THE BIOSIMILAR DEVELOPMENT PATHWAY AND CHALLENGES OF PRACTICAL INTEGRATION

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DISCLOSURES

- None
HISTORY

• Developed in response to questions about the biosimilar development process and potential impact on research at the February 2019 Semi-annual NRG meeting
  • NRG is the NCI Cooperative Group that ACI is a member of

• Presented at the July 2019 Semi-annual NRG meeting
  • Medical Oncology Pharmacy Subcommittee Meeting
    • Full presentation
  • Medical Oncology Workshop
    • Abbreviated presentation

• Expanded this presentation since time allowed
OBJECTIVES

• Contrast the generic and biosimilar medication development pathways

• Outline the biosimilar research requirements for FDA approval

• Identify practical challenges of biosimilar use including interchangeability, formulary restrictions, prescribing, dispensing, and research
BIOSIMILARS ARE ALL OVER THE NEWS!

• FDA approved the 1st biosimilar in March 2015
  • 23 approved as of August 2019
    • 5 supportive oncology
    • 9 therapeutic oncology
• What is a biosimilar & how does it differ from a generic?
WHAT IS THE DIFFERENCE?

Small Molecule
- Copy
- Generic

Biologic
- “Attempted Copy”
- Biosimilar
## WHAT IS THE DIFFERENCE?

<table>
<thead>
<tr>
<th>Small Molecule</th>
<th>Biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low molecular weight</td>
<td>High molecular weight</td>
</tr>
<tr>
<td>Chemical synthesis</td>
<td>Living cell cultures</td>
</tr>
<tr>
<td>Non-immunogenic</td>
<td>Immunogenic</td>
</tr>
<tr>
<td>Simple, well-defined structure</td>
<td>Complex structure</td>
</tr>
<tr>
<td>Able to analytically characterize</td>
<td>Impossible to fully characterize</td>
</tr>
<tr>
<td>Chemically manufactured identical copy → Generic</td>
<td>Manufactured in a living cell line to be highly similar → Biosimilar</td>
</tr>
</tbody>
</table>

BIOLOGICS MANUFACTURING PROCESS

Living Source
Lot-to-Lot Variations
Safety & Efficacy

- Formal process changes must be reported to the FDA
  - Changes at any stage: cell source, purification techniques, storage
  - Demonstrate that the product has been maintained within a preset specification limit so as not to affect safety & efficacy

- Regulations derived from International Quality Guidelines (ICH Q5E)
  - Pre- & post-change product must be “highly similar”

- Highly similar lots of biologics are on the market at the same time & used interchangeably in practice

- Demonstrates complexity of biologic products & the basis of the biosimilar definition

WHAT IS THE FDA DEFINITION OF A BIOSIMILAR?

• Biosimilar
  • “biological product 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 the safety, purity, and potency of the product”

• Companies are attempting to reproduce biologics with expired patents
  • Biosimilar definition replaced the unofficial term “follow-on biologics”

• FDA created a new approval pathway with the definition
FDA APPROVAL PATHWAYS: MARKET COMPETITION

- Generic approval pathway allows for cost savings
  - Bioequivalence didn’t require reproduction of costly clinical trials
- Competition produces cost savings & improved access
  - Biosimilar pathway was approved to promote competition & affordability
- Biosimilar cost savings?
  - Prescription database study 2016 → 2017 G-CSF expenditures decreased by 10.9% in 9 sectors including clinics & nonfederal hospitals
    - 3 products available: 2 biologic G-CSF + 1 biosimilar
  - Research & development costs high with complex manufacturing

RESEARCH REQUIREMENTS

• Bioequivalence
  Same extent/rate absorption & availability
  • Cmax/AUC
  • Pharmaceutical Equivalence
    Active ingredients, dosage form, route of administration, strength

Generic
Therapeutic Equivalence:
expected to produce same clinical effect & safety profile

Analytical & Nonclinical Function Similarity
Same MOA, dosage form, route, strength

• Pharmacological Similarity
  PK/PD

• Clinical Similarity
  Clinical studies in efficacy (+/-), immunogenicity, safety

Biosimilar
Highly Similar

RESEARCH REQUIREMENTS

Innovator Biologic Reference Product

351 (a) Pathway

“Totality of Evidence”

Biosimilar

351(k) Pathway

Clinical Studies

Pharmacology

Nonclinical

Analytical

DEVELOPMENT OF A BIOSIMILAR APPLICATION

• Reverse engineer the reference product and determine the lot-to-lot variability
  • Biosimilar is then developed to fall within this threshold of variation

• Analytical: comparative analytics using advanced technology
  • Structure
    • Identical primary AA sequence & higher order structure
      • Identifying side chain variations
    • Characterize the purity & potency

• Nonclinical: biological function testing
  • To identify if variations in the biosimilar product will affect function
  • In-vitro, in-vivo functional assays, and animal models

DEVELOPMENT OF A BIOSIMILAR APPLICATION

• **Pharmacology:** pharmacokinetic/pharmacodynamic studies
  • Testing required because can’t predict from analytical/nonclinical data

• **Clinical Studies:**
  • Immunogenicity assessment required
    • Assess the incidence/severity human immune response: anaphylaxis or neutralizing antibodies
  • Comparative clinical study: reference product vs. biosimilar
    • Goal: identify if any clinically meaningful differences in safety, toxicity, & efficacy
    • May be deemed unnecessary by FDA
    • Most relevant & sensitive study population
    • Equivalence design to demonstrate the biosimilar does not cross an inferiority or superiority margin

DEVELOPMENT OF A BIOSIMILAR APPLICATION

• **Biosimilar Application**: review of the “Totality of Evidence”
  • Must meet definition of “highly similar” to be approved
  • **Extrapolation**: All reference product indications may be approved even if not studied
    • Scientific justification that all indications use the same MOA & show that the PK/PD, immunogenicity, and toxicity would be similar across the treatment populations

• **Naming Convention**: Biosimilar-kdst
  • Unique random lower-case 4-letter suffix after the non-proprietary name
  • Clearly distinguish what is prescribed, dispensed, administered
  • Useful in adverse event reporting

INTERCHANGEABLE BIOSIMILAR DEFINITION

• Meets the definition of a biosimilar AND
• “Can be expected to produce the same clinical result as the reference product in any given patient” AND

• For products administered more than once:
  • Demonstrate no additional risks and no diminished efficacy when switching between reference product and biosimilar
    • Switching study designs
      • Evaluations of PK/PD, immunogenicity, and safety after at least 3 switches

Reference → Reference (control arm) → Reference
Reference → Biosimilar → Reference

INTERCHANGEABLE BIOSIMILARS

• **Purple book**: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations

• Can be substituted for the reference product **without discussing with the provider**
  - Actual substitution is up to state legislation which regulates pharmacy practice
  - Oncologists have expressed concern over dispensing a different product than what was written for
  - Pharmacy organizations are promoting communication with providers regarding interchangeable biosimilars

• **Important note**: biosimilars are **not** interchangeable with each other!

CURRENTLY APPROVED ONCOLOGY BIOSIMILARS

• None are currently approved as interchangeable
**SUPPORTIVE ONCOLOGY BIOSIMILARS**

- Products are available on the market & incorporated into NCCN and ASCO guidelines

<table>
<thead>
<tr>
<th>Product</th>
<th>Biosimilar Status</th>
<th>Reference Product Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim-sndz</td>
<td>5 of 6</td>
<td>5 of 6 reference product indications</td>
</tr>
<tr>
<td>Filgrastim-aafi</td>
<td>5 of 6</td>
<td>5 of 6</td>
</tr>
<tr>
<td>Tbo-Filgrastim</td>
<td>1 of 6</td>
<td>not a biosimilar</td>
</tr>
<tr>
<td>Pegfilgrastim-jmdb</td>
<td>1 of 2</td>
<td>Pegfilgrastim-cbqv</td>
</tr>
<tr>
<td>Pegfilgrastim-cbqv</td>
<td>1 of 2</td>
<td>1 of 2</td>
</tr>
<tr>
<td>Epoetin alpha-epbx</td>
<td>2 of 2</td>
<td>2 of 2</td>
</tr>
</tbody>
</table>


### Therapeutic Oncology Biosimilars

- Starred (*) products are available on the market, launched in July 2019.
- Being evaluated for use as formulary at our institution.

#### Bevacizumab
- Bevacizumab-awwb* 5 of 6 indications
- Bevacizumab-bvzr 5 of 6

#### Rituximab
- Rituximab-abbs 1 of 6 indications
- Rituximab-pvvr 4 of 6 indications

#### Trastuzumab
- Trastuzumab-pkrb 1 of 2 indications
- Trastuzumab-dkst 2 of 2
- Trastuzumab-dttb 2 of 2
- Trastuzumab-qyyp 2 of 2
- Trastuzumab-anns* 2 of 2

**Purple Book:** Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. [https://www.fda.gov/drugs/biosimilars/biosimilar-product-information](https://www.fda.gov/drugs/biosimilars/biosimilar-product-information).
THERAPEUTIC ONCOLOGY BIOSIMILARS: FDA APPLICATION PACKAGES

• Pharmacology
  • Single dose PK studies in healthy males
  • Several biosimilars (6 out of 9) compared US & EU product to itself
    • Then used EU as comparator arm in clinical trial

• Clinical Studies
  • Equivalence or non-inferiority design
    • Reminder that equivalence design does not mean products are equivalent
  • Pre-specified surrogate endpoints as primary objective
  • Immunogenicity and adverse events evaluated

# THERAPEUTIC ONCOLOGY BIOSIMILARS: COMPARATIVE CLINICAL STUDIES

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Indication</th>
<th>Study Design</th>
<th>Primary Results</th>
<th>Equivalence Margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab-awwb</td>
<td>First line NSCLC</td>
<td>Equivalence</td>
<td><strong>Objective response rate</strong>&lt;br&gt;ORR risk ratio 0.93 (90% CI, 0.80-1.09)&lt;br&gt;ORR biosimilar 39% vs. US-bevacizumab 41.7%</td>
<td>ORR risk ratio 90% CI of 0.67-1.5</td>
</tr>
<tr>
<td>Bevacizumab-bvzr</td>
<td>First line NSCLC</td>
<td>Equivalence</td>
<td><strong>Objective response rate</strong>&lt;br&gt;ORR risk ratio 1.015 (90% CI, 0.886-1.163)*&lt;br&gt;ORR biosimilar 45.3% vs. EU bevacizumab 44.6%</td>
<td>ORR risk ratio 90% CI of 0.73-1.137</td>
</tr>
</tbody>
</table>

# Therapeutic Oncology Biosimilars: Comparative Clinical Studies

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<tr>
<th>Biosimilar</th>
<th>Indication</th>
<th>Study Design</th>
<th>Primary Results</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Rituximab-abbbs</td>
<td>First line follicular lymphoma</td>
<td>Non-inferiority</td>
<td>Overall response Difference (one-sided 97.5 CI) 4.3% (-4.25) OR biosimilar 97% vs. US-rituximab 93%</td>
<td>Non-inferiority met if 97.5% CI OR was greater than -7%</td>
</tr>
<tr>
<td>Rituximab-pvvr</td>
<td>First line follicular lymphoma</td>
<td>Equivalence</td>
<td>Overall response rate at week 26 ORR difference 4.66 (95% CI -4.16- 13.47) ORR biosimilar 75.5 % vs. EU-rituximab 70.7 %</td>
<td>ORR difference -16 to 16% (95% CI)</td>
</tr>
</tbody>
</table>

# Therapeutic Oncology Biosimilars: Comparative Clinical Studies

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<th>Biosimilar</th>
<th>Indication</th>
<th>Study Design</th>
<th>Primary Results</th>
<th>Equivalence Margin</th>
</tr>
</thead>
</table>
| Trastuzumab-pkrb | Neoadjuvant breast cancer | Equivalence | Pathological complete response  
  pCR risk ratio 0.93 (95% CI, 0.78-1.11)  
  pCR biosimilar 46.8% vs. US-trastuzumab 50.4% | pCR risk ratio 95% CI of 0.74-1.35 |
| Trastuzumab-dttb | Neoadjuvant breast cancer | Equivalence | Breast pathological complete response  
  bpCR risk ratio 1.259 (95% CI, 1.085-1.460)  
  bpCR biosimilar 51.7% vs. EU-trastuzumab 42% | bpCR risk ratio 95% CI of 0.785-1.546 |
| Trastuzumab-anns | Neoadjuvant breast cancer | Equivalence | Pathological complete response  
  pCR risk ratio 1.188 (90% CI, 1.033-1.366)*  
  pCR biosimilar 48% vs. EU-trastuzumab 41% | pCR risk ratio 90% CI of 0.759-1.318 |
| Trastuzumab-dkst | Metastatic breast cancer | Equivalence | 24 week overall response rate  
  ORR risk ratio 1.09 (90% CI, 0.974-1.211)  
  ORR biosimilar 69.6% vs. EU-Trastuzumab 64% | 24 week ORR risk ratio 90% CI of 0.81-1.24 |
| Trastuzumab-qyyp | Metastatic breast cancer | Equivalence | 33 week objective response rate  
  ORR risk ratio 0.940 (95% CI, 0.842-1.049)  
  ORR biosimilar 62.5% vs. EU-trastuzumab 66.5% | 33 week ORR risk ratio 95% CI of 0.842-1.049 |

BIOSIMILAR PRACTICAL CHALLENGES: PRESCRIBING

• Caution with names, even in EMR
  • Can be cut short or limited to brand-names only
  • Risk of medication errors: look-alike, sound-alike
  • Inadvertent switching if infusions received at multiple locations
• Provider-specific preference vs. institution formulary decision
• Insurance coverage
• Approved indications only vs. off-label usage
• Comfort level with non-medical switching

BIOSIMILAR PRACTICAL CHALLENGES: DISPENSING

• Substitution of an non-interchangeable product is not allowed except:
  • Therapeutic interchange to maintain a formulary with a policy/procedure from a P&T committee
    • Based on extensive clinical & economic review
    • Voted on by pharmacy and providers
    • Decisions to stock/dispense 1 product
    • Automatic substitution by pharmacy pre-approved & agreed upon by providers

• Interchangeability status granted through FDA
  • State Laws must be followed

BIOSIMILAR PRACTICAL CHALLENGES: INSURANCE

• Payers are working to influence prescribing
  • Biosimilar preferred agent
  • Reference product requires a PA
  • Not covering the non-preferred products
    • Costly for patients & institutions!

• Insurance review prior to dispensing
  • Time/resource consuming
  • Does this mean pharmacy would stock every biosimilar & reference product
    • Multiple Look-Alike, Sound-alike products increases the risk of medication errors at the point of prescribing & dispensing

WHEN WILL WE SEE THERAPEUTIC ONCOLOGY BIOSIMILARS IN CLINICAL PRACTICE?

• Market Availability
  • Hindered by complicated contracting (manufacturer, wholesaler, insurance, PMB)
    • Rebates based on utilization of a reference product can overcome biosimilar cost savings
  • Reference product manufacturers will not go quietly!
    • Legal battles
    • Direct to consumer advertising: brand loyalty

• Cost Savings
  • Potentially not what we thought due to increased costs of the complicated manufacturing process
  • Cost of required switching studies to reach interchangeable status may negate all cost saving potential

WHEN WILL WE SEE THERAPEUTIC ONCOLOGY BIOSIMILARS IN CLINICAL PRACTICE?

- Oncology community
  - Clinical confidence & mainstream acceptance is low
    - In oncology, if it doesn’t work you don’t get a second chance
    - FDA has robust educational materials for patients & providers on the approval process

- Survey of 77 oncologists completed in 2018
  - Most important factors impacting the decision to prescribe a biosimilar
    - Safety and efficacy
    - Cost
  - 41.6% increase in the likelihood that an oncologist would prescribe a biosimilar if it was designated as interchangeable
    - Better demonstration of efficacy
  - Concerns about pharmacy substituting biosimilars without checking with oncologists

WHERE CAN WE FIND THE DATA?

• Biosimilar safety & efficacy data are not included in the label
  • The FDA approved label contains the clinical data from the reference product
    • Extrapolation from the biosimilar approval pathway allows the biosimilar to utilize the safety and efficacy data from the reference product because it has been deemed “highly similar”

• Comparative clinical trials used in the biosimilar applications are published
  • Hard to find because several use their R&D name
Drug Approval Package: OGVRI (Trastuzumab-dkst)

Company: Mylan GmbH
Application Number: 761074
Approval Date: 12/01/2017

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**FDA Approval Letter and Labeling**
- [Approval Letter(s)](PDF)
- [Printed Labeling](PDF)

**FDA Application Review Files**
- [Summary Review](PDF)
- [Officer/Employee List](PDF)
- [Medical Review(s)](PDF)
- [Chemistry Review(s)](PDF)
- [Pharmacology Review(s)](PDF)
- [Statistical Review(s)](PDF)
- [Clinical Pharmacology Biopharmaceutics Review(s)](PDF)
- [Proprietary Name Review(s)](PDF)
- [Other Review(s)](PDF)
<table>
<thead>
<tr>
<th>Protocol</th>
<th>Title</th>
<th>Subjects</th>
<th>Objectives</th>
<th>Route/Dose/Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK Similarity Study</td>
<td>A single-dose, randomized, double-blind, 3-arm, parallel-group study designed to compare the pharmacokinetic profiles of MYL-1401O, US-licensed Herceptin, and EU-approved Herceptin in healthy subjects.</td>
<td>Healthy (N=120)</td>
<td>PK similarity</td>
<td>Single IV 8 mg/kg</td>
</tr>
<tr>
<td>Comparative Clinical Study</td>
<td>A multicenter, randomized, double-blinded, parallel group design to assess the efficacy and safety of MYL-1401O compared to EU-approved Herceptin plus docetaxel or paclitaxel in patients with HER2-positive MBC</td>
<td>MBC (N=642)</td>
<td>Efficacy, safety, immunogenicity</td>
<td>Loading dose 8 mg/kg IV followed by a maintenance dose 6 mg/kg Q3W with docetaxel 75 mg/m² or paclitaxel 80 mg/m² Q3W</td>
</tr>
</tbody>
</table>

PK: pharmacokinetics; IV: intravenous; MBC: metastatic breast cancer
WHERE CAN WE FIND THE DATA?

• Pharmacovigilance
  • Ongoing post approval safety & efficacy monitoring
  • Limited by inconsistent reporting or reporting inaccurate products

• Literature reviews comparing non-medical switching from reference to biosimilar
  • 2018 review of 90 studies demonstrated no difference in safety and efficacy
    • 7 filgrastim biosimilar studies
      • 2 included oncology populations

BIOSIMILAR IMPACT: CLINICAL PRACTICE

Provider prescribes Trastuzumab

• Prescribing
  • EMR limitations
  • Look-alike, sound-alike
  • Non-Medical Switching

Pharmacy dispenses Trastuzumab-anns

• Dispensing
  • Interchangeable status → State laws
  • Therapeutic interchange in place → Formulary substitution
  • Look-alike, sound-alike
  • Inventory management

• Insurance Impact?
BIOSIMILAR IMPACT: CLINICAL RESEARCH

- Research with multiple biosimilars on the market
BIOSIMILAR IMPACT: CLINICAL RESEARCH

• Exclude biosimilars?
  • Negatively impact study participation
  • Impractical due to institutional formularies

Protocol language will need to include “or biosimilars”

Commercial Reference Product + IP

What impact will this have on the primary objective of the trial?

Reference Product  Biosimilar #1  Biosimilar #2

• Document which specific product is used
  • Consider stratifying results by product to identify safety or efficacy signals

• Will anyone conduct large scale comparative studies using commercial products to compare biosimilar & reference product efficacy?
SUMMARY

• Generics are not biosimilars & therefore each has a specific FDA approval pathway & requirements

• Biosimilar approval takes into account the totality of the evidence
  • Analytical, nonclinical, pharmacology, clinical studies

• Practical challenges will require clear communication
  • Prescribing, dispensing, research