Oncology Biosimilars: A 2019 Update

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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

Self Assessment Question
1. The process to evaluate the heterogeneity seen in currently available biologic products is called:
   • A. Biologic double-check
   • B. Variable Analysis
   • C. Comparability
   • D. Fingerprint-Like Analysis

Self Assessment Question
2. Which of the following biosimilar cancer agents is commercially available today:
   • A. Trastuzumab
   • B. Cetuximab
   • C. Rituximab
   • D. None of the above

Self Assessment Question
3. Which company received the first FDA approval for pegfilgrastim:
   A. Apobiologix
   B. Mylan/Biocon
   C. Sandoz
   D. Coherus

Self Assessment Question
4. How many biosimilar versions of Herceptin are FDA approved:
   A. 0
   B. 2
   C. 4
   D. 5
Koeller’s Key Terms

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

Koeller’s First Law:
Biosimilars ARE NOT Generics!

Generic Drugs VS Biologics/Biosimilars

<table>
<thead>
<tr>
<th>SMALL-MOLECULE GENERIC DRUGS</th>
<th>BIOSIMILARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally smaller (low molecular weight) Larger (high molecular weight)</td>
<td>Usually made by organic or chemical synthesis Replicated in cell systems</td>
</tr>
<tr>
<td>Fewer critical process steps Many critical process steps/Post-Translational Modifications</td>
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</tr>
<tr>
<td>Well-characterized Less easily characterized</td>
<td>Well-characterized Less easily characterized</td>
</tr>
<tr>
<td>Homogeneous drug substance Heterogeneous mixtures; may include impurities (e.g., glycan variants, protein fragments)</td>
<td>Homogeneous nature; may include impurities (e.g., glycan variants, protein fragments)</td>
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<tr>
<td>Usually not immunogenic Often immunogenic</td>
<td>Usually not immunogenic Often immunogenic</td>
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Biosimilars are different from small-molecule generic drugs.

How are Biosimilars Defined in the United States?

A biological product that "(a) ... is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that "(b) 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.

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 saving could not be realized...

Developmental Paradigm Shift
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."

Heterogeneity (Variability) in Biologics

- Biologics are a "molecular population" and express heterogeneity
  - Biologics consist of a mix of chemically complex structures and isoforms
  - Potential Sources and Examples of Heterogeneity
    - Dissociation
    - Methylation/deamination
    - Proteolytic cleavage
    - Post-translational modifications
    - Conformation
    - Aggregation
    - Decontamination
    - Sterilization
    - Oxidation
  - Manufacturing processes control heterogeneity to help assure batch consistency
    - The product's quality attributes have to remain within a prospeced range

Inherent Variability in the Manufacturing of Biologics

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

FDA Guidance on Product Comparability

- “FDA guidance on protein comparability has been available since 1995.”
  - Comparability exercises often involve extensive changes of manufacture and may require extended stability studies
  - The comparability exercise is an in-depth protocol that is part of post approval changes and undergoes formal review
  - A detailed ‘fingerprint’ analysis may facilitate approval of changes to manufacturing processes that are similar but not identical to the reference product
Fingerprint Analyses

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**Comparative Clinical Trials**

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

- Reference Biological
- Biologic

The need for additional studies may be influenced by many factors:

- Mechanism of action
- Complexity
- Antigenicity
- Immune relationship
- Clinical evidence


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**Extrapolation of Indications**

- Extrapolation of indications will not be automatic. Scientific justification will be required for additional indication.

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**Identifiability**

- The FDA is taking a "totality of evidence" approach to biosimilar approvals:
  - Builds on the extensive clinical knowledge base of the biologic reference product
  - A robust analytical characterization and preclinical foundation that does not show any "clinically meaningful differences"
  - Immunogenicity testing always required

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**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 physicians approval
What Have We Learned So Far?

- Biosimilars ARE NOT generics
- Variability/heterogeneity exists in current biologics
  - Impurities exist in every bottle (protein fragments, glycans)
- The process for the development and verification of a biosimilar is quite extensive utilizing fingerprint-like analysis
  - Must prove structure, function & mechanism of action
- FDA requirements will be product specific and will vary
- 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 Oncology Biosimilars in the US?
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)

FDA Approved Oncology Biosimilar

- Zarxio* (filgrastim-sndz) – Sandoz/Novartis
- Nвестым* (filgrastim-aafi) – Pfizer/Hospira
- Mvasi* (bevacizumab-awwb) – Amgen/Allergan
- Zirabev (bevacizumab-bvzr) – Pfizer/Hospira
- Ogivri (trastuzumab-dkst) - Mylan/Biocon
- Herzuma (trastuzumab-pkhr) – Celltrion/Teva
- Ontruzant (trastuzumab-dttb) – Samsung/Bioepis
- Trazimera (trastuzumab-qyyg) – Pfizer/Hospira
- Kanjinti* (trastuzumab-anns) – Amgen/Allergan

* Commercially available

FDA Approved Oncology Biosimilar

- Truxima (rituximab-abcs) – Celltrion
- Ruxience (rituximab-pvvr) – Pfizer/Hospira
- Fulphila* (pegfilgrastim-jmdb) – Mylan/Biocon
- Udenyca* (pgfilgrastim-cbqv) - Coherus
- Retacrit* (epoetin alfa-epbx) – Pfizer/Hospira

* Commercially available

Other Oncology Biosimilars Under Review
or Having Received a CRL

- Pegfilgrastim (Sandoz) - CRL - 7/16 – expecting release 4th quarter 2019?

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 in 2017 and have been working with the agency ever since to address ‘concerns’…
<table>
<thead>
<tr>
<th><strong>Fulphila® (pegfilgrastim-jmbd)</strong> (Mylan/Biocon)</th>
<th><strong>Udenyca® (pegfilgrastim-cbqv)</strong> (Coherus)</th>
</tr>
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<tbody>
<tr>
<td>• Mylan/Biocon’s Fulphila® (pegfilgrastim-jmbd) is the first FDA-approved pegfilgrastim (June, 2018).</td>
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<tr>
<td>• Indicated to decrease the chance of infection as suggested by febrile neutropenia in patients with non-myeloid cancer who are receiving chemotherapy</td>
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<td>• Mylan initiated a ‘surgical’ launch at the end of 2018. A more widespread distribution has occurred since then</td>
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<tr>
<td>• Discounts in the 40+% range have been noted…</td>
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<tr>
<td>• Coherus had submitted their 351k application for their pegfilgrastim-cbqv (CHS-1701) in Aug of 2016</td>
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<tr>
<td>– They received their CRL (complete response letter) 6/17 requesting re-analysis of immunogenicity using a more sensitive assay.</td>
<td></td>
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<tr>
<td>– Coherus re-submitted it’s application 5/18 and an FDA approve came in late 2018 with a 1st quarter launch in 2019.</td>
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<th><strong>Retacrit® (epoetin alfa-epbx)</strong> (Pfizer/Hospira)</th>
<th><strong>Mvasi® (bevacizumab-awwb)</strong> (Amgen/Allergan)</th>
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<tr>
<td>• Pfizer had submitted its Retacrit (epoetin alfa) comparing to Amgen’s epogen &amp; Janssen’s procrit epoetin alfa.</td>
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<tr>
<td>– In Oct., 2015, the FDA sent out it’s first rejection, then after re-submitting in 2016, the FDA sent out a second CRL on 6/17</td>
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<tr>
<td>• The FDA approved Retacrit on 5/18 for treatment of anemia caused by CKD, chemotherapy or zidovudine use in HIV.</td>
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<tr>
<td>• Was released summer of 2018</td>
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<td>• The FDA approved Mvasi on 9/17 for Amgen/Allergan a biosimilar version of Avastin</td>
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<tr>
<td>– This is a recombinant Ig1 MoAb VEGF inhibitor</td>
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<td>• The phase III clinical trial was in NSCLC</td>
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<tr>
<td>– Randomized 642 pts, with a risk ratio of objective response of 0.93</td>
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<tr>
<td>• Approved in MCRC, NSCLC, Glioblastoma, RCC, and Cervical CA.</td>
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<tr>
<td>– Note: It does not have an adjuvant colorectal indication</td>
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<td>• Winning an injunction against Genetech, Amgen was able to launch at the beginning of August</td>
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<th><strong>Kanjinti® (trastuzumab-anns)</strong> (Amgen)</th>
<th><strong>Ogivri® (trastuzumab-dkst)</strong> (Mylan/Biocon)</th>
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<tr>
<td>• The FDA approved Kanjinti on 6/19 for Amgen as a biosimilar version of Herceptin</td>
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<tr>
<td>– MoAb that blocks HER2/neu</td>
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<tr>
<td>• Kanjinti has been approved for all indications of Herceptin (HER2+ Breast &amp; gastric)</td>
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<td>• Amgen winning an Genetech injunction, released the drug for sale in early August</td>
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<tr>
<td>• A 2017 ‘LILAC’ study demonstrated Kanjinti to be highly similar to Herceptin</td>
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<tr>
<td>– 725 pt HER+ early stage breast cancer trial</td>
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<tr>
<td>– Following 4-cycles of ‘chemo’, they then received either drug with pac for 4 more cycles</td>
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<tr>
<td>• Primary endpoints: RD (risk differences); RR (risk ratio); pCR</td>
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<tr>
<td>• pCR = 48% vs 40.5%</td>
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<td>• The FDA approved Ogivri on 12/17 for Mylan/Biocon as a biosimilar version of Herceptin</td>
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<td>• Mylan’s clinical trial was in metastatic disease…</td>
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<tr>
<td>• Roche and Mylan reached a licensing agreement for US distribution</td>
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<tr>
<td>– The anticipated launch is 2019/2020…</td>
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‘States’ Biosimilar Legislation

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

Interchangeability

- FDA Final Ruling on Interchangeability came out in June.
- Will require ‘additional’ data to demonstrate no greater risk in terms of safety or efficacy in alternating between the reference and the biosimilar
- Does appear to provide greater flexibility allowing for a global competitor
  - Would need a ‘bridging’ trial between US and non-US forms
  - The primary outcome is PK/PK NOT efficacy
- Would require studies to switch back and forth 2 full times and then back to the reference
  - Two-arm study:
    - one arm: ref. – biosimilar – ref. – bio;
    - second arm: ref. only

Interchangeability

- To prove ‘Biosimilarity’
  - Note: A single transition or conversion from a reference to a biosimilar needs to be done now
  - Current biosimilar clinical trials include at least a single transition step (PK/PK trial or clinical trial)

Interchangeability

- 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 interchangeables
  - 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
    - Litigation and the ‘patent dance’
- My take - It raised more issues than is solved..

FDA’s New Biosimilar Action Plan

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 14 FDA approved oncology agents, with 7 commercially available (refer to Koeller’s 2nd Law), but only 2 are therapeutic agents..
  - Litigation hassles will ultimately determine commercialization
- Be patient, more biosimilars are on their way…

Questions?
1. The process to evaluate the heterogeneity seen in currently available biologic products is called:
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