Biosimilars - Boon or Bane?
Rutgers Business School

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Avalere Health | An Inovalon Company
20 April, 2016
**Biologic:** Worldwide, a simple and practical definition of a biologic is a product the active ingredient of which is made in a living system.

**Biosimilar:** A biological product that is approved based on a showing that it is highly similar to an already approved biological product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product.

**Interchangeable Biologic:** FDA designation that switching patients between such products can be made by a pharmacist.

*BIOSIMILARS ARE TO BIOLOGICS, AS GENERIC ARE TO DRUGS*
Introduction – Biologics are not New

BIOLOGICS HAVE A LONG AND WELL-ESTABLISHED REGULATORY HISTORY

- **Late 18th Century**
  - First reliable Vaccine – Vaccinia for small pox

- **Early 20th Century**
  - PHS Act and early naturally-sourced products

- **Mid 20th Century**
  - Antibiotics
  - Globalization of scientific discoveries
  - Current good manufacturing practices (cGMPs)

- **Late 20th Century**
  - Proliferation of blockbuster small molecule drugs
  - Emergence of the biotechnology industry
  - Beginning of the generic revolution and competition as the stimulus to innovation
  - Globalization of manufacturing
  - International naming conventions established
  - Genome Project ("Big Data")

- **Early 21st Century**
  - Patent cliff in the highly regulated markets
  - Biotech becoming mainstream
  - Multiple special regulatory programs in the highly regulated markets including biosimilars
  - Quality is paramount
  - Globalization in demands for access
“Alternative” Biologics are NOT Biosimilars

THEY ARE NOT “HIGHLY SIMILAR” & NOT APPROVED IN HIGHLY REGULATED MARKETS

- Alternative biologics are not biosimilars but they can and do serve a local market need. However, most of these products are unlikely to achieve global market access.
- Products that are not highly similar should be expected to undergo greater preclinical and clinical evaluation.
- Abbreviated clinical programs are appropriate for those biologics shown to match analytically.

Isoelectric focusing gels

Alternative biologics ≠ biosimilar\(^1\)

Approved biosimilar in EU\(^2\)

NOT similar to Reference E

No difference between reference and biosimilar

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Biologics Vary in Complexity – Even Recombinant Ones

MANY ARE COMPLEX MIXTURES THAT VARY BATCH-TO-BATCH AND OVER TIME

A  Aspirin, 21 Atoms
B  ACE-Inhibitor Ramipril, 62 Atoms
C  Insulin, ca. 790 Atoms
D  Monoclonal Antibody, ca. 20000 Atoms

“Soup”
(Not drawn to Scale)

Derived from a slide presented by Brockmeyer Biopharma GmbH
Source: VFA 2010
Historical Patterns of Drug Development

Derived from a side developed by Mateja Urlap.
Global versus Regional Considerations for all Medicines

**GLOBAL**

<table>
<thead>
<tr>
<th>ACCESS</th>
<th>EUROPEAN PATIENTS ARE EVERYWHERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCIENCE</td>
<td>ESSENTIALLY GLOBAL</td>
</tr>
<tr>
<td>COMPANIES DEVELOP AND MANUFACTURE</td>
<td>FOR MORE THAN ONE MARKET¹</td>
</tr>
<tr>
<td>NAMING</td>
<td>HISTORICALLY HAVE HAD GLOBAL NORMS²</td>
</tr>
</tbody>
</table>

**REGIONAL/NATIONAL**

| Regulations are regional with some harmonization for drugs, and innovator biologics |
| IP varies, and getting a little better harmonized, but barely |
| Healthcare systems vary |
| Determines commercialization (ROI, 1y & 2y markets) |

**TIMING OF PRODUCT APPROVAL AND LAUNCH ALWAYS MATTERS**

**PATIENT ACCESS REQUIRES APPROVAL & COMPETITION BASED ON VALUE**

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2. WHO Administers the International Nonproprietary Naming conventions, see: [http://www.who.int/medicines/services/inn/en/](http://www.who.int/medicines/services/inn/en/)
Biologic Approvals Have Increased and are Expected to Rise

As medicines in development move through the pipeline, the expansion of the biologics market is expected to dramatically increase

1. FDA. “Drug and Biologic Approval Reports.” Not including vaccines and blood products
Manufacturing Changes are a Regulatory Norm: Each Biologic becomes “Biosimilar” to itself

A PRODUCT THAT IS “HIGHLY SIMILAR” HAS THE “SAME” ACTIVE INGREDIENT, AND THE CLINICAL OUTCOME IS EXPECTED TO BE THE “SAME”

Each manufacturing change is approved by the regulators in that jurisdiction:

- Complete extrapolation between all indications
- Interchangeability
- The patient/HCP is not informed of the change because the label on the product does not change - the nonproprietary name stays the same when high similarity is established

THE GOOD NEWS:
Huge experience with the reference products amongst all stakeholders

The Regulatory Concept of Biosimilarity

BIOSIMILARITY IS GROUNDED IN ANALYTICAL HIGH SIMILARITY – WHICH IS NECESSARY BUT NOT SUFFICIENT

351(a) Standalone BLA

- Establish Safety, Purity and Potency a priori
- Clinical Phase 1, 2 & 3 Studies
  Comparator is current standard of care

ClinPharm

Non-Clinical

R&D:
Lead Selection

Every stage is standalone

351(k) Biosimilar

Switching Studies

Confirmation of biosimilarity

Clinical

ClinPharm

Non-Clinical

Analytical:
establish high similarity

Every stage is head-to-head comparison of the biosimilar candidate and the reference originator

Derived from a slide presented by Steve Kozlowski, FDA at EGA 2014

Requirements for Biosimilars Vary Across Highly Regulated Markets because the Laws Differ

HOWEVER, DEVELOPMENT PROGRAMS ARE INCREASINGLY MULTI-JURISDICTIONAL

- First Biosimilar Approval (2006) - 22 Approved to-date (13 separate molecules) • Follows EMA guidelines
- First Biosimilar Approval (2009) - 8 Approved to-date • Follows ICH guidelines
- First Biosimilar Approval (2010) - 10 Approved to-date • Follows EMA guidelines
- First Biosimilar Approval (2009) - 3 Approved to-date • Follows Health Canada guidelines
- First Biosimilar Approval (2009) - 3 Approved to-date • Follows ICH guidelines
- First Biosimilar Approval (2006) - 22 Approved to-date (13 separate molecules) • Follows EMA guidelines
- First Biosimilar Approval (2010) - 10 Approved to-date • Follows EMA guidelines

In Europe Biosimilars are Becoming Established

**EUROPE IS LEADING IN THE DEVELOPMENT AND APPROVAL OF BIOSIMILARS**

<table>
<thead>
<tr>
<th>Year</th>
<th>Product</th>
<th>Molecule / INN</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Omnitrope®</td>
<td>Somatropin</td>
<td>Sandoz</td>
</tr>
<tr>
<td></td>
<td>Binocrit®</td>
<td>Epoetin alfa</td>
<td>Sandoz</td>
</tr>
<tr>
<td></td>
<td>Epoetin alfa HEXAL®</td>
<td>Epoetin alfa</td>
<td>Hexal</td>
</tr>
<tr>
<td></td>
<td>Abseamed®</td>
<td>Epoetin alfa</td>
<td>Medice</td>
</tr>
<tr>
<td>2007</td>
<td>Silapo®</td>
<td>Epoetin zeta</td>
<td>Stada</td>
</tr>
<tr>
<td></td>
<td>Retacrit®</td>
<td>Epoetin zeta</td>
<td>Hospira</td>
</tr>
<tr>
<td></td>
<td>Biographics®</td>
<td>Filgrastim</td>
<td>CT Arzneimittel</td>
</tr>
<tr>
<td></td>
<td>Ratiograstim®</td>
<td>Filgrastim</td>
<td>Ratiopharm</td>
</tr>
<tr>
<td></td>
<td>Tevagrastim®</td>
<td>Filgrastim</td>
<td>Teva</td>
</tr>
<tr>
<td>2008</td>
<td>Filgrastim HEXAL®</td>
<td>Filgrastim</td>
<td>Hexal</td>
</tr>
<tr>
<td></td>
<td>Zarzio®</td>
<td>Filgrastim</td>
<td>Sandoz</td>
</tr>
<tr>
<td>2009</td>
<td>Nivestim®</td>
<td>Filgrastim</td>
<td>Hospira</td>
</tr>
<tr>
<td>2010</td>
<td>Grastofil®</td>
<td>Filgrastim</td>
<td>Apotex</td>
</tr>
<tr>
<td></td>
<td>Remsima®</td>
<td>Infliximab</td>
<td>Celltrion</td>
</tr>
<tr>
<td></td>
<td>Inflectra®</td>
<td>Infliximab</td>
<td>Hospira</td>
</tr>
<tr>
<td></td>
<td>Ovaleap®</td>
<td>Follitropin alfa</td>
<td>Teva</td>
</tr>
<tr>
<td>2013</td>
<td>Bemfola®</td>
<td>Follitropin alfa</td>
<td>Finox Biotech AG</td>
</tr>
<tr>
<td></td>
<td>Accofil®</td>
<td>Filgrastim</td>
<td>Accord</td>
</tr>
<tr>
<td></td>
<td>Abasria®</td>
<td>Insulin glargine</td>
<td>Lilly (BI)</td>
</tr>
<tr>
<td>2016</td>
<td>Benepali®</td>
<td>Etanercept</td>
<td>Samsung Bioepis</td>
</tr>
<tr>
<td></td>
<td>Flixabi® (positive opinion 1Apr16)</td>
<td>Infliximab</td>
<td>Samsung Bioepis</td>
</tr>
</tbody>
</table>

EUROPE IS LEADING IN THE DEVELOPMENT AND APPROVAL OF BIOSIMILARS; HOWEVER THE US HAS MORE EXPERIENCE WITH “GENERIC BIOLOGICS”

<table>
<thead>
<tr>
<th>Year</th>
<th>Product</th>
<th>Molecule / INN</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004/ 05</td>
<td>[Vitrase®, Amphadase®, Hydase®, Hylenex Recombinant®]</td>
<td>[Hyaluronidase]</td>
<td>[Bausch and Lomb, Amphastar Pharm, Akorn Inc, Halozyme Therap]</td>
</tr>
<tr>
<td>2006</td>
<td>[Omnitrope® using 505(b)(2)]</td>
<td>[Somatropin]</td>
<td>[Sandoz]</td>
</tr>
<tr>
<td>2010/ 12/ 14</td>
<td>[Enoxaparin 505(j)]</td>
<td>Enoxaparin</td>
<td>[Sandoz, Amphastar, Teva]</td>
</tr>
<tr>
<td>2015</td>
<td>Zarxio®</td>
<td>Somatropin-sndz</td>
<td>Sandoz</td>
</tr>
<tr>
<td>2016</td>
<td>Inflectra®</td>
<td>Infliximab-dyyb</td>
<td>Celltrion</td>
</tr>
</tbody>
</table>

FDA draft guidance on Implementation of the “Deemed to be a License” Provision of the Biologics Price Competition and Innovation Act of 2009. Some of these biologic drugs “rollover” to become biologics and biosimilars.

Source: [http://www.FDA.gov](http://www.FDA.gov)
Analytics establish “High Similarity/ Similarity” and therefore biosimilarity; functional studies support this conclusion. Targeted clinicals confirm biosimilarity. Reduce residual uncertainty.

One or more indications - clinical studies in each indication expected.

Multiple Indications (clinical studies in each not required).

PK/PD = pharmacokinetics and pharmacodynamics
ImmGen = immunogenicity
# Regulatory Development of Biosimilars Invokes Aspects of Both Originator Products and Generics

<table>
<thead>
<tr>
<th>Small Molecule Generic</th>
<th>Biosimilar/Interchangeable Biologic</th>
<th>Novel Molecular Entity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Already therapeutic options, but may be lack of access through affordability challenges</td>
<td>Unmet need: Lack of therapeutic options</td>
<td></td>
</tr>
<tr>
<td>Established MOA</td>
<td>Often novel mechanism of action (MOA)</td>
<td></td>
</tr>
<tr>
<td>Routine analytics</td>
<td>Exceptional Analytics (&quot;fingerprint-like&quot;)</td>
<td>Routine analytics</td>
</tr>
<tr>
<td>Limited confirmatory clinicals (BE)</td>
<td>Tailored clinical studies to confirm biosimilarity</td>
<td>Broad clinical development program</td>
</tr>
<tr>
<td>Relies on prior finding of safety and efficacy of reference</td>
<td>Demonstration of de novo efficacy &amp; safety</td>
<td></td>
</tr>
<tr>
<td>Clinical expertise unnecessary</td>
<td>Expertise in therapeutic area fundamental</td>
<td></td>
</tr>
<tr>
<td>Quality Manufacturing Essential (cGMP)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FDA News Release

FDA approves first biosimilar product Zarxio

For Immediate Release
March 6, 2015

Release

The U.S. Food and Drug Administration today approved Zarxio (filgrastim-sndz), the first biosimilar product approved in the United States.

Filgrastim-sndz described as “placeholder nonproprietary name”

Launched September 3, 2015
FDA Approves Second Biosimilar

FDA News Release

FDA approves Inflectra, a biosimilar to Remicade

For Immediate Release  April 5, 2016

Release

The U.S. Food and Drug Administration today approved Inflectra (infliximab-dyyb) for multiple indications. Inflectra is administered by intravenous infusion. This is the second biosimilar approved by the FDA.

Inflectra is biosimilar to Janssen Biotech, Inc.’s Remicade (infliximab), which was originally licensed in 1998. Inflectra is approved and can be prescribed by a health care professional for the treatment of:

- adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn’s disease who have had an inadequate response to conventional therapy;
- adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;
- patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;
- patients with active ankylosing spondylitis (arthritis of the spine);
- patients with active psoriatic arthritis;
- adult patients with chronic severe plaque psoriasis.

- Approved for all indications of the reference product Remicade® (infliximab) with Orphan carve out
- Essentially the same label
- Biosimilarity Statement
- Meaningless Suffix to USAN
- Interesting reference to the non-approved Orphan indication
Life Cycle Management of Originator Biologics has Started

COMPLETE EXTRAPOLATION BEFORE CONSIDERING INTERCHANGEABILTY?

In BPCIA, there is no link between extrapolation and interchangeability, but opportunity for LCM is inviting originator companies to add orphan indications

- **Neupogen® (filgrastim)**\(^{20Feb91}\) reference for biosimilar Zarxio® (filgrastim-sndz)\(^{6Mar15}\):
  - Filgrastim - Treatment of subjects at risk of developing myelosuppression after a radiological or nuclear incident (designated 20Nov13\(^1\)), Orphan added to Neupogen 30Mar15. Post market commitment but dependent on an “Event”
  - Neupogen® has been part of USG WMD stockpile for many years
- **Humira® (adalimumab)**\(^{31Dec02}\)
  - Pediatric Crohn’s disease patients aged 6 years or older (Orphan added 23Sep14\(^2\))
  - Polyarticular Juvenile Idiopathic Arthritis (pJIA) in patients 2 to less than 4 years of age (Orphan added 30Sep14\(^3\))
  - Clinical studies on additional indications underway
- **Orphan studies underway for Procrit®, Remicade®, Herceptin®, Rituxan®, Avastin®**

Labeling carve-outs occur for generics – but this means originators stop adding indications as soon as generics are available. For biosimilars, carve-outs expected, but if Orphan exclusivity prevents interchangeability it may offer additional opportunities

1. [http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=413113](http://www.accessdata.fda.gov/scripts/opdlisting/oopd/OOPD_Results_2.cfm?Index_Number=413113)
2. [http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125057Orig1s356ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125057Orig1s356ltr.pdf)
3. [http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125057Orig1s367ltr.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2014/125057Orig1s367ltr.pdf)
What’s in a name?

LLANFAIRPWLLGWYNGYLLGOGERYCHWYRNDROBWLLLLANTYSILOLOGOGOGOCH

Welsh Weatherman Correctly Pronounces a 58-Letter Town Name Without Batting an Eye

by Lori Dorn at 8:48 pm on September 9, 2015

While reporting on the warm weather in Wales, broadcaster Liam Dutton correctly pronounced the name of the 58-letter town Llanfairpwllgwyngyllgogerychwyrndrobwllllantysillogogogoch without batting an eye or breaking a sweat. In fact, Dutton announced on Twitter that he’d be talking about the town in his broadcast and was really appreciative of the growing admiration for his performance.

Is There Any Such Thing as a Meaningless 4-Letter Word?

CURRENT NONPROPRIETARY NAMES FOR BIOLOGICS WILL LIKELY CHANGE

“FDA is proposing to take action with respect to these six products because of the need to encourage routine usage of designated suffixes in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices for the biological products subject to this rulemaking”

FedReg 28Aug15 Docket FDA-2015-N-0648

The FDA proposal should NOT be confused with the WHO Biologics Qualifier (BQ) proposal:
• WHO BQ is separate from nonproprietary name;
• Not yet implemented, is voluntary and at the election of local regulators;
• Product specific and cannot contain any proprietary information (such as company name)

FDA has not finalized its Naming Rule, nor its Naming Guidance, however:
• Inflectra™ (infliximab-dyyb) certainly appears to have a meaningless suffix (Remicade® will become infliximab-hjmt if the rule is finalized)
• “Remicade®” is used on the biosimilar label as part of the biosimilarity statement
• All other aspects of the label are essentially the same
A slew of Guidance Activity at FDA

Along with education and commentary from FDA,

From our perspective:


Promised in 2016:

**CATEGORY – Biosimilarity**

- Considerations in Demonstrating Interchangeability With a Reference Product
- Labeling for Biosimilar Products
- Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity

**Implementation of the Provision of “Deemed to be a License” Covered Biologics Price Competition and Innovation Act of 2009**

**Labeling for Biosimilar Products**
What is the Initial Market for a Biosimilar?

Anti-TNF Market Share by US Revenue 2015

- Humira: 43%
- Enbrel: 26%
- Remicade: 23%
- Cimzia: 4%
- Simponi: 4%

Total $19.5 Billion

For example: Remicade® (infliximab)

Initial market may be:
- Naïve patients who would otherwise get Remicade®
- All Remicade® market = $4.45 Billion
- Entire anti-TNF market (depending on indication) = $19.5 Billion

Source: Gal personal communication
### CMS Coding for Biosimilars & their Reference Product

<table>
<thead>
<tr>
<th>Originator Reference</th>
<th>Biosimilar 1</th>
<th>Biosimilar 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Code A</td>
<td>Code B</td>
<td>Code C</td>
</tr>
<tr>
<td>Code A</td>
<td>Code B</td>
<td>Code B</td>
</tr>
<tr>
<td>Code A</td>
<td>Code A</td>
<td>Code A</td>
</tr>
</tbody>
</table>

- **Position biopharma advocates**: Current CMS position shared codes for biosimilars
- **Generic drugs share code with reference**: Either biosimilar could be designated as interchangeable; this does not change the coding.
## Biosimilars Represent a New Commercial Model

<table>
<thead>
<tr>
<th>Estimated Initial Development Costs</th>
<th>Driver of Sales</th>
<th>Value for Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand Biologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$1.4 Billion</td>
<td>Brand Biologic</td>
<td><strong>Brand:</strong> Innovative new medicines, premium prices (high margin) Initial LOW volume</td>
</tr>
<tr>
<td>&lt;$250 Million</td>
<td>Interchangeable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detailing</td>
<td></td>
</tr>
<tr>
<td><strong>Biosimilar</strong></td>
<td></td>
<td><strong>Biosimilars:</strong> Cost to patients will depend on development cost for market access and payor uptake (market share)</td>
</tr>
<tr>
<td>$1-5 Million</td>
<td>Generic Drug</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interchangeable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low Price</td>
<td></td>
</tr>
<tr>
<td><strong>Generic Drug</strong></td>
<td></td>
<td><strong>Generic:</strong> Established products at lower prices (low margin) Initial HIGH volume</td>
</tr>
<tr>
<td>$1-5 Million</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Initial development costs decided by the extent and cost of studies FDA requires for product approval; details for biosimilars remain uncertain.
Commercialization of Any Biologic is Case-by-Case

Sponsors Have to Weigh the Risks and Benefits of Each Pathway for Each Product to Decide Which Path Will Present the Greatest Potential Return on Investment in Each Market

<table>
<thead>
<tr>
<th>351(a) “Standalone” BLA</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Data exclusivity 12 years (+)</td>
</tr>
<tr>
<td>• Clinical trials required (-)</td>
</tr>
<tr>
<td>o One indication</td>
</tr>
<tr>
<td>o All indications</td>
</tr>
<tr>
<td>• Patents independently litigated</td>
</tr>
<tr>
<td>• Known payer/physician/consumer perceptions regarding new entrants in a product “class”*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>351(k) “New” Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Limited exclusivity (1 year, 1st IC) (-)</td>
</tr>
<tr>
<td>• Extrapolation (+++)</td>
</tr>
<tr>
<td>• Interchangeability (++)</td>
</tr>
<tr>
<td>• Compulsory patent provisions(-)</td>
</tr>
<tr>
<td>• Regulatory uncertainty – highly similar a high standard</td>
</tr>
<tr>
<td>• Unknown payer/physician/consumer perceptions</td>
</tr>
</tbody>
</table>

Extrapolation Between Indications is Key to Successful Biosimilar Development

* Not a regulatory term, but is a term used in BPCIA (but undefined)
For more information /

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