Biosimilars

Stakeholders' Changing Expectations and the Role of Real-World Evidence

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Kamali Chance, MPH, PhD, RAC
Your Presenters

Jaclyn Bosco, PhD, MPH
Epidemiologist, Scientific Affairs
Quintiles Outcome, Real-World and Late Phase Research

Jaclyn Bosco is an Epidemiologist at Quintiles Outcome and is the Lead Scientist on Real-World and Late Phase research studies. Dr. Bosco possesses considerable expertise in epidemiologic methods, including propensity scoring, instrumental variable methods, bias analysis, and other methods for addressing bias in non-interventional studies. She is responsible for the design, analysis, and interpretation of observational studies of the natural history of disease and comparative safety and effectiveness of medical treatments, and she has been developing strategies for using registries and other observational studies to generate evidence for the safety and effectiveness of biosimilars to support decision-making.

Kamali Chance, MPH, PhD, RAC
Sr. Director, Quintiles
Head, Global Biosimilars Regulatory Strategy
Global Biosimilars Strategic Unit

Dr. Chance advises biotechnology companies for region specific and/or global regulatory strategy for the development of biosimilars. Her overall regulatory experience encompasses strategic regulatory planning, preparation of briefing documents, meetings with FDA, IND/CTA submissions, Marketing Applications (NDAs, BLAs, ANDAs) in the CTD format. Dr. Chance has considerable experience directly interacting with numerous FDA divisions at CDER and CBER. She has authored/co-authored four articles on biosimilars: Follow on biologics in EU & US ; CMC, Preclinical and Clinical Considerations for Biosimilar Biologics; The US Approval Pathway for Biosimilar Products; US Biosimilar Guidelines: Summary and Insights
Overview

- What are biosimilars?
- Regulatory pathway to market
- Market access controversies and stakeholder perspectives
- Registry design and implementation considerations
- Q & A
Today’s Webinar Audience

- Academia
- Biostatistician
- Clinical Operations
- Epidemiology
- Health Economics/Health Outcomes
- Medical Affairs
- Market Access
- Regulatory Affairs
- Risk Management
- Other
What are biosimilars?
Context

• Biologics are effective, life-altering therapies
  > Expensive
  > Limited access
  > Many originators nearing end of patent life

• Need for high quality biologic therapies
  > Affordability
  > Accessibility
<table>
<thead>
<tr>
<th>Terminology</th>
<th>Synonyms</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biologic Product</td>
<td>• Reference</td>
<td>• Virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except chemically synthesized polypeptides), or analogous product applicable to the prevention, treatment, or cure of a disease or condition in humans</td>
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<tr>
<td></td>
<td>• Innovator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Comparator</td>
<td></td>
</tr>
<tr>
<td>Originator</td>
<td></td>
<td>• Novel biological medicine that has been patented</td>
</tr>
<tr>
<td>Biosimilar</td>
<td>• Follow-on biologic (USA)</td>
<td>• Biologic medicine with identical primary amino acid sequence to an originator medicine</td>
</tr>
<tr>
<td></td>
<td>• Bioequivalent biologic</td>
<td>• Developed with intention to be as close to originator as possible</td>
</tr>
<tr>
<td></td>
<td>• Subsequent entry biologic (Canada)</td>
<td>• Demonstrated similarity in physiochemical characteristics, efficacy, and safety</td>
</tr>
<tr>
<td></td>
<td>• Biocomparable (Mexico)</td>
<td></td>
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<tr>
<td>Biobetter</td>
<td>• Second-generation biologic</td>
<td>• Biological medicine based on an originator medicine, but with improvements to increase efficacy, potency, marketability, safety (including immunogenicity), patient adherence, and/or ease of administration</td>
</tr>
<tr>
<td></td>
<td>• Biosuperior</td>
<td></td>
</tr>
<tr>
<td>Copy Biologic</td>
<td>• Alternative biologic</td>
<td>• Copy of an originator medicine that has been approved in a country where no official biosimilar regulatory pathway exists or existed</td>
</tr>
<tr>
<td></td>
<td>• Biopharmaceutical-not-subject-to regulatory-approval (B-NSRA)</td>
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</table>
Biological medicine examples

Simple Biologics
- EPO
- EPOGEN (Epoetin Alfa)
- PROCRIT (Epoetin Alfa)
- G-CSF
- Neupogen
- Neulasta ( Pegfilgrastim )
- HGH
- Genotropin (Somatropin)
- norditropin (Somatropin Original)
- IFN-α
- INTRON A
- IFN-β
- Rebif

Complex Biologics
- ETANERCEPT
- ADALIMUMAB
- HUMIRA (Adalimumab)
- BEVACIZUMAB
- AVASTIN (Bevacizumab)
- CETUXIMAB
- ERBITUX CETUXIMAB
- INFliximab
- Remicade
- Rituximab
- Herceptin

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Biosimilar ≠ Generic

Small molecule
- Proof of quality and bioequivalence
- No substantial clinical data required
- Reference to originator's data

Biological medicine
- Different manufacturing processes can and often do yield differences in the end product
- After the quality of a biological medicine is demonstrated, some non-clinical and clinical studies are necessary
- Immunogenic response cannot be predicted and therefore must be tested

Generics

Biosimilars

Biosimilar Development

Biological medicines due to come off patent (numbers)\(^2\)

2010–2015 (99)  
2016–2020 (91)  
Post-2020 (46)

Source:
2. Haag T (Lonza) and Krattiger C (GfK). The emergence of biosimilars—How are they different from generics and what are the implications from marketing? EphMRA presentation. June 29, 2011.

*All trademarks referenced herein are the property of their respective owners.*
<table>
<thead>
<tr>
<th>Country</th>
<th>Companies</th>
<th>Marketed biosimilars</th>
<th>Marketed alternative biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>Sandoz, Momenta, Merck (Bioventures Division), Pfizer, Lilly, Janssen, Protalix, Biotherapeutics, Momenta Pharma, Hospira, Itero, Phage Biotech, Baxter, Pharmacia-Upjohn, Teva</td>
<td>GH, heparin, rGlucagon, Calcitonin-Salmon, hyaluronidase, G-CSF</td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td>Sandoz, Hexal, Teva, Biopartners, Medice Arzneimittel Pütter, CT Arzneimittel, Ratiopharm, AstraZeneca, GSK, Novo Nordisk, Sanofi Aventis, Hospira</td>
<td>GH, EPO, G-CSF, somatropin hGH</td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>Sandoz, Daiichi Sankyo (Ranbaxy), JCR, Kissei, Nippon Kayaku, Nipro, Otsuka Holdings, Roche, Nektar Therapeutics</td>
<td>GH, G-CSF, GM-CSF, IL-2, Zenotech, EPO-kappa, IFNa</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>Bharat Biotech International, Dr. Reddy's Laboratories, Shantha Biotechnics Ltd, Wockhardt, Biocon, Intas Biopharmaceuticals, Lupin, Reliance Life Sciences, Zydu, Intas, Ranbaxy, Sanofi, CP GuoJian Pharmaceutical</td>
<td>GH, EPO, G-CSF, Peg-GSF, IFNa, insulin, teriparatide, mAbs, Regen-D (rhEGF), Indikina, se (streptokinase), Glargine, Lispro, Aspart, EPO, G-CSF, streptokinase, Rituximab, IL-2, IFNb, Etanercept</td>
<td></td>
</tr>
</tbody>
</table>

*GH and heparin approved in US under FFD&C Act via 505(b)(2) pathway
Source: Datamonitor strategic analysis pipeline trends December 2011; ADIS, EvaluatePharma and PharmaProjects May 2013
# 2012/2013 Global Clinical Use of Biosimilars and Alternative Biologics

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<th>Country</th>
<th>Companies</th>
<th>Marketed biosimilars</th>
<th>Marketed alternative biologics</th>
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</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>Probiomed, SICOR Biotech UAB, Pfizer</td>
<td></td>
<td>rEPO, R IFN alpha2B, IFN alpha2A, rHu G-CSF, Taliglucerase alfa</td>
</tr>
<tr>
<td>Brazil</td>
<td>Instituto Butantan, FK Biotecnologic, Bio-Manguinhos, Novo Nordisk, Pfizer, Aspen Pharmacare, Cristália, Enzon Pharmaceuticals, Silvestre Labs</td>
<td></td>
<td>Rh insulin, rEPO-α, monoclonal antibodies, Taliglucerase alfa, PEG-IFN alpha2b, G-CSF, EPO</td>
</tr>
<tr>
<td>Israel</td>
<td>Teva</td>
<td>HGH, IFN alpha2B, G-CSF</td>
<td></td>
</tr>
<tr>
<td>Switzerland</td>
<td>Biopartners, JW Group</td>
<td>Rh-insulin, rhGH, EPO-beta</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>Cangene, Biocon, Celltrion, Hospira, Roche, Nektar Therapeutics, Sandoz</td>
<td>hGH, R Insulin glargine, EPO-zeta, PEG-IFN alpha2A</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>Stada, Medice Arzneimittel Pütter</td>
<td></td>
<td>EPO-zeta, EPO</td>
</tr>
<tr>
<td>S. Africa</td>
<td>Bioclones</td>
<td></td>
<td>EPO</td>
</tr>
<tr>
<td>S. Korea</td>
<td>LG Lifescience, Daewoong, Dong-A, Celltrion, Boryung Group, CJ (CheilJedang), Genexine, Hanlim Pharm</td>
<td></td>
<td>Epogen, hGH, EPO, EGFR, GCSF, IFN alpha2A, follitropin, infliximab, EPO-alpha, hCG</td>
</tr>
</tbody>
</table>

*Source: Datamonitor strategic analysis pipeline trends December 2011; ADIS, EvaluatePharma and PharmaProjects May 2013*
Pathway to the Market: US and EU Biosimilar Development
Polling Question

Is your company currently developing a biosimilar or alternative biologic?

> Yes

> No
A similar biological or 'biosimilar' medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use and it does not have any meaningful differences from the reference medicine in terms of quality, safety or efficacy.

Article 8 of Directive 2001/83, as amended.

The PHS Act defines biosimilarity “to mean that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and…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.”

Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.
Biosimilar regulations in EU and USA: different stages of development

- The EU pioneered the development of biosimilar regulations
- US overarching guidelines issued
# Generics vs. Biosimilars

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Generics (chemical drugs)</th>
<th>Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Production source</td>
<td>Chemical synthesis</td>
<td>Living organisms, i.e. cultured yeast, bacteria or animal/plant cells</td>
</tr>
<tr>
<td>Active pharmaceutical ingredient</td>
<td>Must be identical to the reference product</td>
<td>Same primary amino acid sequence, the biosimilar active pharmaceutical ingredient is not identical to the reference product</td>
</tr>
<tr>
<td>Development batches</td>
<td>One batch</td>
<td>Generally more than three batches</td>
</tr>
<tr>
<td>Characterization</td>
<td>Non-comparative</td>
<td>Compared with reference product</td>
</tr>
<tr>
<td>In vitro non-clinical testing</td>
<td>No</td>
<td>Yes, compared with the reference product</td>
</tr>
<tr>
<td>Non-clinical animal testing</td>
<td>No</td>
<td>• Comparative PK/PD (if PD marker is available) in relevant species</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• One comparative repeat dose toxicity study in relevant species. If the relevant species is non human primates, FDA/EMA generally do not require an in- vivo non-clinical study unless it is absolutely needed</td>
</tr>
</tbody>
</table>
# Generics vs. Biosimilars

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<th>Parameter</th>
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<th>Biosimilars</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical – Phase I study</strong></td>
<td>Comparative PK/PD (if PD marker available) study in healthy volunteers</td>
<td>Comparative PK/PD (if PD marker available) in healthy volunteers or patients – scientific justification required</td>
</tr>
<tr>
<td><strong>Clinical – Phase III studies:</strong></td>
<td></td>
<td>Comparative clinical study (ies) required against the reference product; Number of studies required will depend upon the mechanism of action (MOA) for all indications. The number of studies required is assessed by regulators on a case-by-case basis</td>
</tr>
<tr>
<td>Safety (including immunogenicity) and efficacy</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacovigilance plan</strong></td>
<td>Generally not required, but depends on the drug</td>
<td>Generally required, often mimics reference product’s requirements, but may include additional data for the biosimilar</td>
</tr>
<tr>
<td><strong>Post-marketing studies</strong></td>
<td>Generally not required</td>
<td>Often may be required for late developing adverse events.</td>
</tr>
<tr>
<td><strong>Pediatric studies</strong></td>
<td>No</td>
<td>In the USA, pediatric studies must be addressed for a biosimilar; however, they are not required for products found to be interchangeable. Not required in the EU.</td>
</tr>
</tbody>
</table>
What should be characterized and compared with reference product?

> Comparison of physicochemical parameters (multiple lots of reference products and biosimilar)

  » Primary structures, such as amino acid sequence
  » Higher order structures, including secondary, tertiary, and quaternary structure (including aggregation)
  » Enzymatic post-translational modifications, such as glycosylation, phosphorylation, deamidation and oxidation, among others
  » N or C terminal truncations; charge variations (isoforms);
  » Degradants and impurities

> Stability profile
Biosimilars: Non-clinical Studies

What should be compared with reference product?

> In vitro studies- generally performed to assess any possible differences in bioactivity

  - Binding to target antigen
  - Binding to receptors
  - Fab associated functions (e.g., neutralization, receptor activation or receptor blockade)
  - Fc-associated functions (ADCC and CDC assays, complement activation)

> Safety pharmacology, reproduction, mutagenicity and carcinogenicity are generally not required

> In vivo studies-depend upon the need for additional information (residual uncertainty), and the availability of a relevant animal model

  - Generally, 28 day repeat dose toxicity study is required. If a relevant animal model not available, determine if transgenic animals or transplant models are available.
  - If the relevant animal model is a non-human primate, FDA/EMA generally do not require an in- vivo non-clinical study unless it is absolutely needed
Clinical Safety & Pharmacovigilance

Type of data required:

> Comparison of type, frequency and severity of adverse events

> Assessment of anti drug antibodies, including neutralizing antibodies (immunogenicity assessment)

> Because all differences cannot be detected pre-licensing, a risk assessment will need to be provided for late occurring safety events seen for the innovator product

> Risk management/ pharmacovigilance plan may be required:

  - Any PhV measures for the reference product generally will need to be adopted for the biosimilar product
  - Any differences seen for the biosimilar product will also need to be addressed
Immunogenicity: Risk Factors that Can Affect Immunogenic Response

**Patient Related**
- Underlying disease
- Immune status
- Concomitant medications
- Genetics
- Age
- Dosing schedule
- Route of administration
- Previous exposure to related proteins

**Product Related**
- Manufacturing process
- Varying glycosylation
- Degradation products
- Formulation
- Structural homology
- Post translational modifications
- Chemical modifications
- Impurities from host cells
- Stability
Biosimilar Product Development

If US or EU only

Both agencies expect a step-wise development plan that can ensure similarity/comparability at each step. The reference product (active comparator) has to be sourced from the respective region. All assessments will be two way comparability.

- Chemistry Manufacturing and Controls- Analytical comparability
- Non-clinical comparability - in vitro and in vivo (if relevant animal model is available)
- Human PK/PD (if PD biomarker is available) comparability data
- Immunogenicity comparability data
- Efficacy and Safety comparability data
Biosimilar Product Development

*If both for US and EU*

- Both agencies expect a **step-wise** development plan that can ensure similarity/comparability at each step.

- Three way comparability for the following:
  - Chemistry Manufacturing and Controls - Analytical comparability
  - Non-clinical comparability - in vitro and in vivo (if relevant animal model is available)
  - Human PK/PD (if PD biomarker is available) comparability data

- Two way comparability for the following (reference product can come from either region):
  - Immunogenicity comparability data
  - Efficacy and Safety comparability data
Extrapolation to other Indications

• The mechanism of action (MOA) in each condition of use for which licensure is sought may include the following:
  > The target/receptor(s) for each relevant activity/function of the product
  > The binding, dose/concentration response, and pattern of molecular signaling upon engagement of target/receptor(s)
  > The relationship between product structure and target/receptor interactions
  > The location and expression of the target/receptors(s)

• The PK and bio-distribution of the product in different patient populations; PD measures may provide important information on MOA

• Differences in expected toxicities in each condition of use and patient population

• Any other factor that may affect the safety or effectiveness of the product in each condition of use and patient population for which licensure is sought
Market Access Challenges and Stakeholder Perspectives
Polling Question

What information would you want to consider before prescribing/ reimbursing/ taking a biosimilar?

> RCT data only
> RCT and post-marketing safety data
> RCT and any non-interventional data on safety and effectiveness
> Trusted expert opinion would suffice
Innovation and Competition: Will Biosimilars Succeed?

Are biosimilars safe and effective?

The creation of an FDA approval pathway for biosimilars is complex and fraught with hazard. Yes, innovation and market competition are at stake. But so are efficacy and patient safety.

Biologics go through a Biologics License Application (BLA) process. The FDA is developing a pathway for approving biosimilars through an abbreviated BLA (aBLA) process, and the first applications are expected to be for biosimilars already approved in the EU (Table).

Biosimilars in the EU are usually

Source: Blackstone EA, Fuhr JP. Biotechnol HealthCare; Spring 2012
Do clinicians consider marketed biosimilars a treatment option?

Market Access Challenges

How Will Biologics Fit Into Healthcare Reform?

With so many variables, it’s hard to predict what kind of market will exist for biologics and other specialty drugs in 2014. Current trends may provide some insight.

What impact will biosimilars have on costs?

Oct. 6, 2011, could become a red-letter day in the annals of healthcare policy. On that day, the Institute of Medicine took a big step forward in the national discussion about the finite quality of healthcare technologies — and are causing some lost sleep among health plans, providers, and manufacturers.

“Everyone’s got a bull’s eye on biologics because they are the fastest-growing trend in the healthcare sector,” says Dia Batali, PharmD, MPH, operating in 2014, are under pressure to limit premiums. Individuals who can’t find coverage at a cost of 8 percent or less of income are exempt from the individual mandate.

Source: Dalzell MD. Biotech Healthcare; Winter 2011
What’s considered a “clinically meaningful difference”?

Are there data on biosimilar effectiveness in real-world settings?
## Top 3 Interests of Stakeholders

<table>
<thead>
<tr>
<th>Interests</th>
<th>Stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regulators</td>
</tr>
<tr>
<td>Safety (including immunogenicity)</td>
<td>1</td>
</tr>
<tr>
<td>Effectiveness</td>
<td>3</td>
</tr>
<tr>
<td>Costs</td>
<td>1</td>
</tr>
<tr>
<td>Treatment heterogeneity</td>
<td>2</td>
</tr>
<tr>
<td>Delayed risks and benefits</td>
<td>2</td>
</tr>
<tr>
<td>Off-label use</td>
<td></td>
</tr>
</tbody>
</table>

Source: Consultation with regulators; review of literature, guidance documents and regulatory requirements; clinical opinion
Registry Design and Implementation Considerations
Multipurpose Goals of Patient Registries

**Regulators**
- meet commitments
- demonstrate safety
- prove value
- secure reimbursement
- generate publications
- create relationships

**Payers**
- determine value and coverage
- monitor usage within criteria

**Patients**
- My own health - what choices do I have?
- What are the risks/benefits?

**Physicians**
- obtain evidence
- advance science
- improve care
- help to ensure reimbursement

**Industry/Sponsors**
- detect safety signals
- help to ensure long-term effectiveness and outcomes
Registry Design and Implementation Considerations

• Attribute safety and effectiveness outcomes to the correct product

• Accurate identification of the biosimilar versus the originator product is critical
  - Switching
  - Interchangeability
  - Concomitant meds and other conditions
Registry Design and Implementation Considerations

*Choice of comparator groups may depend on the product’s availability and clinical practice in local countries*
Registry Design and Implementation Considerations

Clinical Meaningful Outcomes

Safety & Clinical Effectiveness
- Identify from originator product

Treatment Heterogeneity
- Explanatory variables

Delayed Risks & Benefits
- Evaluate long-term* outcomes from chronic use

*“long-term” could simply mean longer than a typical 16-week RCT or it could be 5-10 year survival rate, which may be an unrealistic expectation
Registry Design and Implementation Considerations

Confounding

Concomitant Treatments

Distinguish effects from concomitant treatments (e.g., methotrexate)

Channeling Bias

• Physician preference
• Availability and affordability of products
Registry Design and Implementation Considerations

Investigator Interest (not usually RCT)

Publication opportunities

Site Burden

- Minimize administrative burden
- Reduce data collection burden
  - Paper-based medical charts
  - Collect product trade name and batch number
Registry Design and Implementation Considerations

Patient Attrition

Patients may not return to enrolling physician or complete treatment course

• Track patient visits
• Send reminders to sites for upcoming visits
• Collect primary physician contact information
• Consider various modalities depending on target population, e.g., email, text messaging
Build an Evidence Base to Support Decision Making

Use registries and other observational study designs to:

- Generate evidence for safety and effectiveness of biosimilars
- Support decision-making across multiple stakeholder perspectives
Case Study:
A real-world biosimilar research paradigm
Case Study

Strategic application of observational study data

Chart Review

Prospective Disease Registry

Prospective Product Registry

> Chart review to understand treatment practices and customary documentation
> Build relationships with providers and characterize sites
> Test feasibility and assumptions for prospective studies

> Launch disease registry to describe current treatments
> Include direct data collection from health care professional and/or patients
> Augment with other available data, as appropriate

> Adapt disease registry to product registry and/or safety study after market authorization
> Consider including patients from RCT for longer-term follow-up

- Generate clinically meaningful publications about the natural history of disease
- Establish availability of data that will be used to support regulatory and payer needs
Conclusions

• Many patents of biologics will be expiring soon
• Expect the availability of biosimilars and/or copy biologics to increase across the globe
• Registries can serve many purposes and can be used to address multiple needs of various stakeholders
• Careful design and implementation of registries will generate quality evidence to support decision-making
Contact Information

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kamali.chance@quintiles.com
Upcoming Events

Safety Evaluation in Post-Marketing Environment

September GRP Webinar

Safety Evaluation in the Post-Marketing Environment: Overview & Analytical Considerations

- Tuesday, September 24, 2013 10:00 AM - 11:00 AM EDT
- Register Online: https://www1.gotomeeting.com/register/890442200