Clinical Considerations for Development of Biosimilars in Oncology

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Global spending on cancer medicine is expected to exceed 150 billion USD by 2020\textsuperscript{a}

Annual global growth rate for oncology drugs is expected to be 7.5% to 10.5% through 2020\textsuperscript{b}

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b. IMS The Global Use of Medicines, 2013
Biosimilar: Increasing Access to Cancer Therapy

- In US, 67 billion USD worth of biosimilar patents are expiring before 2020\(^a\)
- 250 billion USD could be saved through 2024 if 10 biosimilars are approved in the US\(^b\)

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\(a\). US$67 billion worth of biosimilar patents expiring before 2020; Gabi Online, 2014

\(b\). S. Miller, Infographic: Two biosimilars to save $22.7 Billion, 2016
Definition of Biosimilars by Regulatory Agencies

**FDA**

“…that the biological product (proposed product) is **highly similar to the reference product** notwithstanding minor differences in clinically inactive components…there are **no clinically meaningful differences** between the biological product and the reference product **in terms of the safety, purity, and potency of the product**”

**EMA**

“A biosimilar is a biological medicinal product that **contains a version of the active substance of an already authorised original biological medicinal product**…. **Similarity** to the reference medicinal product **in terms of quality characteristics, biological activity, safety and efficacy** based on a comprehensive comparability exercise needs to be established.”

**MFDS**

“A ‘biosimilar product’ is a biological product that is **comparable to already marketed reference products** in terms of **quality, safety and efficacy**.”

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a. FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015; b. EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins, 2014; c. MFDS. Guidelines on the evaluation of biosimilar products, 2010
# Current Development Status of Biosimilars

- The EMA has approved over 20 biosimilars to date; the US FDA approved its first biosimilar in 2015\(^{a,b}\).
- To date, rituximab approval in Europe is the only world-wide oncology biosimilar approval; more biosimilar candidates are under review\(^{a,b}\).

![Map of approved biosimilars](image)

<table>
<thead>
<tr>
<th>Approved by FDA</th>
<th>Approved by EMA</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Under Review by FDA</th>
<th>Under Review by EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (2017)</td>
<td></td>
</tr>
</tbody>
</table>

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\(^{a}\) FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015

\(^{b}\) EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins, 2014
Biosimilar Developmental Pathway Differs from that of Novel Drugs

- Biosimilar development uses a step-wise approach to build “totality of evidence”\textsuperscript{a,b}
- The level of evidence required for biosimilar approval is different to originator biologics: “The guiding principle is to demonstrate similar clinical efficacy and safety compared to the reference medicinal product, not patient benefit per se, which has already been shown for the reference medicinal product.” (EMA)\textsuperscript{a,b}

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\textsuperscript{a} FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015
\textsuperscript{b} EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins, 2014
Exemptions for Biosimilar Development

- **Non-clinical study may not be necessary**
  - “*In vitro* studies should be conducted first and a decision made as to the extent of what, in any, *in vivo* work will be required”\(^a\) (EMA)

- **A single dose pharmacokinetic study is sufficient**
  - A single dose study with full characterization of PK profile, including the late elimination phase, is preferrable\(^a\)

- **Clinical study may be carried out in only one indication**
  - “If the proposed product *meets the statutory requirements* for licensure as a biosimilar product...based on...data derived from a clinical study or *studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use*, the applicant may seek licensure of the proposed product for one or more additional conditions of use for which the reference product is licensed.”\(^b\) (FDA)

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\(^a\) EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins, 2014
\(^b\) FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015
SB3 has been extensively tested for its structural, physiochemical, and biological aspects by state-of-the-art technologies to show similar and comparable characteristics to the reference product.

**46 methods used for physicochemical analysis**

- **Structural Characterization**
  - Full amino acid sequencing
  - Total mass by mass spectrometry
  - N-terminal sequencing, C-terminal sequencing
  - Peptide mapping
  - N-glycosylation site determination
  - Disulfide bonds
  - Free sulfhydryl group
  - Oxidation, deamidation, Pyro-E

- **Physicochemical: Electrophoresis**
  - Imaged capillary isoelectric focusing
  - Capillary electrophoresis-SDS

- **Physicochemical: Glycan profile**
  - N-glycan profile
  - Glycan identification

- **Physicochemical: Chromatography**
  - SE-HPLC, CEX-HPLC
  - Protein G-HPLC for titer

- **Process-Related Impurity**
  - Product specific HCP Assay
  - HCD, Insulin, Protein A leachate, Dextran Sulfate
  - Anti-foam, MPA
  - LDAO, PF-68

- **USP/EP/JP/KP**
  - Appearance (color, clarity)
  - Osmolality, Moisture, pH, Visual particles
  - CCIT, Sterility
  - Protein content

- **High-Order Structure**
  - Fluorescence spectra: Intrinsic, extrinsic
  - Circular Dichroism: Near, Far
  - Differential scanning calorimeter
  - Dynamic light scattering
  - Analytical ultracentrifugation
  - Hydrogen-Deuterium Exchange
  - MFI

**19 methods used for functional analysis**

- **Fab-mediated Function**
  - Binding assay (HER2)
  - Potency assay (Proliferative assay) by cell-based assay

- **Fc-mediated Function**
  - ADCC
  - FcRn binding assay
  - FcγRIa binding assay
  - FcγRIIa binding assay
  - FcγRIIib binding assay
  - C1q binding assay

- **Additional biological assays**
  - Surface HER2 level measurement
  - In-vitro angiogenesis
  - Phopho AKT measurement
  - HER2 shedding
  - Combination chemotherapy

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Data on file, Samsung Bioepis, Co. Ltd.
Science-based systemic quality evaluations are used to maximize clinical biosimilarity

65 assays developed for sensitive and reliable quality evaluation

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>PK</th>
<th>Safety</th>
<th>Immunogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary structure</td>
<td>• Glycoform</td>
<td>• Adventitious agents</td>
<td>• Glycoform</td>
</tr>
<tr>
<td>• Higher order structure</td>
<td>• Activity</td>
<td>• Process/host cell</td>
<td>• Formulation</td>
</tr>
<tr>
<td>• Content</td>
<td></td>
<td>impurities</td>
<td>• Product-related</td>
</tr>
<tr>
<td>• Product-related</td>
<td></td>
<td>• Process additives</td>
<td>• impurities and/or</td>
</tr>
<tr>
<td>impurities and/or</td>
<td></td>
<td>• Primary structure</td>
<td>• variants</td>
</tr>
<tr>
<td>variants</td>
<td></td>
<td>• Formulation</td>
<td>• Primary structure</td>
</tr>
<tr>
<td>• Charge variants</td>
<td></td>
<td></td>
<td>• Higher order structure</td>
</tr>
<tr>
<td>• Formulation</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>• Activity</td>
<td></td>
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</table>
Manufacturing Changes May Lead to Change in Quality Profile

- Manufacturing process changes are common for biological products
  - The pre- and post-process change versions of originator products are also marketed under the same label.

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Quality attributes were continuously monitored over 5 years by analyses of 103 lots of EU- or US-marketed Herceptin®.

A marked downward drift in glycosylation, Fc receptor binding, and ADCC activity was observed in lots manufactured during a select period of time.

Decrease in the fucose of Fc-linked glycan directly affects ADCC activity via FcγRIIIa binding.

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Pharmacokinetics

- “A comparative pharmacokinetic study in a sufficiently sensitive and homogeneous study population (healthy volunteers or patients) normally forms an initial step of biosimilar mAb development.” (EMA)
- “The choice of study population should allow for an assessment of clinically meaningful differences between the proposed product and the reference product.” (FDA)

<table>
<thead>
<tr>
<th>Pharmacokinetics (PK): Healthy Volunteer vs Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Healthy Volunteer</strong></td>
</tr>
<tr>
<td>• Relatively homogeneous population</td>
</tr>
<tr>
<td>• Fewer complicating factors that affect PK (e.g., disease status, concomitant medications)</td>
</tr>
<tr>
<td>• If safety differences are not a concern, healthy subjects generally are preferred for the PK comparability</td>
</tr>
<tr>
<td>• Trastuzumab biosimilar: Healthy male</td>
</tr>
</tbody>
</table>


Recommended population to be used varies by indication and/or product

Only healthy male subjects were enrolled in SB3 or SB8 pharmacokinetic (PK) studies, which was aligned with FDA.

- For SB3 (proposed trastuzumab biosimilar): Healthy female subjects who are more likely to be treated with trastuzumab for breast cancer were excluded to avoid any risk of development of anti-trastuzumab antibodies.
- For SB8 (proposed bevacizumab biosimilar): Healthy female subjects were avoided due to safety concerns linking bevacizumab to ovarian failure or fertility.

FDA may encourage inclusion of both genders.

- For SB2 (proposed remicade biosimilar): Both healthy male and female subjects were included as per FDA’s recommendation to use a population representative of the target population (age and gender).

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a. Data on file, Samsung Bioepis, Co. Ltd.
Pharmacokinetics Study Design

- Study arms and population: SB3 vs EU- or US-trastuzumab in healthy male subjects
- Equivalence margin: 0.8 to 1.25 for the 90% CI for geometric least square means of $AUC_{inf}$, $AUC_{last}$, and $C_{max}$

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Clinical Considerations for Establishing Biosimilarity

“The guiding principle is to demonstrate similar clinical efficacy and safety compared to the reference medicinal product, not patient benefit per se, which has already been shown for the reference medicinal product”

a. FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015
b. EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins, 2014
Clinical Considerations for Establishing Biosimilarity: Statistical Design

- An **equivalence trial** that demonstrates similar effect to the reference product is typically used for biosimilars\(^a,b\)
- In general, an equivalence design should be used with **pre-specified comparability margin**, but a **non-inferiority study** may be appropriate for biosimilars in certain cases\(^a,b\)

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*a*  FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015.

*b*  FDA, Non-inferiority clinical trials to establish effectiveness, 2012
Clinical Considerations for Establishing Biosimilarity: Statistical Design

- **M1**: Lower boundary of 95% CI of a placebo-controlled trial or meta-analysis of trials
- **M2**: Clinical judgment regarding how much of the M1 active comparator treatment effect can be lost (usually, half of M1)
- **Eq. Margin**: Upper (superiority) margin as symmetric to lower margin (M2)

Data on file, Samsung Bioepis, Co. Ltd.
Clinical Considerations for Establishing Biosimilarity: Statistical Design

- Two different metrics, ratio (relative risk) and absolute difference, can be used to assess the primary efficacy endpoint.

- FDA: The ratio metric is less likely to fluctuate and provides a better adjustment in equivalence studies.

### Breast pCR (bpCR) Rate From Reference Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Herceptin® Event/Total</th>
<th>No Herceptin® Event/Total</th>
<th>Difference</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study A</td>
<td>15/23 (65%)</td>
<td>5/19 (26%)</td>
<td>39%</td>
<td>2.5</td>
</tr>
<tr>
<td>Study B</td>
<td>50/117 (43%)</td>
<td>26/118 (22%)</td>
<td>21%</td>
<td>2.0</td>
</tr>
<tr>
<td>Study C</td>
<td>4/13 (31%)</td>
<td>1/11 (9%)</td>
<td>22%</td>
<td>3.4</td>
</tr>
<tr>
<td>Study D</td>
<td>85/217 (39%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Meta-analysis</strong></td>
<td></td>
<td></td>
<td>23.3% [16.6, 29.9]</td>
<td>2.07 [1.546, 2.795]</td>
</tr>
<tr>
<td><strong>Equivalence Margin</strong></td>
<td></td>
<td></td>
<td>[−13%, 13%]</td>
<td>[0.785, 1.546]</td>
</tr>
</tbody>
</table>

1. 80% CI
2. 90% CI
3. Difference of bpCR rates between treatments is calculated with the 80% CI of [16.6%, 29.9%] from meta-analysis; i.e., 13% (= 16.6% × 0.8)
4. Upper limit is taken from the lower limit of 90% CI of the ratio between treatments, and lower equivalence limit is preserving at least 50% of Herceptin® treatment effect over the placebo; i.e., 0.785 = 1/(1+0.5 ×(1.546-1))

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a. FDA, Non-inferiority clinical trials to establish effectiveness, 2016
Clinical Considerations for Establishing Biosimilarity: Study Population

- Biosimilar clinical trials should be conducted in the most sensitive and homogenous patient population\(^a\)
- The choice of study population should allow for an assessment of clinically meaningful differences\(^b\)

### Study Population: EBC vs MBC

<table>
<thead>
<tr>
<th>Early Breast Cancer (EBC)</th>
<th>Metastatic Breast Cancer (MBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• More homogeneous due to less confounding factors(^c)</td>
<td>• Highly heterogeneous due to a large number of confounding factors (e.g. metastases location, time of metastatic recurrence, performance status, and number and type of previous therapies)(^c)</td>
</tr>
<tr>
<td>• Most sensitive and will allow closer assessment of similarity(^d)</td>
<td></td>
</tr>
<tr>
<td>• No previous exposure to any anticancer treatments(^c)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins, 2014; \(^b\) FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015; \(^c\) X. Pivot et al. Anti-Cancer Drugs 2015; \(^d\) C. Jackisch et al. Future oncol., 2015
Clinical Considerations for Establishing Biosimilarity: Study Endpoint

- “The focus of the comparability exercise is to demonstrate similar efficacy and safety compared to the reference medicinal product, not patient benefit per se” (EMA)

- Long-term survival endpoints may not be feasible or sufficiently sensitive for establishing biosimilarity, due to confounding factors and suggests assessment of ORR or pCR (EMA)

<table>
<thead>
<tr>
<th>Setting</th>
<th>Study Endpoint for Drug Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curative</td>
<td><strong>Adjuvant</strong> DFS, RFS, EFS, OS etc.</td>
</tr>
<tr>
<td></td>
<td><strong>Neoadjuvant</strong> DFS, RFS, EFS, OS + rate of conservative surgery, pCR¹</td>
</tr>
<tr>
<td>Metastatic</td>
<td>PFS, OS, <strong>ORR¹</strong></td>
</tr>
<tr>
<td>Palliative</td>
<td>Pain relief, skeletal-event free survival, social QoL etc.</td>
</tr>
</tbody>
</table>

1. Per EMA guidelines, may be used as a surrogate marker for long-term survival endpoints for development of biosimilars or breast cancer neoadjuvant therapy

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a. EMA, Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies. 2012
Most trastuzumab biosimilars currently in development use pCR and ORR as primary endpoints for HER2-positive breast cancer\(^a,b\)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Study Indication</th>
<th>Primary Endpoint</th>
<th>Biosimilar</th>
<th>Study Indication</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOAH HannaH NeoSphere NeoALTTO</td>
<td>Neoadjuvant</td>
<td>Locally advanced or operable breast cancer(^1)</td>
<td>- pCR - EFS</td>
<td>ABP-980 Amgen</td>
<td>Early</td>
</tr>
<tr>
<td>BCIRG-006 ALTTO HERA</td>
<td>Adjuvant</td>
<td>Early or operable HER2+ breast cancer(^1)</td>
<td>- DFS - OS</td>
<td>CT-P6 Celltrion</td>
<td>Early</td>
</tr>
<tr>
<td>CLEOPATRA EMILIA TH3RESA</td>
<td>Metastatic</td>
<td></td>
<td></td>
<td>MYL141O Mylan/Biocon</td>
<td>Metastatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PF-05280014 Pfizer</td>
<td>Early</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SB3 Samsung Bioepis</td>
<td>Metastatic</td>
</tr>
</tbody>
</table>

1. Simplified; the exact tumor staging varies from study to study

1. tPCR was a secondary endpoint in study

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\(^a\) Jackisch et al. *The Breast*, 2016

\(^b\) Rugo et al. *Cancer Treatment Reviews*, 2016
- pCR following neoadjuvant chemotherapy might be an acceptable endpoint for testing trastuzumab biosimilars\(^\text{a,b}\)

### Primary efficacy endpoint: tpCR vs bpCR

<table>
<thead>
<tr>
<th>Total pCR (tpCR)</th>
<th>Breast pCR (bpCR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• May correlated more with oncologic outcomes, yet still controversial(^\text{a,c,d})</td>
<td>• Influenced by disease factor such as T staging but <strong>extent of confounding factors is much limited.</strong></td>
</tr>
<tr>
<td>• <strong>More confounding factors</strong> in determining tpCR compared to bpCR (e.g. imbalance of axillary lymph node dissection between arms(^\text{d}))</td>
<td>• Various neoadjuvant studies in HER2-positive EBC has shown <strong>consistent bpCR rates.</strong></td>
</tr>
</tbody>
</table>
Clinical Considerations for Establishing Biosimilarity: Safety and Immunogenicity

- Biosimilarity should be determined based on the totality of the evidence considering the full data including quality, non-clinical, clinical PK, clinical efficacy, safety, and immunogenicity\(^a\)

- Safety\(^a\)
  - Incidence of adverse events (AEs) and serious adverse events (SAEs)
  - Incidence of adverse events of special interest (infusion-related reaction, asymptomatic left ventricular systolic dysfunction, heart failure) as per detailed reporting guidelines
  - Assessment of cardiac function using echocardiography at every 3-4 months and as medically indicated
  - Incidence of significant cardiac events up to 5 years after end of study

- Immunogenicity\(^a\)
  - Incidence of anti-drug antibody (ADA) and neutralizing antibody (Nab)

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\(^a\) EMA, Guideline on similar biological medicinal products containing biotechnology, 2014
Extrapolation of clinical data to other indications of the reference product may be acceptable.

Clinical Considerations for Establishing Biosimilarity: Extrapolation

- Extrapolation of clinical data to other indications of the reference product may be acceptable.

Totality of Evidence

Scientific justification to support extrapolation

1. Scientific justification includes the following in each condition or in different patient populations:
   - Mechanism of action(s) in each condition of use
   - PK and bio-distribution
   - Immunogenicity
   - Expected toxicities
   - Other factors that may affect safety or efficacy

a. FDA, Scientific considerations in demonstrating biosimilarity to a reference product, 2015
b. EMA, Guideline on similar biological medicinal products containing biotechnology-derived proteins, 2014
Biosimilarity is established through an extensive comparison exercise, based on the concept of “totality of evidence”

Key factors to consider for clinical development for oncology biosimilars are: statistical design, study population, and study endpoint

- A two-sided test is most commonly used to demonstrate equivalence
- Clinical trials should be conducted in the most sensitive and homogenous population
- The most sensitive and feasible endpoints should be used