

PRAHEALTHSCIENCES

THE FUTURE OF CLINICAL DEVELOPMENT

Challenges in demonstrating biosimilarity and interchangeability of biosimilar products

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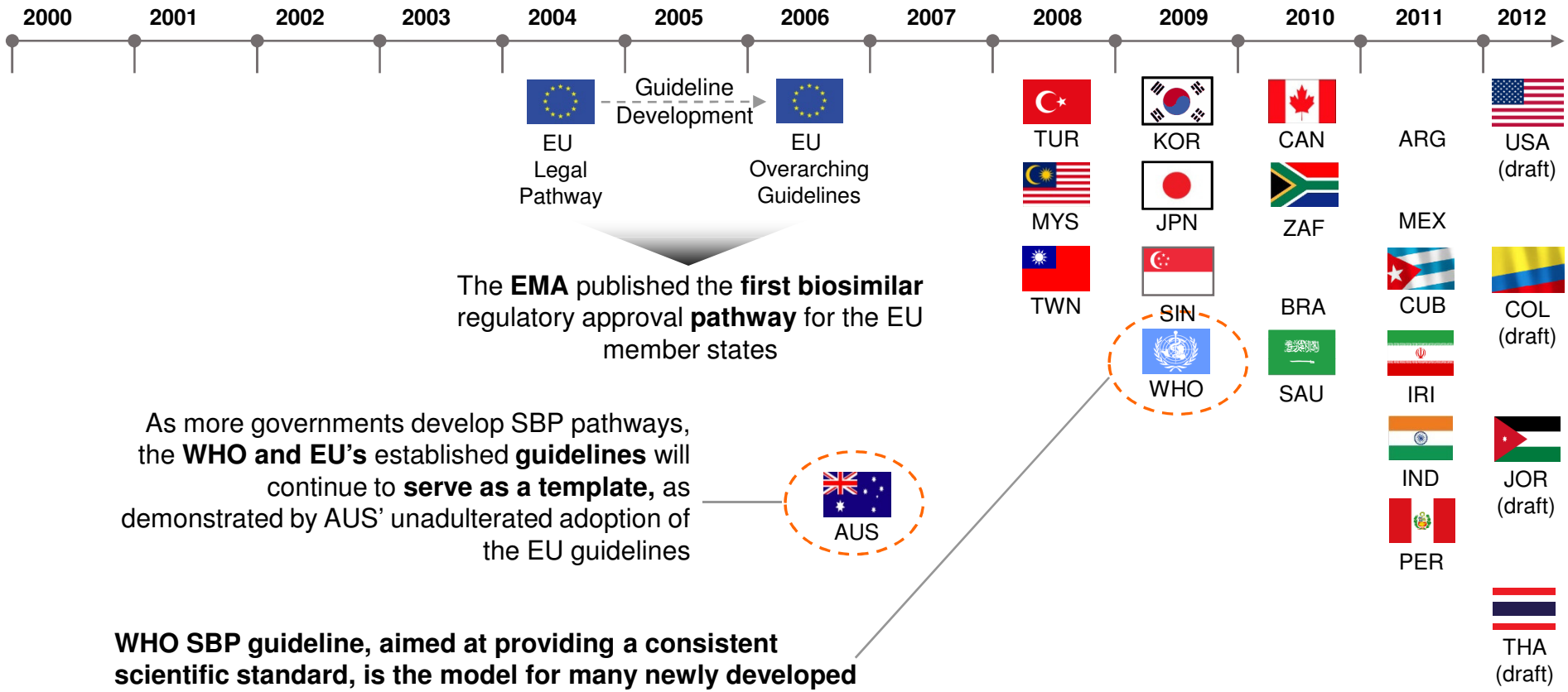
Global Biosimilar Concept

- Generic approach is not appropriate
- Step-wise comparability approach
- *Global* similarity in all aspects related to safety, purity, and potency of the biosimilar products.
  - Similar to the reference product in terms of quality, safety and efficacy
  - Quality is a pre-requisite for abbreviated non-clinical and clinical
  - Case by case approach
  - Pharmacovigilance is critical

Status Biosimilar Guidelines- Global

BIOSIMILAR REGULATION

GLOBAL GUIDELINE/REGULATION DEVELOPMENT



The **EMA** published the **first biosimilar** regulatory approval **pathway** for the EU member states

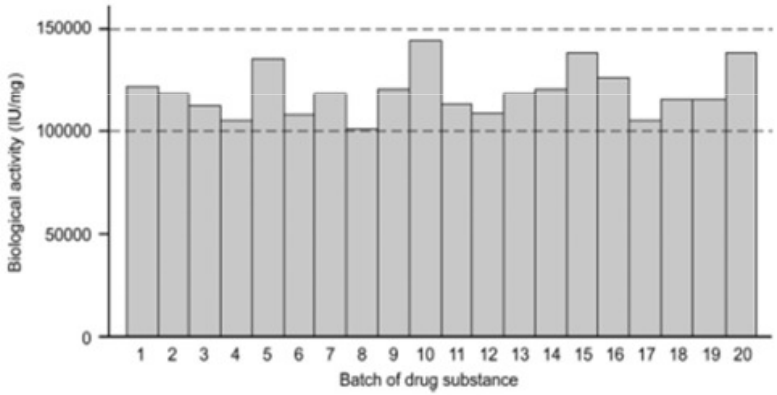
As more governments develop SBP pathways, the **WHO and EU's** established **guidelines** will continue to **serve as a template,** as demonstrated by AUS' unadulterated adoption of the EU guidelines

WHO SBP guideline, aimed at providing a consistent scientific standard, is the model for many newly developed SBP pathways.

Similarity

"Similar but not identical"

- „Non-identicality" 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

Demonstrating “similarity”

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

Similarity non-clinical animal comparability

EMEA/CHMP/BMWP/42832/2005 Rev. 1; Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues

"…. the focus of the study/studies (PK and/or PD and/or safety) depends on the need for additional information….. The principles of the 3Rs (replacement, refinement, reduction) should be considered when designing any *in vivo* study "..

FDA draft guideline: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

"….a single-dose study in animals comparing the proposed product and reference product using PK and PD measures may contribute to the totality of evidence that supports a demonstration of biosimilarity. Specifically, sponsors can use results from animal studies to support the degree of similarity based on PK and PD profiles of the proposed product and the reference product…."

Similarity clinical “bioequivalence”

Average bioequivalence (ABE) in terms of drug absorption between the small molecule drug products through the conduct of bioequivalence (pharmacokinetic) studies

ABE criterion only focuses on average bioavailability regardless of the variability of bioavailability between drug products

- 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.)

FDA Guidance for Industry- May 2014

Clinical Pharmacology Data to support a demonstration of biosimilarity to a reference product- May 2014

- Detailed guidance on end points
- PK/PD Assay considerations
- Study design
- Immunogencity
- Statistical comparison (80-125%) as a start point but falling outside range does not necessarily preclude similarity
- Utility of simulation tools

Demonstrating Biosimilarity- Clinical phase III

Sensitive homogenous population

Assay sensitivity/ Similarity

Sensitive* Homogeneous Population

"In principle, the most sensitive model and study conditions (pharmacodynamic or clinical) should be used in a homogeneous patient population, since this reduces variability and thus the sample size needed to prove similarity, and can simplify interpretation" (EMA/CHMP/BMWP/572828/2011)*

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

**Sensitive meaning most likely to show differences between the biosimilar and the reference medicine, if these exist*

Selection of end-points

- The most sensitive clinical endpoint that is able to detect product-related differences, if present and, at the same time, to reduce patient and disease-related factors to a minimum in order to increase precision
- Continuous endpoints are more sensitive to detect differences in clinical effects, but there could be situations where discrete endpoints are more appropriate

EMA monoclonal antibody guidance: 'for a new anticancer drug, the preferred endpoint to establish patient benefit would be progression free/disease free survival or overall survival. But these endpoints may not be feasible or sensitive enough for establishing biosimilarity to a reference product since they may be influenced by various factors not attributable to differences between the biosimilar and the reference products themselves, but by factors like tumour burden, performance status, previous lines of treatments, underlying clinical conditions, subsequent lines of treatment (for OS).

Determination of margins-Effect size

An appropriate equivalence margin that is deemed adequate to enable the detection of clinically meaningful differences in effectiveness and safety between the biosimilar and the reference products

- The smaller the equivalence margin, the narrower the confidence interval must be in order to fall within the margin, and the larger the sample size will be needed. Hence, determining the margin is a critical problem and major focus when designing a biosimilar trial.
- 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, e.g. study population and concomitant therapy, to the current study design to ensure ‘constancy’.

Assay Sensitivity- ICH E10

As for all clinical comparability trial designs, assay sensitivity (see ICH topic E10) has to be ensured (EMEA/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

EMEA/CHMP/BMWP/42832/2005 Rev. 1 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

FDA Non-Inferiority

- In some cases, a one-sided test – non-inferiority design may be appropriate for comparing safety and effectiveness and also advantageous as it would generally allow for a smaller sample size than an equivalence (two-sided) design

- If it is well established that doses of the reference product higher than are recommended in its labeling do not create safety concerns, a one-sided test may be sufficient for comparing the efficacy of certain protein products

Interchangeability

Terminology

Table 1: Terminology relevant for interchanging biologicals [34]
Switching: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.
Interchanging: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.
Substitution: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

European Commission. What you need to know about biosimilar medicinal products. in Europe. Available from: http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf

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
- 2013: The agency has only released limited information on the principles of interchangeability.
- Dug 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

ROW

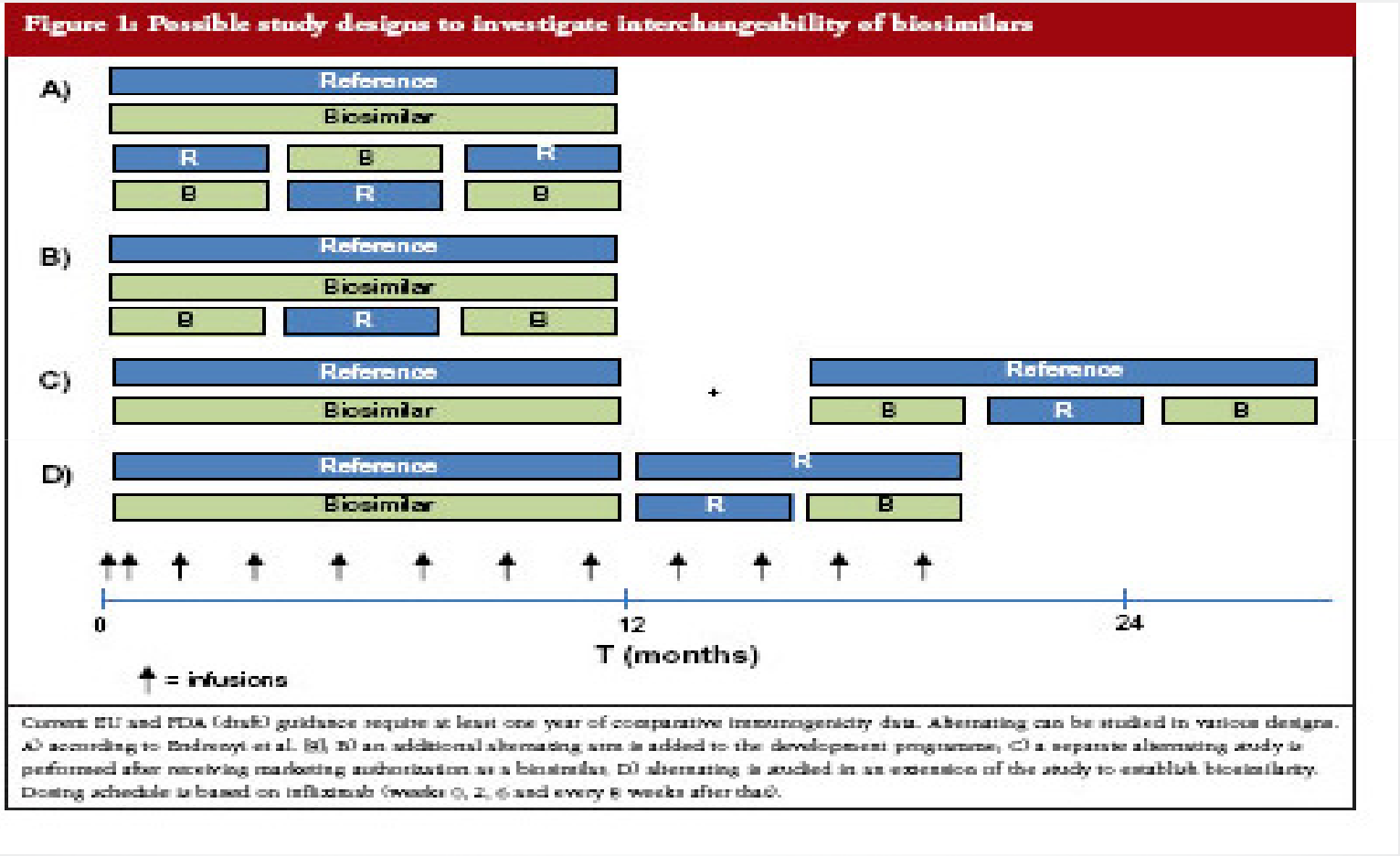
- EU: biosimilars developed in line with EU requirements can be considered therapeutic alternatives to their respective reference products but
- Health Canada : biosimilar products are not interchangeable; Canadian provinces could still pay for SEB
- South Africa does not allow biosimilars to be interchangeable 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

Demonstrating Interchangeability. Is it possible?

Interchangeable study designs

- Several designs have been suggested and it has been proposed to include a combined RBR, BRB design, where R is the reference product and B the biosimilar product
- Alternatively, switching and/or alternating can be studied in a supplementary study or as an extension to the registration study

Interchangeable designs



Ref: Hans C Ebbers: GaBI Journal Feb 2014: Interchangeability. An insurmountable fifth hurdle

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?

Switching studies

- Disease progression over time
  - May obscure product differences
  - Clinical difference may show up if switch is done at one point in treatment regimen but not in another
- “Time to” type endpoints–
  - Time to disease progression
  - Time to death (survival time)
- Some products show much faster PD/clinical response after initial dosing than return to baseline after withdrawal (rituximab, teriparatide)
- Immunogenic effects of two products confounded

High Risk and Costly!



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."

THANK YOU