Biosimilars: Advancing Clinical Development

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Biosimilars Pave the Way for a New Era of Affordable Medicines

- Need for more affordable biologic drugs in order to reduce spending and reallocate resources either to another treatment or to increase access of the same biologic
- Biologics are complex molecules, very different from small molecules
- Biosimilars are not generic versions of biologic drugs
- First biosimilar was approved in the EU in 2006 and in 2015 in the US
- 13-year experience with biosimilars in the EU with >750 million patient days safety experience in the EU
- No safety/efficacy concerns were identified

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Lessons learned from biosimilar sales in the EU

- Uptake of EPOs, filgrastims, GHs highly variable between EU countries (EPOs - 90% in Norway; <5% in Italy; Norway -100% biosimilar infliximab;
- Discounting of both reference and biosimilar products is considerable: e.g. EPO/adalimumab – 80% discount; biosimilar infliximab -70% discount; etanercept -50-60%; trastuzumab, rituximab – up to 50%
- The dynamics is affected by pricing and to certain extent by nationwide payer / medical community decisions
- Remicade: <40%; Enbrel <50%; Mabthera: <70% - EU share

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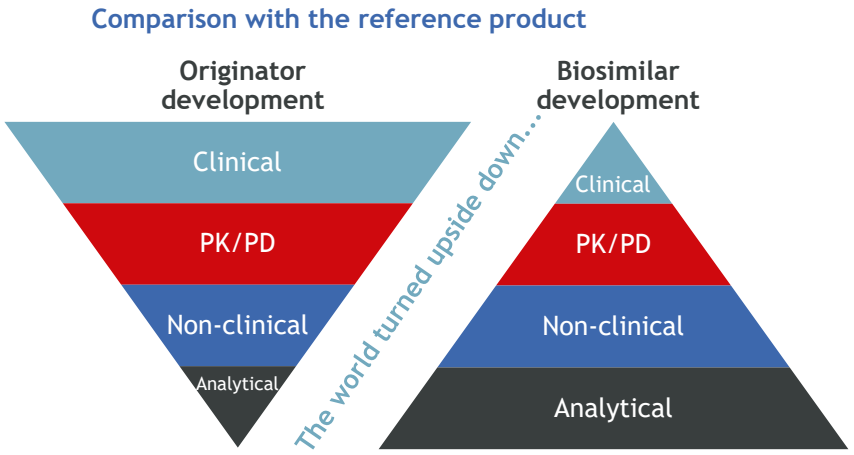
Development of a Biosimilar is a Different Paradigm



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EMA and FDA differences in evaluation of the biosimilarity

EMA	FDA
Similar target profile but without formal statistical criteria	Highly similar target profile defined by statistical approach
Risk driven non-clinical package	Some animal data still needed for biosimilar MABs
PK/PD study	PK/PD study (address any differences between US and EU reference product)
Equivalence efficacy study with symmetrical margin / Non-inferiority study	Equivalence efficacy study / Asymmetric margin is allowed
RMP in all cases	N/a
Not appropriate	Single transition data from the reference product is required for chronic systemic conditions
Not appropriate	Interchangeability designation is a separate development and a separate clinical study
INN = RMP	Unique suffix
Label for biosimilar = RMP	Partial label is possible without all RMP label

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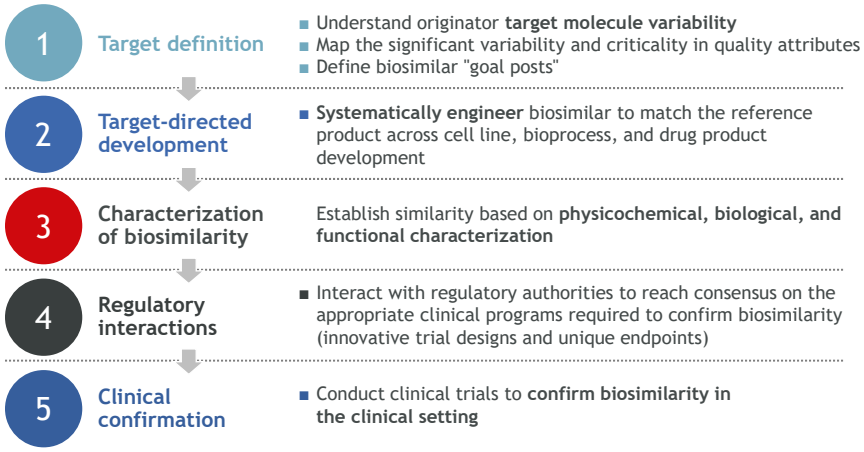
Biosimilar Development is an Iterative and Target Direct Approach



Sandoz, FDA Advisory Committee, 2016

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Main factors in designing the SBP program

Target attributes

- Non-target and target-mediated clearance
- Half-life
- Linearity of dose-dependent response in selecting the dose
- Immunogenicity
- Safety

Indication attributes

- Prior historical data with RMP
- Margin definition
- Homogeneity and sensitivity
- Monotherapy / combination
- Timing for primary endpoint evaluation
- Current and evolving paradigm

SBP attributes

- Residual uncertainties?
- Issues with extrapolation?
- Requirements from different authorities
- PV and RMP requirements
- Interchangeability requirements

Other attributes

- Operationally feasible?
- Sufficient patient pools?
- Attractive to investigators / patients?
- Attractive to payers?
- Projected market changes and size

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Case study 1: Infliximab SBP candidate

This case study is based on a virtual/hypothetical product constructed as a hypothetical model to help discuss key principles of the clinical and statistical sections of the WHO guidance on similar therapeutic proteins. It does not represent any approved product nor a product in development as a SBP or RBP. The specific study designs and outcomes discussed are hypothetical and developed only for the purpose of this exercise.

Objectives:

- To familiarize participants with construction of the equivalence margin, designing pivotal equivalence study for a virtual SBP infliximab candidate and interpret the outcomes of the completed study.
- To discuss extrapolation approach for infliximab SBP and whether the data in the current scenario are sufficient to achieve full label approval.

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Case study 2: Rituximab SBP candidate

This case study is based on a virtual/hypothetical product constructed as a hypothetical model to help discuss key principles of the clinical and statistical sections of the WHO guidance on similar therapeutic proteins. It does not represent any approved product nor a product in development as a SBP or RBP. The specific study designs and outcomes discussed are hypothetical and developed only for the purpose of this exercise.

Objectives:

- To familiarize participants with the design of rituximab SBP clinical program and interpret whether proposed studies address observed residual difference(s).
- To discuss whether the data in the current scenario are sufficient to achieve full label approval and satisfy extrapolation requirements.

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Case study 3: Trastuzumab SBP candidate

This case study is based on a virtual/hypothetical product constructed as a hypothetical model to help discuss key principles of the clinical and statistical sections of the WHO guidance on similar therapeutic proteins. It does not represent any approved product nor a product in development as a SBP or RBP. The specific study designs and outcomes discussed are hypothetical and developed only for the purpose of this exercise.

Objectives:

- To familiarize participants with the design of trastuzumab SBP clinical program and interpret whether proposed studies address observed residual difference(s).
- To discuss whether the data in the current scenario are sufficient to achieve full label approval and satisfy extrapolation requirements.

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