Evaluating Biosimilars:
A Value Proposition for Health Systems, Hospitals, Practices & Payers

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Learning Objectives:

• Summarize the differences between biosimilars and common generic pharmaceuticals.
• Describe the biosimilar approval process and associated regulations.
• Explain the value provided by biosimilars and the various stakeholders involved.
• Describe the institutional review process and the various types of actions which can be taken to manage drug use.
• List 3 major critical categories that would be part of a ‘checklist’ for the review of a biosimilar product.

Biological product definition

Biologic
A wide range of products derived from cell lines from living organisms, such as vaccines, blood and blood components, and recombinant therapeutic proteins that prevent, treat, or cure a disease. Examples:

- Therapeutic proteins (e.g., EPO, G-CSF)
- Monoclonal antibodies (e.g., rituximab, bevacizumab, trastuzumab, cetuximab)

Reference Biologic
Originally licensed biologic product used for comparison

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.

Generics & Small-Molecules Are Different

Small-Molecule Generic Drugs
- Generally smaller (low molecular weight)
- Usually made by organic or chemical synthesis
- Fewer critical process steps
- Well-characterized
- Known structure
- Usually not immunogenic

Biologics
- Larger (high molecular weight)
- Made with/from cells/organisms
- Many critical process steps
- Less easily characterized
- Structure may or may not be completely defined or known
- Heterogeneous mixtures; may include variants
- Often immunogenic

Biosimilars are different from small-molecule generic drugs.
FDA Approval Pathways

Top 6 Biologic Oncology Products

Cost savings potential of biosimilar drugs in the United States

Economic impact of biological products use in Cancer Therapy

Patent expiration for selected Oncology Biologics, 2015-2024


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

2. Camacho LH, et al.


Estimated cost savings potential of biosimilars was $44.2 billion over 10 years, using available information and published literature.

• Assumptions in estimating savings:
  – Year-on-year originator growth of 10%
  – Share of originator sales exposed to biosimilar competition increased from 10% in year 1 to 20% in year 10
  – Market penetration of 60%
  – Biosimilar price discount of 35% results in $44.2 billion savings (high end); $12.6 billion with 10% discount (low end)

• Projected savings:
  – Monoclonal antibodies, 13%
  – Colony stimulating factors—eg, G-CSF and pegylated G-CSF-6%

1. PHSA, Public Health Service Act

†FDCA, Federal Food Drug and Cosmetic Act

Efficacy must be demonstrated

Safety and efficacy must be demonstrated

Safety and efficacy must be demonstrated

Interchangeable biosimilars require more data

Examples of biological products; not all-inclusive


• Recombinant Proteins
  – Cytokines
    – Interferons
    – Interleukins
  – Hematopoietic growth factors
    – Erythropoietin
    – G-CSF
    – Pegylated G-CSF
    – GM-CSF

• Monoclonal Antibodies
  – Rituximab
  – Trastuzumab
  – Bevacizumab
  – Cetuximab
  – Ipilimumab
  – Nivolumab
  – Pembrolizumab

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

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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."

Modern Facility for the Manufacturing of Biologics/Biosimilars

Biologic Manufacturing Variability

Economic impact of biological products use in Cancer Therapy

- The high cost of biologics raises concerns about patients’ ability to access essential therapies.¹
- Biologics use a disproportionate amount of healthcare resources relative to the number of patients treated.²
- Seven biologics used to treat cancer accounted for $5.8 billion (62%) of the total 2013 Medicare Part B expenditures for the top 10 drugs.²
- Global spending on oncology medicines reached $100 billion in 2014, 50% of which was for targeted therapies that include biological products.³

FDA Guidance on Product Comparability

- Manufacturing processes of biologics undergo changes after approval
  - Intended changes may be implemented during production or transferred 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 is part of postapproval changes and undergoes health authority review

European etanercept (Enbrel) Manufacturing variability

Product labels were unaltered indicating changes did not result in clinically meaningful differences

Biologics Manufacturing Changes

(Chinese Manufacturing Data)

Analytical Analysis For Biosimilars Is More Complex Than Establishing Comparability

- Demonstrating biosimilarity to a reference biologic requires more validation than establishing comparability between manufacturing changes
- Biosimilars have their own specifications needed for approval:
  - Manufacturing process
  - Industry standards
  - Regulatory specifications
  - Data from comparisons with the reference biologic
- This rigorous analytical testing is called ‘Fingerprint-Like Analyses’ by the FDA

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

“Advances in manufacturing science... may facilitate ‘fingerprint-like’ analysis.”

- Analytical testing is a major component of biosimilar development.
- Fingerprint-like analysis covers product attributes and their combinations.
- 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.

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

Analytical Comparison For Biosimilars Are More Extensive Than For Reference Biologics After A Manufacturing Change

Fingerprint Analyses

Physicochemical Properties

Peptide Mapping

Higher Order Structures

Glycans

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

2. FDA. Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference product. 2012.
Fingerprint Analyses

- Bioactivity Assays
  - Receptor Binding
  - Cytokine Function
  - Signal Transduction

Immunogenicity & Biologics/Biosimilars

- Anti-drug antibodies
  - Immunogenicity refers to the tendency of a biologic to induce the formation of anti-drug antibodies.1,2
  - Anti-drug antibodies often have no clinically relevant consequences.3,4

- Potential Clinical Consequences of Anti-Drug Antibodies
  - Loss of efficacy
  - General immune reactions (allergy; anaphylaxis)
  - Neutralizing antibodies

Comparative Clinical Trials

Comparative safety and effectiveness data will be necessary if there are residual uncertainties about the biosimilarity of the two products.1

Extrapolation of Indications

- MOA in each condition
  - Binding and molecular signaling
  - Location and expression of target/receptor
- PK and biodistribution
  - PKO measures may provide important MOA information
- Expected toxicities
  - Differences may exist in each condition of use and patient population
- Any other factor
  - Other factors may include comorbidities or concomitant medications

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

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
  - A robust analytical characterization and preclinical foundation that does not show any “clinically meaningful differences”
  - Reduces need for extensive animal and clinical testing
  - Immunogenicity testing always required

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

1. FDA guidance for industry: scientific considerations in demonstrating biosimilarity. 2015.
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
• 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

• To key to 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?

P&T Committee Oversees Formulary (as per ASHP)

• P & T Committee has multidisciplinary membership (Physicians, Pharmacists, Nurses, Finance, Legal, Administrators, Others)
• Existing processes can be used for biosimilars
• For specialty drugs, a subcommittee or working group is often designated to recommend decisions. This approach should be used for biosimilars.
• Formulary management tactics will likely be used.

The ‘BIG 3’ Formulary Considerations

• Efficacy
• Safety
• Financial

### Biosimilar Evaluation Template

- **Three categories for review consideration:**
  - **Product**
  - **Manufacturing**
  - **Institution Specific**

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

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### Product

- **Drug name:** (different from reference)
- **Drug background information:**
  - Molecular characterization; pre-clinical; PK/PD; immunogenicity
- **Efficacy:** (clinical trials data)
  - Phase III US reference comparator study
  - Additional clinical trials data
  - European (or other) data & ‘real world’ use data including toxicity & immunogenicity

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### Immunogenicity

- Johnson & Johnson’s epoetin alfa (Eprex)
  - Eprex had a small change in formulation ~ switching from human serum albumin to polysorbate 80
  - Some patients developed neutralizing antibodies to both Eprex and native epoetin
  - Those who developed the antibodies experienced red cell aplasia, sudden-onset anemia
  - A subsequent FDA study found that the risk of death to Eprex was 78% higher than placebo (16% vs 9%)

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### Storage, Preparation & Administration:

- Vial sizes & packaging
  - Volumes/concentrations
  - Multi-dose vial
  - Shelf-life (before/after reconstitution)
    - Reconstituted volumes and solutions used
  - Refrigeration
  - Barcoding (Pharmacovigilance)
    - Tracking by lot

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### Production

- **Production Facilities**
  - Number & location of plants (backup)
  - Plant production history
  - History of any regulatory actions
  - Recall history
  - Product shortages history
  - Product availability (how much on hand...)
  - Quality control procedures
Institution Specific

- Implementation Strategy: (single/multi-site)
  - P & T committee approval
  - Any limitations/restrictions (approved indication(s))
  - Is it replacing all or some indications?
  - Switching all at once, or only new patients?
  - Staggered/sequencing switch
  - Staff training
    - Who, what, where, when...
    - Any special patient education materials needed?
    - Creating needed material, reprogramming, etc

- Preparation & Administration
  - Product distribution (wholesale vs specialty Rx)
  - Vial sizes & available packaging (multi-dose vial)
    - Volumes/concentrations
    - Shelf-life (before/after reconstitution)
      - Reconstituted volumes and solutions used
    - Refrigeration?
    - Recommended stability/in-house sterility
    - Bar coding (tracking by lot), supply chain security, counterfeit protections (pharmacovigilance)

- Risk Mitigation/Monitoring
  - Roll under current ‘REM’
  - DUE program to monitor initial usage
    - 3, 6, 12 month program
  - Corporate product support
    - Billing & coding guidance
    - Reimbursement support
    - Co-pay assistance/Patient Foundations
    - Indigent patient program
    - Patient education materials

- Economic considerations:
  - Product distribution (Wholesale vs GPO vs Specialty Rx)
  - Drug pricing (coding issues)
  - Incentives (rebates, market share, bundles, exclusivity)
  - Medicare (J-code)
  - Private Payer issues (restrictions?)
    - Pre-authorization/preferences
    - Implementation costs

- Other considerations:
  - Organizational position paper/guidelines
    - NCCN, ASCO, ACCC, ONS, HOPA
  - State laws addressing interchangeability
  - FDA guidance on coding/reimbursement
  - New healthcare delivery models
    - ACO’s; Oncology medical Home; Bundled payment

So, Where do we stand right now with Biosimilars in the US?
In March, 2015 the FDA approved Zarzio as a ‘biosimilar’ to Amgen’s neupogen for all 5 indications at the time.

- Zarzio has been approved in Europe and other countries since 2009 (100,000+ pts) and the ‘totality’ of their data was given to the FDA
- The PIONEER study in chemotherapy neutropenia showed equivalence, and the additional 4 indications were done by ‘extrapolation’ of all data
- Following legal delays, product was released in Sept. 2015
  * Announced for sale at a 15% discount, but with specialty pharmacy distribution.
  * Since then, have seen more significant discounting...

Amgen’s filgrastim holds roughly 76% of the market (~$1.4 billion)
- Teva - Granix
- Sandoz - Zarzio

Amgen just announced that the FDA accepted its application for its version of Humira (adalimumab) for rheumatoid arthritis and psoriasis, expecting a decision by Sept. 2016
- This has started a legal patent war — which AbbVie says they have patent exclusivity through 2022...
- Sandoz has just purchased from Pfizer, the EU rights to infliximab biosimilar

S. Korean’s Celltrion submitted it’s Remicade biosimilar, Remsima comparing it to Janssen’s infliximab in early 2015 (Hospira’s inflectra-infliximab dyyb, hold the US marketing rights).

- FDA approval for all 6 indications came April, 2016 (Crohn’s; UC; RA; PA; Psoriasis; AS)
  * First approved MoAB in US
- Patent litigation has ensued (Janssen claims protection into 2018)
- Mylan’s trastuzumab biosimilar to Roche’s Herceptin compared favorably (safety & efficacy) in Her2+ breast cancer in a Phase III study

Apothe’s Apobiologix has submitted its version of Filgrastim (Grastofil) (compared to Amgen’s neupogen) and Peg-filgrastim (Amgen’s neulasta)

- Legal battle as to when the 180 day (6 months) delay starts (when provided, or after approval)
- Still no approval
- Neulasta is a $4.4 billion dollar market

Hospira has submitted its Retacrit (epoetin zeta comparing to Amgen’s epogen & Janssen’s procrct epoetin alfa.
- Oct. 2015 the FDA announced it had rejected the application
- Hoping for a 2nd quarter 2016 re-submission and providing additional data

Note: Pfizer bought Hospira for 17 billion dollars...

The Purple Book

- Will be the FDA’s ‘orange’ reference book for biologics
- Will consist of two lists:
  - Reference biologic and its corresponding interchangeable biosimilar (if it exists).
  - Other biologic products (vaccines, etc)
- Each list will include: BLA #, product name, brand name, date of licensure, expiration date of reference drug, pediatric exclusivity, withdrawals

‘States’ Biosimilar Legislation

- States have been busy putting state laws in effect that create standards for substitution of a ‘biosimilar’
- As of May 2016, 20 states have enacted laws dealing with biosimilars (4 are pending)
- 16/20 require the RPh to contact the MD
- 12 require the patient to be notified
- 10 require the name and manufacturer to be provided to the MD
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.
• With therapeutic interchange generally a state issue, numerous states have enacted laws to handle biosimilars

Thank You