Biosimilars: A 2018 Update

Jim Koeller, MS
Professor
University of Texas at Austin & the
Health Science Center, San Antonio, TX

Learning Objectives

- Describe the science and process related to biologic and biosimilar manufacturing and commercialization
- List 2 of the most recent FDA guidance’s on biosimilars and explain how they may impact your institution
- List the current FDA approved oncology biosimilars and the impact they may have on the US market
- Describe the current oncology biosimilar pipeline and what products we can expect in the next couple years

Koeller’s Key Terms

- Biosimilar
- Variability - Comparability
- Quality of Design – Quality Attributes
- Developmental Paradigm Shift
- Fingerprint-Like Analysis
- Totality of Evidence
- Extrapolation
- Interchangeability

Koeller’s First Law:
Biosimilars ARE NOT Generics!

How are Biosimilars Defined in the United States?

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

Biosimilars must demonstrate safety, purity, and potency

FDA. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. April 2015.

Biologics & Small-Molecules Are Different

Filgrastim
18,800 daltons

Aspirin
180 daltons

Rituxan
143,860 daltons

Biologics

Small-Molecule Drugs

Filgrastim: 18,800 daltons

Rituxan: 143,860 daltons

- Size & Complexity

Biosimilars

- The biosimilar category was not created to repeat the entire product developmental program.
- The goal of biosimilar development is to demonstrate no clinically meaningful differences based on the totality of evidence, NOT to reestablish the total clinical benefit of a product.
  - Otherwise, cost savings could not be realized.

Potential misunderstandings when comparing biosimilars to reference products

- "The sentence 'biosimilar and biological reference medicines are similar but not identical' (...) is perhaps one of the most frequently misunderstood sentences in the history of biosimilars and has almost become a mantra when raising concerns around biosimilars."

- "No batch of any reference product is 'identical' to the previous one—'non-identicality' is a normal feature of biotechnology that has to be controlled by tight specifications of critical product attributes, within current technical and scientific limitations (inherent variability)."

- Normally, "manufacturing processes are updated during the life cycle of any medicine, and this is welcome as these are often improvements."


Figure adapted from Millstedt H. Ann Oncol. 2008;19:411-414.

Heterogeneity (Variability) in Biologics

- Biologics are "molecular population" and express heterogeneity.
  - Biologics consist of a mix of chemically complex structures and isoforms.

Potential Sources and Examples of Heterogeneity:
- Glycosylation
- Methylation/acylation
- Phosphorylation/ubiquitination
- Conformation
- Aggregates
- Dissociation
- Substitution
- Oxidation

- Manufacturers carefully control heterogeneity to help assure batch constancy.
  - The product's quality attributes have to remain within a prespecified range.

FDA Guidance on Product Comparability

- Manufacturing processes of biologics undergo changes after approval.
  - "Intended changes may be implemented during production or translate to alternative facility.
  - Process changes extensively characterized through comparability studies.
  - Assess potential impact of observed differences on safety profile or efficacy.
  - The comparability exercise is an in-depth protocol that part of postapproval changes and undergoes health authority review.
**Biologics Manufacturing Changes**

(European Manufacturing Data)


Robust Analytical Testing Is Used To Establish High Similarity To The Reference Product

"Advances in manufacturing science... may facilitate ‘fingerprint-like’ analysis." 2

- Analytical testing is a major component of biosimilar development.1
- Fingerprint-like analysis covers product attributes and their combinations.2
- Advanced analytical tools such as peptide mapping to evaluate proteins are available.
- More than 1 test method may be used to measure a single quality attribute.1

Analytic comparisons for a biosimilar are likely to be more extensive and comprehensive than those made for reference biologics after a manufacturing change.

---

**Fingerprint Analyses**

- Physicalchemical Properties
- Primary Sequence
- Phosphorylation
- Phosphate Measurement
- Secondary Structures
- Tertiary Structures

---

**Comparative Clinical Trials**

Comparative safety and effectiveness data will be necessary if there are residual uncertainties about the biosimilarity of the two products.

---

**Totality of Evidence Used to Support Biosimilarity and Extrapolation**

- The FDA is taking a ‘totality of evidence’ approach to biosimilar approvals:
  - Builds on the extensive clinical knowledge base of the biologic reference product.
  - Robust analytical characterization and preclinical assessment that does not show any ‘clinically meaningful differences’.
  - Reduces need for extensive animal and clinical testing.
  - Immunogenicity testing always required.

Fingerprint Analyses

Bioactivity Analyses

Signal Transduction

Effective functions

Catalysis

---

1. FDA. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. April 2015.
Extrapolation of Indications

- Extrapolation of indications will not be automatic, scientific justification will be required for additional indication

Interchangeable

- To be found ‘interchangeable’ a product must:
  - Be expected to produce the same clinical results as the reference product
  - If the product is administered more than once to a patient, the risk associated with switching between products cannot be greater than repeated treatment with the reference product
  - This would necessitate cross-over trials (or some call them switching trials)...
  - With this designation, pharmacist can switch out without a physician’s approval

What Have We Learned So Far?

- Biosimilars ARE NOT generics
- Variability exists in current biologics
- Current Biologics have inherent variability and need to be acknowledged
- The process for the development and verification of a biosimilar is quite extensive utilizing fingerprint-like analysis
- The review of a biosimilar will need to be somewhat different and more extensive than the review of a standard generic

What Should Be The Review Process For Bringing a Biosimilar Into Your Practice?

Formulary System

- The key for market access to various providers (hospitals, healthcare networks, practice management groups, etc), is through the Formulary process
- Based on that, what information is needed by formulary committee’s to make an ‘informed’ product decision?

The ‘BIG 3’ Formulary Considerations

- Efficacy
- Safety
- Financial
Biosimilar Evaluation Template

• Three categories for review consideration:
  – Product
  – Manufacturing
  – Institution Specific & Economic

• Once reviewed and deemed a ‘biosimilar’ will you then ‘allow’ substitution or selected utilization?


So, Where do we stand right now with Biosimilars in the the US?

FDA Guidance Activities

• Naming:
  – All biosimilars will have a random 4-letter suffix
  – Filgrastim-sndz (Sandoz/Novartis)
• In Jan., 2017 the FDA put out a proposed rule for a biosimilar to be designated ‘interchangeable’
  – Comment period ended in June and over 50 comments were received and no one was happy…
  – Must meet ‘additional’ standards beyond biosimilarity
    • Questions remain on the use of a foreign reference product
    • Still waiting for the final rule...

Interchangeability

– No greater risk in terms of safety or efficacy in alternating between the reference and the biosimilar
– Would require studies which switched back and forth 2 full times and then back to the reference
  • (ref. - biosimilar - ref. - biosimilar - ref.)
  • Are switching trials needed for one indication or more?
    – Clearly the industry wants more specific directions!

• Note: A single transition or conversion from a reference to a biosimilar can be done now
  – Most current biosimilar clinical trials include a single transition step (and moving forward they must…)

Koeller’s Second Rule:
Just Because it’s FDA Approved, Doesn’t Mean it’s Commercially Available…
(Months to Years of Litigation Could Ensue)

Patent Litigation

• In June of 2017, the US Supreme Court rules that the biosimilar ‘patent dance’ is not mandatory!
  – The issue before the supreme court was at what point was the 180-day marketing notice due to the reference company from the biosimilar company
    • This was based on the Sandoz appeal of Appeals Court win by Amgen
      – At the time of FDA approval or prior to the approval date
      – Biosimilar companies argued that waiting till FDA approval gave the reference company an extra 6 months of exclusivity
      – The supreme rules biosimilars did not have to wait till FDA approval
    – The original intent of this data sharing, was for the reference company to have time to review the biosimilar companies product to look for patent problems, thus the term ~ ‘patent dance’
    – In the supreme courts ruling, they stated that the need to provide commercialization materials is not mandatory by federal law, but would come under state law (eg., CA)
Currently, there are 5 approved agents

- Zarxio® (filgrastim-sndz) – Sandoz/Novartis (3/15)
- Mvasi® (bevacizumab-awwb) – Amgen/Allergan (9/17)
- Ogivri® (trastuzumab-dkst) - Mylan/Biocon (12/17)
- Fulphila® (pegfilgrastim-jmdb) – Mylan/Biocon (6/18)
- Retacrit® (epoetin alfa-epbx) – Pfizer/Hospira

Zarxio® (filgrastim-sndz) (Sandoz is a subsidiary of Novartis)

- First US biosimilar of Amgen’s filgrastim
  - Approved March, 2015, released commercially Sept., of 2015
    • 180 delay marketing dossier data submission based on FDA approval date
  - At the time of approval all 5 indications were given (one with clinical data, 4 by extrapolation)
    • Clinical trial data on Myelosuppressive chemo
    • Extrapolated; AML receiving induction/consolidation chemo; BM/T; severe chronic neutropenia; stem cell mobilization

Fulphila® (pegfilgrastim-jmdb) (Mylan/Biocon)

- Mylan/Biocon’s Fulphila® (pegfilgrastim-jmdb) is the first FDA approved pegfilgrastim (June, 2018).
- Indicated to decrease the chance of infection as suggested by febrile neutropenia in patients with non-myeloid cancer who are receiving chemotherapy
- Mylan has announce it will launch Fulphila at a 33% discount off of Amgen’s neulasta WAC ~ $4,175.

Other ‘Biosimilar’ Activities (The Neulasta Saga)

- Apotex’s Apobiologix submitted it version of filgrastim (Grastofil) (compared to Amgen’s neupogen) and peg-filgrastim (Amgen’s neulasta) back in Dec of 2014
  - Note: peg-filgrastim is a bigger and more complex molecule than filgrastim, and apparently much harder to make...
  - The legal battle as to when the 180 day (6 months) delay starts (when provided, or after approval) was settled by the Supreme Court
  - Still no approval…

- Coherus had submitted their 351k application for their pegfilgrastim (CHS-1701) in Aug of 2016
  - They received their CRL (complete response letter) 6/17 requesting re-analysis of immunogenicity data and additional manufacturing data (but no additional clinical data ~ no clinical data in cancer pts exists)
  - Coherus has addressed the FDA’s issues and has re-submitted it’s application 5/18
  - Expecting approval 4th Quarter 2018...
Other ‘Biosimilar’ Activities (The Neulasta Saga)

- Sandoz/Novartis submitted their 351k application to the FDA for their peg-filgrastim (LA-EP2006) back in Nov of 2015. They received their CRL last summer and have been working with the agency ever since to address ‘concerns’…
  - It is not known when Sandoz will re-submit their application

Retacrit® (epoetin alfa-epbx) (Pfizer/Hospira)

- Hospira had submitted its Retacrit (epoetin alfa comparing to Amgen’s epogen & Janssen’s procrit epoetin alfa.
  - In Oct., 2015, the FDA sent out it’s first rejection, then after re-submitting in 2016, the FDA sent out a second On CRL on 6/17
- The FDA approved Retacrit on 5/18 for treatment of anemia caused by CKD, chemotherapy or zidovudine use in HIV.
  - We are still waiting for the commercial release…

Mvasi® (bevacizumab-awwb) (Amgen/Allergan)

- The FDA approved Mvasi on 9/17 for Amgen/Allergan a biosimilar version of Avastin
  - This is a recombinant IGI MoAb VEGF inhibitor
- The phase III clinical trial was in NSCLC
  - Randomized 642 pts, with a risk ratio of objective response of 0.93
- Approved in MCRC, NSCLC, Glioblastoma, RCC, and Cervical CA.
  - Note: It does not have an adjuvant colorectal indication
- Avastin retains its US patent until 2019, so it is still not clear when this drug will launch…

Ogivri® (trastuzumab-dkst) (Mylan/Biocon)

- The FDA approved Ogivri on 12/17 for Mylan/Biocon as a biosimilar version of Herceptin
  - MoAb that blocks HER2/neu
- Ogivri has been approved for all indications of Herceptin (MBC & stomach)
- Roche and Mylan reached a licensing agreement for US distribution
  - The anticipated launch is 2019/2020…

Other ‘Biosimilar’ Activities (The Cancer Agent’s Saga)

- States have been busy putting state laws in effect that create standards for substitution of a ‘biosimilar’
- Multiple states has put their own biosimilar laws on the books, so you really need to check your own states laws…

‘States’ Biosimilar Legislation

- Sandoz/Novartis submitted its application to the FDA on 9/17 for its rituximab biosimilar
  - It had completed its phase III, ASSIST-FL trial in follicular lymphoma.
- Sandoz received their CRL on 5/18, delaying what they were hoping to be a 4th quarter 2018 launch.
  - Rituxan has a 8.6 billion dollar market in the US
- NOTE: Genentech has submitted a BLA to the FDA for its obinutuzumab (Gazyva) + chemo in NHL based on the GALLIUM study
  - There head-to-head trial vs rituxan + chemo showed a 28% improvement in DFS, though toxicity appeared higher
**FDA’s New Biosimilar Action Plan**

- On 7/18 the FDA released its long-awaited ‘action plan’
- It addressed 4 key issues:
  - Improve the development and approval process for biosimilars and interchanges
  - Maximize scientific & regulatory clarity for product development
  - Develop effective communications to improve understanding of biosimilars by all parties
  - Support market competition by reducing the ‘gaming’ of the FDA requirements for market release
- My take - It raised more issues than is solved...

**Summary**

- Biosimilars are not generics
- Due to the nature of these products, a more comprehensive review will be required.
- This comprehensive review process should look at Product, Manufacturing, and practice factors to determine appropriate use.
- There are now 5 FDA approved oncology agents, but only 2 are commercially available (refer to Koeller’s 2nd Law)
  - Litigation hassles will ultimately determine commercialization
- Be patient, more biosimilars are on their way...

**Questions?**