines

- CHMP/437/04 Rev 1: Guideline on similar biological medicinal products, 23 October 2014
- EMA/CHMP/BWP/247713/2012: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1), 22 May 2014
- FDA, Draft Guidance for Industry Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, May 2014
- EMEA/CHMP/BMWP/42832/2005 Rev. 1; Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
- FDA draft guideline: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product



• THANK YOU