Ask the Experts: Biosimilars

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- Dr. Stevenson lists no disclosures related to this program

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Learning Objectives

1. Describe the regulatory process for the approval of biosimilars and the current state of biosimilar introduction in the United States.

2. Discuss factors that should be considered by payers and health systems when assessing the use of formulary structures and utilization management strategies for biosimilars.

3. Compare strategies regarding how to display biologics and biosimilars in electronic ordering, dispensing, and administration systems in order to prevent name confusion and wrong product selection errors.

4. Discuss strategies for communicating with patients about biosimilars in order to answer common questions and to facilitate appropriate transitions of care.

5. Review the current status of interchangeability and drug substitution practices related to biosimilars, including requirements at the state level.
1. Assessment Question

In Europe, there are over 30 biosimilars that have been approved and marketed. How does the US compare?

A. There are the same number of approved and marketed biosimilars in the US
B. There are more biosimilars approved and marketed in the US
C. There are fewer biosimilars approved and marketed in the US
D. Europe has had more biosimilar approvals but many have been removed from the market
2. Assessment Question

Which of the following is likely to be the best way to list biological products in information systems in order to prevent wrong product selection or miscommunication?

A. Use the US Adopted Name (USAN) (core name plus suffix) exclusively
B. Use the product's brand name only
C. Use a combination of the USAN and the product's brand name
D. List the USAN followed by the NDC number
3. Assessment Question

What factor is NOT considered by the FDA in the extrapolation of indications in the biosimilar regulatory approval process?

A. A clinical trial of the biosimilar demonstrating safety and efficacy for each indication
B. Mechanism of action of the biologic
C. Understanding of the interaction of the biologic with target receptors
D. Pharmacokinetics in various populations
4. Assessment Question

Which of the following is NOT a consideration in the formulary selection and integration of biosimilars into clinical practice?

A. Dosage forms available relative to the population
B. Economic impact on payers, providers, and patients
C. The number of similar products on the formulary and their naming in electronic systems
D. Dosing modifications of the biosimilar relative to the reference product
Biologics Price Competition and Innovation Act of 2009

- Signed into law in 2010
- Created the 351(k) or “biosimilar” pathway
- Intended to be an “abbreviated” process
- Biosimilars must not have any clinically meaningful differences in safety, purity and potency as compared to the reference product.
Approval Pathways in the US

**Small-Molecule Drugs**

- Food, Drug, and Cosmetic Act (FDCA)
  - New Drug Application (NDA) 505(b)(1)
  - 505(b)(2)
  - Safety and Efficacy must be demonstrated

- Abbreviated New Drug Application (ANDA) 505(j)
  - Bioequivalence must be demonstrated

**Biologics**

- Public Health Service Act (PHSA)
  - Biologics License Application (BLA) 351(a)
    - Safety and Efficacy must be demonstrated
    - Extensive comparability exercise addresses drift (Q5E)

- Biosimilar Biologics License Application 351(k)
  - Must demonstrate highly similar to reference
  - Interchangeable designation requires more data

**Insulin LMWH**

- Generics

Biologics Price Competition and Innovation Act approved as part of the Accountable Care Act in 2010 authorized the FDA to create an abbreviated pathway for biosimilars approval.
General Principles for Demonstrating Biosimilarity

- Biosimilars approved via an abbreviated pathway
- Demonstration of biosimilarity is a comparability exercise and not a therapeutic equivalence study
- Goal of the biosimilarity exercise is to establish that the candidate biosimilar is not significantly different from the reference product and is unlikely to have any clinically significant differences
  - Smaller-scale direct comparisons and extrapolation are used

Biosimilar and Biologic Development

No “one size fits all” assessment:

FDA scientists will evaluate the applicant’s integration of various types of information to provide advice on scope and extent of develop plan and, ultimately, an overall assessment that a biological product is (or is not) biosimilar to an approved reference product.

Paradigm Shift of Biosimilar Pathway

Biosimilar Development Program Objective:
*Establish Biosimilarity* Based Upon Totality of Evidence,
*Not Re-Establish Benefit*

I’ve heard that there is variation in reference products over time so that they might be considered to be “biosimilars of themselves”. Is there any truth to this?
Manufacturing Changes Can Slightly Alter Physicochemical Characteristics

<table>
<thead>
<tr>
<th>Reference Product</th>
<th># of Changes after Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>37</td>
</tr>
<tr>
<td>Etanercept</td>
<td>21</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>18</td>
</tr>
<tr>
<td>Abatacept</td>
<td>7</td>
</tr>
<tr>
<td>Rituximab</td>
<td>6</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>4</td>
</tr>
</tbody>
</table>

Changes made to tighten specifications and controls on the process and to increase production capacity

Originator Manufacturing Process Changes

- Small modifications may result in slight changes in structure

Darbepoetin alfa

Rituximab

Etanercept

Despite these differences, when the products are within a prespecified acceptable range, the products are marketed with no change in label.

Biologic Manufacturing Changes: Demonstration of Comparability

"The demonstration of comparability does not necessarily mean that the quality attributes of the prechange and postchange product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product."

Are there aspects of biosimilarity that are different for larger monoclonal antibodies?
Phases of Biosimilar Development

- **Short-acting G-CSF**
  - DMARDs
    - Infliximab
    - Adalimumab
    - Etanercept

- **Oncology monoclonal antibodies**
  - Long-acting G-CSF
  - Short-acting epoetin

- **Long-acting epoetin**
- **Immunotherapy agents**

G-CSF = granulocyte colony stimulating factor; DMARD = disease-modifying antirheumatic drugs.
How Do Small Biologics and Monoclonal Antibodies Differ?

**Filgrastim**
\[ C_{845}H_{1343}N_{233}O_{243}S_{9} \]

**Epoetin**
\[ C_{815}H_{1317}N_{233}O_{241}S_{5} \]

**Etanercept**
\[ C_{2224}H_{3475}N_{621}O_{698}S_{36} \]

**Infliximab**
\[ C_{6428}H_{9912}N_{1694}O_{1987}S_{46} \]

**Rituximab**
\[ C_{6416}H_{9874}N_{1688}O_{1987}S_{44} \]

How Do Small Biologics and Monoclonal Antibodies Differ?

<table>
<thead>
<tr>
<th>Small Biologic</th>
<th>Revenue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>$602,436,960</td>
</tr>
<tr>
<td>Epoetin</td>
<td>$2,416,580,281</td>
</tr>
<tr>
<td>Etanercept</td>
<td>$7,362,086,000</td>
</tr>
<tr>
<td>Infliximab</td>
<td>$5,309,916,000</td>
</tr>
<tr>
<td>Rituximab</td>
<td>$3,913,944,000</td>
</tr>
</tbody>
</table>

Protein Heterogeneity Assessment Must Be Evaluated Whether Small or Large Biologic

- Amino acid substitution
- N- and C-terminal mods
- Mismatched S-S bonds
- Folding
- Truncation
- Aggregation
- Multimer dissociation

- Denaturation
- Acetylation
- Fatty acylation
- Deamidation
- Oxidation
- Carbamylation
- Carboxylation
- Formylation

- Gamma-carboxyglutamylation
- O-linked glycosylation
- N-linked glycosylation
- Methylation
- Phosphorylation
- Sulphation
- PEGylation
Analytical Tools to Evaluate Proteins

- **Amino acid sequence and modifications:**
  - MS, peptide mapping, chromatographic separations

- **Folding:**
  - S-S bonding, calorimetry, HDX- and IM-MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, fluorescence

- **Subunit interactions:**
  - Chromatography, IM-MS

- **Heterogeneity of size, aggregates, charge, hydrophobicity:**
  - Chromatography resins; gel and CE, light scatter, IM-MS, analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy

- **Glycosylation:**
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS

- **Bioactivity:**
  - Cellular and animal bioassays; ligand and receptor binding (ELISA, surface plasmon resonance), signal transduction

- **Impurities:**
  - Proteomics, immunoassays, metal and solvents analysis

MS = mass spectrometry; HDX = hydrogen/deuterium exchange; IM = ion mobility; NMR = nuclear magnetic resonance; CE = capillary electrophoresis; ELISA = enzyme-linked immunosorbent assay.
## Current Biosimilars in the U.S.

<table>
<thead>
<tr>
<th>Product</th>
<th>US Approval Pathway</th>
<th>US Biosimilar</th>
<th>EU Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>505(b)(2) – abbreviated pathway under FDCA</td>
<td>No</td>
<td>Yes (Inhixa, Thorinane)</td>
</tr>
<tr>
<td>Tbo-filgrastim</td>
<td>351(a) – full BLA</td>
<td>No (Granix)</td>
<td>Yes (Tevagrasmid)</td>
</tr>
<tr>
<td>Filgrastim-sndz*</td>
<td>351(k)</td>
<td>Yes (Zarzio, Sandoz)</td>
<td>Yes (Zarzio)</td>
</tr>
<tr>
<td>Insulin glargine</td>
<td>505(b)(2)</td>
<td>No (Basaglar)</td>
<td>Yes (Abasaglar, Lusduna)</td>
</tr>
<tr>
<td>Infliximab-dyyb*</td>
<td>351(k)</td>
<td>Yes (Inflectra, Celltrion/Pfizer)</td>
<td>Yes (Inflectra, Remsima, Flixabi)</td>
</tr>
<tr>
<td>Etanercept-szzs</td>
<td>351(k)</td>
<td>Yes (Erelzi, Sandoz)</td>
<td>Yes (Benepali, Erelzi)</td>
</tr>
<tr>
<td>Adalimumab-atto</td>
<td>351(k)</td>
<td>Yes (Amjevita, Amgen)</td>
<td>Yes (Amjevita, Solymbic)</td>
</tr>
<tr>
<td>Infliximab-abda*</td>
<td>351(k)</td>
<td>Yes (Renflexis, Samsung Bioepis/Merck)</td>
<td>Yes (Inflectra, Remsima, Flixabi)</td>
</tr>
<tr>
<td>Adalimumab-adbm</td>
<td>351(k)</td>
<td>Yes (Cyleto, Boehringer Ingelheim)</td>
<td>Yes (Amjevita, Solymbic)</td>
</tr>
<tr>
<td>Bevacizumab-awwb</td>
<td>351(k)</td>
<td>Yes (Mvasi, Amgen)</td>
<td>No</td>
</tr>
<tr>
<td>Trastuzumab-dkst</td>
<td>351(k)</td>
<td>Yes (Ogivri, Mylan/Biocon)</td>
<td>No</td>
</tr>
<tr>
<td>Infliximab-qbtx</td>
<td>351(k)</td>
<td>Yes (Ixifi, Pfizer)</td>
<td>No</td>
</tr>
</tbody>
</table>

*currently marketed biosimilar

Why Are Biologics Important

- 12 of the top 25 overall drug expenditures in 2016 were biologics
- 20 of the top 25 drug expenditures for agents administered in outpatient clinics were biologics or vaccines
- Many of the drugs in the development pipeline are biologics (over 50%)
- Due to their costs, biologics have a substantial impact on healthcare expenditures for patients, health systems, and society

Biologics Patent Expirations Will Be a Powerful Driver for Biosimilars

<table>
<thead>
<tr>
<th>Europe Union (EU)</th>
<th>United States (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2010  2015  2020  2025</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Epoetin alfa 2015</td>
</tr>
<tr>
<td>Pegfilgrastim 2015</td>
<td>Insulin Glargine 2015</td>
</tr>
<tr>
<td>Trastuzumab 2016</td>
<td>Insulin Glargine 2015</td>
</tr>
<tr>
<td>Adalimumab 2018</td>
<td>Bevacizumab 2019</td>
</tr>
<tr>
<td>Bevacizumab 2019</td>
<td>Adalimumab 2023</td>
</tr>
<tr>
<td>Bevacizumab 2019</td>
<td>Etanercept 2029?</td>
</tr>
</tbody>
</table>

Biosimilar Pipeline for 2018

<table>
<thead>
<tr>
<th>INN</th>
<th>Manufacturer</th>
<th>Application Submitted</th>
<th>Estimated FDA Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab (CT-P10)</td>
<td>Teva and Celltrion</td>
<td>04/2017</td>
<td>2/2018</td>
</tr>
<tr>
<td>Trastuzumab (CT-P6)</td>
<td>Teva and Celltrion</td>
<td>05/2017</td>
<td>03/2018</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Sandoz</td>
<td>07/2017</td>
<td>05/2018</td>
</tr>
<tr>
<td>Trastuzumab (PF-05280014)</td>
<td>Pfizer</td>
<td>07/2017</td>
<td>05/2018</td>
</tr>
<tr>
<td>Trastuzumab (ABP 980)</td>
<td>Amgen and Allergan</td>
<td>07/2017</td>
<td>05/2018?</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>Adello Biologics</td>
<td>07/2017</td>
<td>05/2018</td>
</tr>
<tr>
<td>Adalimumumab</td>
<td>Novartis</td>
<td>01/2018</td>
<td>?</td>
</tr>
</tbody>
</table>

Pending Biosimilars Without Known User Fee Dates

Filgrastim
- Apotex – likely complete response letter

Pegfilgrastim
- Apotex – likely complete response letter
- Sandoz – confirmed complete response letter
- Coherus – confirmed complete response letter
- Mylan – confirmed complete response letter

Epoetin
- Pfizer – complete response letter
I’ve heard that biosimilars have been available in Europe for quite a while. What has been their experience?
Europe Has Led the Development of Regulatory Processes for Biosimilars

- First biosimilar approved in 2006
- 37 biosimilars for reference products on the market in Europe
  - Somatropin, epoetin alfa/zeta, follitropin, filgrastim, infliximab, insulin glargine, insulin lispro, etanercept, adalimumab, teriparatide, enoxaparin, rituximab
- 3 applications denied
  - Interferon alpha-2a, interferon beta-1a, human insulins (Marvel LifeSciences)

EMA = European Medicines Agency

European Union Experience with Biosimilars

- All biosimilars authorized have been approved for the same indications as reference products (through extrapolation)

- In contrast to the FDA, the EMA does not have an “interchangeable” category—substitution policies determined by individual countries

- Substitution and reimbursement policies vary widely

- Biosimilar discounts typically reported in the 25% range, but other rebates may exist. In some cases, discounts are substantially higher

Use of Biosimilars in the European Union

- Market uptake has been somewhat slow making up about 25% of sales of biologics with expired patents in 2015; but, growing at a rate greater than other market segments
- Filgrastim biosimilars have 60% to 80% market share
- Germany, United Kingdom, France are leading uptake of biosimilars across the European Union
- European Union biosimilars have enhanced market competition, helped stabilize health care costs, and increased access—even without high overall uptake
- EMA has not identified any specific safety issues for approved and marketed biosimilar products, even with relatively robust pharmacovigilance programs

What are the key considerations in formulary selection/ placement of biosimilars?
Considerations for Formulary Selection of Biosimilars

**Efficacy/Safety**
- Clinical data
- Range of indications
- Immunogenicity concerns
- Potential for therapeutic interchange
- Number of similar agents on formulary
- Pharmacovigilance requirements

**Manufacturer Considerations**
- Supply reliability
- History of drug shortages
- Supply chain security
- Anti-counterfeit measures
- Patient assistance programs
- Reimbursement support

**Product Considerations**
- Product packaging and labeling
- Bar coding
- Compatibility with CSTDs,* robotics
- Product preparation and administration
- Storage requirements

**Hospital and Patient Factors**
- Economic considerations
  - Hospital
  - Payer
  - Patient
- Payer policies
- Transitions of care
- IT and medication system changes
- Educational requirements

* CSTDs = closed system transfer devices

Considerations Impacting Formulary Selection and Use of Biosimilars

- How many agents to carry
  - Range of indications
  - Dosage forms
  - Special populations

- Financial impact from perspectives of health system and patient
  - CMS reimbursement policy – ASP* + % of ASP of the REFERENCE Product
  - Position within prescription drug plans (patient out-of-pocket costs)
  - Patient assistance support

- Dosage forms available

- Transitions of care management
  - Switch to workhorse agent or maintain patient on current biologic?
  - Consideration of coverage if in prescription benefit

- Safe integration into healthcare system (naming)

* ASP = Average Sales Price
I’ve heard some mention that the approach to biosimilars “with curative intent” might be different than for biosimilars that provide supportive care. What is the rationale?
Understanding Biosimilar Clinical Trials

- In addition to analytic studies and animal studies, 351(k) of the PHSA requires:
  - A clinical study or studies (including immunogenicity and PK or PD) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed...

- Equivalence/Non-inferiority vs superiority ("biobetter")

- Must be clinically meaningful
  - Study size and design sufficient to detect clinically meaningful differences
  - Population to study (eg, patients vs healthy volunteers)
  - Duration
  - Clinical endpoints to measure

- Sensitive enough to detect differences in safety and efficacy (Do pharmacodynamic measures correlate with clinical outcomes?)
  - Use clinically relevant and sensitive endpoints in the right population

- Other considerations
  - Understanding of MOA of the biologic
  - Extrapolation
  - Bridging of data

PHSA = Public Health Service Act; MOA = mechanism of action.

Biosimilar Comparative Clinical Studies

- Efficacy and safety/immunogenicity: specific clinical trial design will depend on which residual questions remain
  - Clinical studies should be designed to demonstrate neither decreased nor increased activity
  - Use clinically relevant and sensitive endpoints in the right population
  - Biosimilar sponsor to justify comparability data

## Trastuzumab Biosimilars with Registered Phase III Clinical Trials

*(Patent Expiration: 2019)*

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Primary Endpoint</th>
<th>Disease</th>
<th>Available Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCD-022 NCT01764022, complete</td>
<td>ORR</td>
<td>HER2+ MBC</td>
<td>Phase I: BCD-022 showed similar PK and safety to trastuzumab in patients with HER2+ MBC. Phase III: Noninferiority to trastuzumab; similar safety, tolerability, and immunogenicity (N=126)</td>
</tr>
<tr>
<td>PF-05280014 NCT01989676, active</td>
<td>PK, pCR (2nd), ORR</td>
<td>HER2+ EBC</td>
<td>Preclinical: PF-05280014 showed similar structural and functional properties, PK, and immunogenicity profiles to trastuzumab. Phase I: PF-05280014 showed similar PK, safety, and immunogenicity to trastuzumab in 105 healthy volunteers. Phase III: Positive top-line results announced via press release (N=226)</td>
</tr>
<tr>
<td>ABP 980* NCT01901146, complete</td>
<td>pCR</td>
<td>HER2+ EBC</td>
<td>Phase I: ABP 980 showed comparable PK, PD, safety, tolerability, and immunogenicity to trastuzumab in healthy volunteers</td>
</tr>
</tbody>
</table>

*BLA submitted to FDA July 31, 2017. **BLA accepted by the FDA. ***Approved by FDA ODAC.

OS = overall survival; PFS = progression-free survival; TTP = time to progression; TTR = time to response.

**Trastuzumab Biosimilars with Registered Phase III Clinical Trials (Patent Expiration: 2019)**

<table>
<thead>
<tr>
<th>Biosimilar</th>
<th>Primary Endpoint</th>
<th>Disease</th>
<th>Available Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT-P6**</td>
<td>pCR</td>
<td>HER2+ EBC</td>
<td>Phase I/II: CT-P6 showed equivalent PK and similar safety to trastuzumab in patients with HER2+ MBC</td>
</tr>
<tr>
<td></td>
<td>ORR</td>
<td>HER2+ EBC</td>
<td>Phase III: Similar efficacy (pCR) to neoadjuvant trastuzumab; also similar secondary endpoints (ORR, PK, PD, and safety; N=549)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2+ MBC</td>
<td>Phase III: CT-P6 showed similar efficacy (ORR) and safety to trastuzumab in combination with paclitaxel</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2+ MBC</td>
<td>Phase III: Similar efficacy (ORR, TTP, TTR) and safety to trastuzumab (N=475)</td>
</tr>
<tr>
<td>SB3-G31-BC</td>
<td>pCR</td>
<td>HER2+ EBC</td>
<td>Phase III: Equivalent breast pCR rate to trastuzumab; similar safety, PK, and immunogenicity (N=875)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HER2+ MBC</td>
<td></td>
</tr>
<tr>
<td>Hercules/Myl14010***</td>
<td>ORR</td>
<td>HER2+ MBC</td>
<td>Phase III: Equivalent Week 24 ORR in combination with taxanes; equivalent Week 46 TTP, PFS, or OS (N=500)</td>
</tr>
</tbody>
</table>

*BLA submitted to FDA July 31, 2017. **BLA accepted for review by the FDA. ***Recommended for approval by ODAC to the FDA.

OS = overall survival; PFS = progression-free survival; TTP = time to progression; TTR = time to response.


Evaluation of Biosimilar Trastuzumab CT-P6 (NCT02162667)

- Study drugs were administered at 8 mg/kg (cycle 1) and 6 mg/kg every 3 weeks in combination with docetaxel (Cycles 1-4) and 5-fluorouracil, epirubicin, and cyclophosphamide (Cycles 5-8)
- Primary endpoint: pCR rate at surgery
- Secondary endpoints: ORR, PK, PD and safety

# Biosimilar Trastuzumab CT-P6—Efficacy

<table>
<thead>
<tr>
<th>pCR rate (ypT0/is ypN0)</th>
<th>PPS</th>
<th>ITT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CT-P6 (n=248)</td>
<td>Trastuzumab (n=256)</td>
</tr>
<tr>
<td>pCR rate</td>
<td>46.8</td>
<td>50.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(40.4 – 53.2)</td>
<td>(44.1 – 56.7)</td>
</tr>
<tr>
<td>Risk ratio estimate (95% CI)</td>
<td>0.9282 (0.7753 – 1.1113)</td>
<td>0.9240 (0.7687 – 1.1108)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pCR rate (ypTo ypNo)</td>
<td>39.9</td>
<td>41.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(33.8 – 46.3)</td>
<td>(35.3 – 47.7)</td>
</tr>
<tr>
<td>Risk ratio estimate (95% CI)</td>
<td>0.9641 (0.7806 – 1.1906)</td>
<td>0.9593 (0.7749 – 1.1877)</td>
</tr>
<tr>
<td>ORR (independent review)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>87.1</td>
<td>86.3</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(82.3 – 91.0)</td>
<td>(81.5 – 90.3)</td>
</tr>
<tr>
<td>Risk ratio estimate (95% CI)</td>
<td>1.0089 (0.9423 – 1.0803)</td>
<td>1.0083 (0.9386 – 1.0831)</td>
</tr>
</tbody>
</table>

Biosimilar Trastuzumab CT-P6 (NCT02162667)

- Safety Results:
  - Rate of at least 1 treatment-related AE was 6.6% for CT-P6 and 7.6% for trastuzumab
  - 1 patient in each group withdrew due to significant LVEF decrease
  - 8.5% of patients receiving CT-P6 and 9.0% of patients receiving trastuzumab reported Infusion-related reactions

- Trial concluded that CT-P6 demonstrated similarity of efficacy through both primary and secondary efficacy endpoints and that CT-P6 exhibited a similar safety and tolerability profile to the reference product

Clinical Trial Design: Biosimilar Trastuzumab (HER2 Positive, Metastatic Breast Cancer)

Part 1: Combined Treatment/PK Analysis

- Hercules
  - Loading dose: 8 mg/kg
  - Maintenance dose: 6 mg/kg Q3W
  - The day after Trastuzumab infusion
  - Docetaxel: 75 mg/m² Q3W cycles
  - Paclitaxel: 80 mg/m² weekly 30 min after Trastuzumab infusion

- Herceptin®
  - Loading dose: 8 mg/kg
  - Maintenance dose: 6 mg/kg Q3W

Part 2: Single Treatment

- Hercules
  - Maintenance dose until disease progression

- Herceptin®
  - Maintenance dose until disease progression

8 Cycles = 24 Weeks

*Continue 3 week cycles; if stable disease after 8 cycles, can continue combination treatment on Part 1 at investigator’s discretion.

R = Randomization (within 3 days prior to Cycle 1, Day 1).


www.fda.gov/downloads/Advisor/Committees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisory
### Superiority vs Equivalence

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trastuzumab + Taxane ORR (n/N)</th>
<th>Taxane ORR (n/N)</th>
<th>ORR Ratio&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasparini&lt;sup&gt;12&lt;/sup&gt;</td>
<td>85% (33/39)</td>
<td>48% (20/42)</td>
<td>1.78 (1.26, 2.51)</td>
</tr>
<tr>
<td>Marty&lt;sup&gt;11&lt;/sup&gt;</td>
<td>61% (56/92)</td>
<td>34% (32/94)</td>
<td>1.79 (1.29, 2.48)</td>
</tr>
<tr>
<td>Slamon&lt;sup&gt;13&lt;/sup&gt;</td>
<td>49% (33/68)</td>
<td>17% (13/77)</td>
<td>2.87 (1.65, 5.00)</td>
</tr>
<tr>
<td>Meta-Analysis (Fixed-effect model)</td>
<td>—</td>
<td>—</td>
<td>1.92 (1.54, 2.39)</td>
</tr>
</tbody>
</table>

- To maintain 50% of the treatment effect (ie, the lower bound of the 95% CI: 1.54), the equivalence region was calculated to be from 0.81 to 1.24.

<sup>a</sup>IHC3+ and/or FISH positive patients from 3 randomized trials. <sup>b</sup>ORR Ratio: ORR of (trastuzumab + Taxane) / ORR of Taxane. n/N = number of responders/number of total patients in the treatment arm.

## Overall Response Rate (Biosimilar vs Originator)

Table 12. ORR per Central Review at Week 24, ITT1 Population

<table>
<thead>
<tr>
<th></th>
<th>MYL-1401O + Taxane (N=230)</th>
<th>EU-Herceptin + Taxane (N=228)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response (CR), n (%)</strong></td>
<td>4 (2)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Partial response (PR), n (%)</strong></td>
<td>157 (68)</td>
<td>146 (64)</td>
</tr>
<tr>
<td><strong>Stable disease (SD), n (%)</strong></td>
<td>48 (21)</td>
<td>49 (21)</td>
</tr>
<tr>
<td><strong>Progressive disease (PD), n (%)</strong></td>
<td>9 (4)</td>
<td>20 (9)</td>
</tr>
<tr>
<td><strong>N/A, n (%)</strong></td>
<td>12 (5)</td>
<td>13 (6)</td>
</tr>
<tr>
<td><strong>Overall response rate, n (%)</strong></td>
<td>161 (70%)</td>
<td>146 (64%)</td>
</tr>
</tbody>
</table>

**Ratio of ORR (MYL-1401O vs EU-Herceptin)**

```
Ratio ORR = 1.09, well within pre-defined range of 0.81 to 1.24
```

**Complete response (CR), n (%)**

```
(0.98, 1.22)
```

---

Is it true that biosimilars might be granted approval for some indications without performing any clinical trials in those indications?
Extrapolation of Indications

- Extrapolation of data from a clinical trial in one disease to support approval for additional indications

- Factors to be considered
  - Clinical experience with the reference product
  - MOA in each indication
  - Target receptors
  - Product structure and target/receptor interactions
  - PK in different patient populations
  - Differences in the safety/immunogenicity profile between indications

Science of Extrapolation

Similarity between molecules allows extrapolation

Extrapolation is not from one clinical study of the biosimilar to other indications

I’ve heard a lot of opinions about the naming of biosimilars and the importance of pharmacovigilance. Why is this important?
The Conundrum of Biosimilar Naming

<table>
<thead>
<tr>
<th>Biosimilars should have a distinct USAN to differentiate from reference and other biosimilars</th>
<th>Biosimilars should have the exact same United States Adopted Name (USAN) as the reference product</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Pros</strong></td>
</tr>
<tr>
<td>• Communicate that these products are “highly similar”</td>
<td>• Improved pharmacovigilance</td>
</tr>
<tr>
<td>• Facilitate adoption and substitution of interchangeable biologics</td>
<td>• Recognize as distinct products</td>
</tr>
<tr>
<td><strong>Cons</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>• Hard to trace for pharmacovigilance</td>
<td>• Confusion about whether they are “interchangeable”</td>
</tr>
<tr>
<td></td>
<td>• May impede adoption</td>
</tr>
<tr>
<td></td>
<td>• Issues with substitution</td>
</tr>
</tbody>
</table>

FDA Guidance on Naming

- US Adopted Name (USAN) with an added random four-letter suffix “devoid of meaning” for all biologics (including reference products)
  - replicamab-cznm
  - replicamab-hixf

- Benefits
  - Ability to differentiate products for pharmacovigilance purposes
  - Common core name will group similar biologics in electronic systems
  - Having suffix for all products reduces perception that biosimilar is inferior to reference product

FDA Guidance on Naming

- Concerns
  - Unless interchangeable biosimilar has the same name, it will inhibit interchange
  - Potential for errors when using four-letter suffix that is not memorable (“devoid of meaning”)
  - More complex naming system increases likelihood that errors could occur, actually harming pharmacovigilance
  - Need to change name of current biologics on market creates confusion

http://www.healio.com/rheumatology/psoriatic-arthritis/news/online/%7Bfd74beb9-177e-4618-8a94-aab7cd3f77b7%7D/physician-groups-support-proposed-fda-biosimilar-naming-convention-but-also-call-for-maker-id
### Naming Existing Biologics/Biosimilars

- Manufacturer to submit up to 10 proposed suffixes to FDA for consideration

<table>
<thead>
<tr>
<th>Current</th>
<th>Example Proposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim</td>
<td>Filgrastim-jcwp</td>
</tr>
<tr>
<td>Filgrastim-sndz</td>
<td>Filgrastim-bflm</td>
</tr>
<tr>
<td>Tbo-filgrastim</td>
<td>Filgrastim-vkzt</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>Epoetin alfa-cgkn</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Infliximab-hjmt</td>
</tr>
</tbody>
</table>

**Scenarios with the Listing of Multiple Biologics in Electronic Systems**

<table>
<thead>
<tr>
<th>Filgrastim-rbsz</th>
<th>Rapiolastim*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filgrastim-sndz</td>
<td>Xarzio</td>
</tr>
<tr>
<td>Filgrastim-trby</td>
<td>Stimogram</td>
</tr>
<tr>
<td>Filgrastim-zsrc</td>
<td>Neupogen</td>
</tr>
</tbody>
</table>

* Brand names in this column hypothetical or based on EU names not linked to specific INN+suffix

Which scenario do you believe is less prone to wrong-selection errors by prescribers, pharmacists, nurses?
Implications/Actions

- High potential for wrong product selection errors in all phases of medication use process
  - Care during medication histories, transitions of care, when communicating with patients and among health care providers
  - Care when setting up products in electronic systems involved in the medication use process (e.g. CPOE, pharmacy information system, eMAR)
  - Advisable to use Brand Names in addition to US Adopted Name (USAN) where feasible to prevent wrong product selection errors
Importance of Pharmacovigilance

- Abbreviated pathway and complexity of molecule and manufacturing process necessitates a strong post-marketing surveillance approach.

- Critical to be able to distinguish the correct products patients are on for both active and passive surveillance methods.

- FDA has developed naming approach to facilitate pharmacovigilance.

- Concern that naming convention could actually lead to wrong product selection errors or identification of incorrect product.

- Pharmacists will need to play a critical role in working with patients and other health professionals to assure accurate identification of products.

Why do we have interchangeable biosimilars and what is the significance in practice compared to standard biosimilars?
Pathways for Approval in the US

**DRUGS**
- Small-molecules
- Approved via FDCA

**BIOLOGICS**
- Proteins
- Approved via PHSA

**New Drug Application (NDA)**
- Safety and Efficacy must be demonstrated

**Abbreviated New Drug Application (ANDA)**
- Bioequivalence must be demonstrated

**Biologics License Application (BLA)**
- Safety and Efficacy must be demonstrated
  - Extensive comparability exercise addresses drift (Q5E)

**Biosimilar Biologics License Application**
- Must demonstrate that it is highly similar to reference
  - Interchangeable biosimilars require more data

Genetics
Biosimilars
Interchangeability

- The biological is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient, and the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is not greater than the risk of using the reference product without such alteration or switch.

- State substitution laws will impact practice.


Factors Impacting Interchangeability

- Analysis of critical quality attributes and product complexity
- Analysis of the MOA for each condition
  - Target receptor(s)
  - Binding, dose response curve
  - Structure/receptor interactions
- Pharmacokinetics
- Immunogenicity (anti-drug antibodies, etc.)
- Differences in toxicity across various indications or patient populations

Interchangeable Biosimilars

- No FDA guidance until draft published in Jan 2017; thus, initial biosimilars are not “interchangeable”

- Guidance also uses a “totality of the evidence” approach

- Expected to produce the same clinical result as the reference product in any given patient

- For a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such an alternation or switch

Switching Studies

- For products that are intended to be administered to an individual more than once
- FDA has outlined a flexible approach regarding design
- Primary endpoint may be PK or PD parameters, as these are generally sensitive to changes in immunogenicity
- Will also likely include safety, efficacy, and immunogenicity measures

Typical Features of State Legislation

- Prescriber can prevent substitution with DAW
- Prescriber must be notified of substitution
- Patient must be notified and consent
- Records of substitution must be retained
- State should keep a list of interchangeable products

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

- Designed to enable a user to determine if a biological product is biosimilar or interchangeable with a reference biologic per FDA evaluation
- Cross-references biological products licensed under 351(a) with biosimilar or interchangeable products licensed under 351(k)

What are some key points that I can use when discussing biosimilars with physicians and other prescribers?
Key Points With Physicians

- Help them understand the rationale, approach and rigor of the abbreviated biosimilars pathway
- Provide information on the European experience with biosimilars
- Explain the goal of improved access and reduced costs for the health system in general but also for patients
- Growing support for the use of biosimilars and limited switching by some physician specialty organizations
European Crohn’s and Colitis Organisation Position Statement (2013)

- “Different biological and biosimilar medicines targeting the same molecule are neither identical in efficacy nor toxicity, even in the same clinical entity.”

- “A biosimilar proven effective and safe for one indication may not necessarily be effective and safe for a second indication for which the reference biological has been shown to be safe and effective.”

- “Specific evidence obtained in patients with IBD should be required to establish efficacy and safety for this specific indication, because experience with currently licensed biological medicines has already shown that clinical efficacy in IBD cannot be predicted by effectiveness in other indications, such as rheumatoid arthritis.”

- “Any decision to substitute a product should only be made with the prescribing health care provider’s specific approval and patient knowledge.”

European Crohn’s and Colitis Organisation Position Statement (2017)

- “Biosimilarity is more sensitively characterised by performing suitable *in vitro* assays than clinical studies.”

- “Clinical studies of equivalence in the most sensitive indication can provide the basis for extrapolation. Therefore data for the use of biosimilars in IBD can be extrapolated from another sensitive indication.”

- “When a biosimilar product is registered in the EU, it is considered to be as efficacious as the reference product when use in accordance with the information provided in the Summary of Product Characteristics.”

- “Switching from the originator to a biosimilar in patients with IBD is acceptable. Studies of switching can provide valuable evidence for safety and efficacy. Scientific and clinical evidence is lacking regarding reverse switching, multiple switching, and cross-switching among biosimilars in IBD patients.”

British Society of Gastroenterology Guidance

- Infliximab biosimilar (CT-P13, Remsima or Inflectra) available since 2013 and is now widely used

- “For patients starting infliximab: Remicade, Remsima, or Inflectra can be prescribed, taking into account the evidence showing similar clinical effectiveness. There is evidence that monitoring of patients, including measurement of drug and anti-drug antibody levels, is no different... The choice of preparation should take into account the cost of the drug and its administration.”

- “There is sufficient evidence to recommend that patients who are in a stable clinical response or remission on Remicade therapy can be switched to Remsima or Inflectra at the same dose and dose interval.”

- Automatic substitution without consulting the prescriber is not appropriate

European Society for Medical Oncology
Position Paper (2017)

- Biosimilars can positively impact patient access and financial sustainability of health care systems
- Biosimilars should be tested for efficacy and immunogenicity in the most sensitive populations
- Pharmacovigilance and phase IV studies should occur post-marketing
- Extrapolation of indications can occur assuming justified by relevant data
- Interchange and switching can occur if physician and patient are informed and patient is monitored for adverse events

What are some strategies to consider when communicating about biosimilars with patients?
Potential Strategies for Communicating with Patients

- Complexity of regulatory process makes it difficult to communicate with patients and advocacy groups
  - Keep discussion simple
  - Explain that biologics are complex molecules and small variations in structure between biosimilars and reference products are similar to small variations that occur in reference products themselves over time
  - FDA approval process is designed to demonstrate that biosimilars are no more or less effective, and no more or less safe
  - Purpose is to produce competition, similar to generics with small molecule drugs
  - Many specialty professional organizations now support the use of biosimilars to reduce costs and improve access to important treatments
  - European approval process is very similar to US, and there is a good track record of use

- Insurance coverage and out-of-pocket cost concerns
- Manufacturer identify/ clarity around name of product
- Communicate through patient advocacy groups with general information on biosimilars
Key Points

- Biologics are complex drugs that are not considered “generic”; emerging guidance on “interchangeable biosimilars”

- The FDA approval process to demonstrate that a biosimilar is “highly similar” to a reference biologic is scientific, robust, and regulated

- All biosimilar candidates are subject to rigorous analytical characterization

- No specific safety issues have been identified for approved and marketed biosimilars in Europe

- Most early experience has been with smaller, less complex biologics
Key Points

- The analytical evaluation of biosimilars for monoclonal antibodies is more complex and requires a greater level of understanding by clinicians.
- This awareness is particularly important as multiple biosimilar monoclonal antibody products become available.
- Integration of biosimilar agents into clinical practice presents many operational and clinical challenges.
- Incorporation of biosimilars into clinical practice should offer cost savings and increased patient access.
- Regulatory actions, pricing, reimbursement policies, clinical experience and emerging data, will play key roles in determining future use of biosimilars and product selection in the U.S.
1. Assessment Question

In Europe, there are over 30 biosimilars that have been approved and marketed. How does the US compare?

A. There are the same number of approved and marketed biosimilars in the US
B. There are more biosimilars approved and marketed in the US
C. There are fewer biosimilars approved and marketed in the US
D. Europe has had more biosimilar approvals but many have been removed from the market
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2. Assessment Question

Which of the following is likely to be the best way to list biological products in information systems in order to prevent wrong product selection or miscommunication?

A. Use the US Adopted Name (USAN) (core name plus suffix) exclusively
B. Use the product’s brand name only
C. Use a combination of the USAN and the product’s brand name
D. List the USAN followed by the NDC number
2. Assessment Question

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A. Use the US Adopted Name (USAN) (core name plus suffix) exclusively

B. Use the product’s brand name only

C. **Use a combination of the USAN and the product’s brand name**

D. List the USAN followed by the NDC number
3. Assessment Question

What factor is NOT considered by the FDA in the extrapolation of indications in the biosimilar regulatory approval process?

A. A clinical trial of the biosimilar demonstrating safety and efficacy for each indication
B. Mechanism of action of the biologic
C. Understanding of the interaction of the biologic with target receptors
D. Pharmacokinetics in various populations
3. Assessment Question

What factor is NOT considered by the FDA in the extrapolation of indications in the biosimilar regulatory approval process?

A. A clinical trial of the biosimilar demonstrating safety and efficacy for each indication
B. Mechanism of action of the biologic
C. Understanding of the interaction of the biologic with target receptors
D. Pharmacokinetics in various populations
4. Assessment Question

Which of the following is NOT a consideration in the formulary selection and integration of biosimilars into clinical practice?

A. Dosage forms available relative to the population
B. Economic impact on payers, providers, and patients
C. The number of similar products on the formulary and their naming in electronic systems
D. Dosing modifications of the biosimilar relative to the reference product
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Which of the following is NOT a consideration in the formulary selection and integration of biosimilars into clinical practice?

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