THE EVOLVING ROLE OF BIOSIMILARS IN ONCOLOGY

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BIOSIMILARS

KEY DISCUSSION TOPICS

• Background- Biologicals
• Background- Rising Health care costs
• Definitions
• Production process
• Regulatory and Approval process

• Concerns
• Benefits
• Currently approved Biosimilars
• Questions for future
WHAT IS A BIOLOGIC?

Definition of Biological Product
Section 351, Public Health Service (PHS) Act

(1) The term “biological product” means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

42 U.S.C. § 262(i)
• Biologics are innovative medications that aren’t made, they are grown in living cells.

• Biologics are complex molecules– up to 1,000 times larger than conventional medicines.

• Manufacturing a biologic is a complex process that takes several months from start to finish.

• It’s important to remember that biologic medicines can never be exactly duplicated by two different manufacturers in the way that simpler medications can.

EXAMPLES OF BIOLOGICS

- Treat or help prevent a range of diseases including
  - Cancers, Hemophilia, Hepatitis, Ulcerative colitis,
  - Diabetes, RA, macular degeneration, migraine
  - MI, CHF, infection prophylaxis, Cystic Fibrosis, Asthma, Derm-cosmetic

- Examples Include:
  - Vaccines
  - Recombinant Antibodies
  - Monoclonal Antibodies (mAb)
  - Interleukins
  - Interferons
  - Growth Factors
  - Gene Therapy
  - Cell Therapy
  - Antisense
### HOW ARE BIOLOGICS DIFFERENT?

<table>
<thead>
<tr>
<th>Small Molecule Drugs</th>
<th>Biological Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generally low molecular weight</td>
<td>Generally high molecular weight</td>
</tr>
<tr>
<td>Usually organic or chemical synthesis</td>
<td>Made with/from live cells/organisms ⇒ inherent &amp; contamination risk</td>
</tr>
<tr>
<td>Fewer critical process steps</td>
<td>Many critical process steps</td>
</tr>
<tr>
<td>Well-characterized</td>
<td>Less easily characterized</td>
</tr>
<tr>
<td>Known structure</td>
<td>Structure may or may not be completely defined or known</td>
</tr>
<tr>
<td>Homogeneous drug substance</td>
<td>Heterogeneous mixtures ⇒ May include variants</td>
</tr>
<tr>
<td>Usually not immunogenic</td>
<td>Often Immunogenic</td>
</tr>
</tbody>
</table>
SIZE AND COMPLEXITY OF PROTEINS

Aspirin 180 Da

Monoclonal Antibody ~150,000 Da
BIOTECHNOLOGY PRODUCTION PROCESS

1. **Fermentor**
   - Live cells
   - Harvest Protein mixture

2. **Columns Purify Protein**
3. **Concentration**
4. **Biological Drug Substance**
5. **Formulation Filling**

**Biological Drug Product**
EXAMPLE CHALLENGES IN HANDLING BIOLOGICS

- Must be processed under tightly controlled conditions/controls throughout production to
  - consistently produce a safe, pure, and potent product, and
  - preclude the introduction of environmental contamination

- Biological products may be susceptible to extreme temperatures and light
- typically need refrigeration but may need frozen storage or preservatives
- shelf life may be limited
TIME, COST AND DEVELOPMENT ARE VERY DIFFERENT FOR GENERICS, BIOSIMILARS, AND REFERENCE PRODUCTS

<table>
<thead>
<tr>
<th></th>
<th>TIME</th>
<th>COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generics</td>
<td>3-4</td>
<td>&lt;$5</td>
</tr>
<tr>
<td>Biosimilars</td>
<td>7-8</td>
<td>= $200 M</td>
</tr>
<tr>
<td>Reference</td>
<td>10+ years</td>
<td>$1.2 B</td>
</tr>
</tbody>
</table>

DEVELOPMENT

RISING HEALTH CARE COSTS: CASE FOR BIOSIMILARs
Great variability in cost and quality of medical treatment across healthcare systems

Pts bear an ever-increasing share of the expense: financial toxicity

Cost affects access to care, treatment decisions, and pt outcomes

“Price is what you pay; value is what you get.” — Warren Buffett

More than 30% of spending on therapeutic drugs is concentrated in the top 5 therapy areas.

<table>
<thead>
<tr>
<th>Therapy Area</th>
<th>$Bn</th>
<th>% Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>27.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Antidiabetes</td>
<td>24.3</td>
<td>12.1</td>
</tr>
<tr>
<td>Mental health</td>
<td>23.8</td>
<td>-5.2</td>
</tr>
<tr>
<td>Respiratory</td>
<td>20.4</td>
<td>-5.2</td>
</tr>
<tr>
<td>Pain</td>
<td>18.7</td>
<td>4.1</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>17.9</td>
<td>18.0</td>
</tr>
<tr>
<td>Lipid regulators</td>
<td>13.6</td>
<td>-17.5</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>12.5</td>
<td>-5.3</td>
</tr>
<tr>
<td>HIV antirvirals</td>
<td>12.5</td>
<td>9.9</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>10.6</td>
<td>20.7</td>
</tr>
<tr>
<td>Antiulcerants</td>
<td>10.1</td>
<td>2.7</td>
</tr>
<tr>
<td>ADHD</td>
<td>9.9</td>
<td>-3.9</td>
</tr>
<tr>
<td>Dermatologicals</td>
<td>8.9</td>
<td>15.0</td>
</tr>
<tr>
<td>Antibacterials</td>
<td>8.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>8.1</td>
<td>16.0</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>7.4</td>
<td>-22.2</td>
</tr>
<tr>
<td>Vaccines</td>
<td>6.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>5.8</td>
<td>9.3</td>
</tr>
<tr>
<td>Vaccines</td>
<td>5.6</td>
<td>12.0</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>5.6</td>
<td>2.1</td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>5.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>
COST OF CHEMOTHERAPY VS BIOLOGICS

US Sales, 2005-2009

- 2005: $4.8 billion
- 2006: $5.7 billion
- 2007: $6.4 billion
- 2008: $7.4 billion
- 2009: $8.1 billion

Targeted Therapy: Share of US Market, 2009

- Bevacizumab: $3.00 billion (28%)
- Trastuzumab: $1.40 billion (14%)
- Rituximab: $2.70 billion (26%)
- Imatinib: $1.10 billion (11%)
- Erlotinib: $0.50 billion (5%)
- Dasatinib: $0.13 billion (1%)
- Others: $0.52 billion (5%)

Targeted Therapy:

- Sunitinib: $0.27 billion (3%)
- Cetuximab: $0.73 billion (7%)
COSTS OF CANCER CARE

Cumulative Percent Increase\(^1\)

<table>
<thead>
<tr>
<th>Top 10 Medicare Drugs (2014)(^2)</th>
<th>Cost in Millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranibizumab</td>
<td>1310</td>
</tr>
<tr>
<td>Aflibercept</td>
<td>1239</td>
</tr>
<tr>
<td>Rituximab (oncology)</td>
<td>853</td>
</tr>
<tr>
<td>Infliximab</td>
<td>786</td>
</tr>
<tr>
<td>Pegfilgrastim (oncology)</td>
<td>641</td>
</tr>
<tr>
<td>Bevacizumab (oncology)</td>
<td>593</td>
</tr>
<tr>
<td>Denosumab (oncology)</td>
<td>506</td>
</tr>
<tr>
<td>Trastuzumab (oncology)</td>
<td>289</td>
</tr>
<tr>
<td>Pemetrexed (oncology)</td>
<td>288</td>
</tr>
<tr>
<td>Bortezomib (oncology)</td>
<td>283</td>
</tr>
</tbody>
</table>


Slide credit: clinicaloptions.com
TOP 10 DRUGS BY 2018 SALES ($BILLION)
ONCOLOGY DRUGS CONSTITUTE 12% OF TOTAL DRUG SPEND

Total Cost of Oncology Medicines in the US

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost in Billions</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>21.9</td>
</tr>
<tr>
<td>2015</td>
<td>37.8</td>
</tr>
</tbody>
</table>

↑ $15.9 Billion

TOTAL SPENDING ON BIOLOGICS TRENDING UP

Global Biologics Sales, 2002-2017\(^1\)

- Biologics continue to outpace overall pharmaceutical drug spending growth\(^1\)
  - Expected to represent ~ 20% of global market value by 2017
- Pt access to biologic therapies is a concern\(^2\)

UNIQUE CHALLENGES FOR ONCOLOGY

• Out-of-control cancer drug and test prices
  • Expensive treatments make appropriate cancer care a hardship or unaffordable
• Pressure to use newest technologies/treatments
  • Sense of urgency as many cancer pts have a poor prognosis and are facing imminent death
• In addition to high costs, most cancer treatments have potential serious complications
• Providers often reluctant to switch to best supportive care, even at end of life

Institute of Medicine. Assessing and Improving the Value in Cancer Care: Workshop Summary 2009.
WHAT ARE BIOSIMILARS?

- Biologic products designed to mimic existing, approved biologic agents
  - Not identical to reference biologic
- FDA approval process outlined in Affordable Care Act\(^1\)
  - Biosimilars must demonstrate no clinically meaningful differences in safety and efficacy from reference biologic
  - Minor variations in clinically inactive components permitted
- Simplification of development process anticipated to reduce production costs and encourage competition\(^2\)

1. FDA. Information on biosimilars. 2016.
“A biological product that is highly similar to a US-licensed reference biological product, notwithstanding minor differences in clinically inactive components, and for which 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.”¹
WHAT FEATURES DO BIOSIMILARS SHARE WITH THEIR REFERENCE BIOLOGICS?

<table>
<thead>
<tr>
<th>Reference Biologic</th>
<th>Biosimilar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Host cell line</td>
<td>Host cell line</td>
</tr>
<tr>
<td>Manufacturing processes</td>
<td>Manufacturing processes</td>
</tr>
<tr>
<td>Protein structure</td>
<td>Protein structure</td>
</tr>
<tr>
<td>Inactive ingredients</td>
<td>Inactive ingredients</td>
</tr>
<tr>
<td>Proven efficacy, safety</td>
<td>Proven similarity to reference biologic</td>
</tr>
</tbody>
</table>

Amino acid sequence

Mechanism of action

## HOW DO BIOSIMILARS VS SMALL MOLECULE GENERICS COMPARE?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Biosimilar</th>
<th>Generic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Structure</strong></td>
<td>▪ Large, complex biologic molecule</td>
<td>▪ Small, simple, reproducible molecule</td>
</tr>
<tr>
<td><strong>Comparison to reference agent</strong></td>
<td>▪ Same amino acid sequence</td>
<td>▪ Identical active ingredients</td>
</tr>
<tr>
<td></td>
<td>▪ May differ in posttranslational modifications, protein folding, impurities, excipients(^1)</td>
<td>▪ Same dosage, route of administration, indications, bioequivalence, strength, purity, quality(^2)</td>
</tr>
<tr>
<td></td>
<td>▪ Higher potential for immunogenicity(^1)</td>
<td></td>
</tr>
<tr>
<td><strong>Manufacturing process(^3)</strong></td>
<td>▪ Created in living systems</td>
<td>▪ Chemical synthesis</td>
</tr>
<tr>
<td></td>
<td>▪ Unique cell lines and set of production steps</td>
<td>▪ Predictable set of chemical reactions</td>
</tr>
<tr>
<td><strong>FDA approval process</strong></td>
<td>▪ Biosimilar Biologics License Application(^4)</td>
<td>▪ Abbreviated New Drug Application(^5)</td>
</tr>
<tr>
<td></td>
<td>▪ Demonstrate similar safety, potency, and efficacy(^5)</td>
<td>▪ Demonstrate bioequivalence(^1)</td>
</tr>
</tbody>
</table>

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WHAT IS THE NAMING CONVENTION FOR BIOSIMILARS?

<table>
<thead>
<tr>
<th>Core name</th>
<th>FDA-designated suffix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>atto</td>
</tr>
<tr>
<td>Etanercept</td>
<td>szzs</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>sndz</td>
</tr>
<tr>
<td>Infliximab</td>
<td>abda</td>
</tr>
<tr>
<td>Infliximab</td>
<td>dyyb</td>
</tr>
</tbody>
</table>

- No recognizable meaning
- 4 letters
- Lowercase
TIME, COST AND DEVELOPMENT

CONCERNS WITH BIOSIMILARS

- Efficacy
- Safety
- Biologic variability
- Immunogenicity
- Extrapolation
- Interchangeability
CAN WE ASSURE COMPARABLE SAFETY AND EFFICACY OF BIOSIMILARS TO THEIR REFERENCE BIOLOGICS?

• Biosimilars are designed to replicate purity, potency of reference biologics, which is anticipated to translate into clinical comparability[1]

• After thorough assessment of this comparability by regulatory bodies, approval of biosimilar is:
  • Based on preclinical/clinical studies of pharmacology, efficacy, safety, immunogenicity
  • For specific indications only; extrapolation to other indications must be justified
  • Subject to postmarketing surveillance to identify any unique safety signals

2. FDA. Scientific considerations in demonstrating biosimilarity to a reference product. 2015
WHAT IS THE REGULATORY AND APPROVAL PATHWAY FOR BIOSIMILARS IN THE US?

- Abbreviated licensure pathway
- Sequential, risk-based approach
- Demonstration that the biosimilar and reference biologic have no clinically meaningful differences in terms of safety, purity, and potency

<table>
<thead>
<tr>
<th>Efficacy/Safety of Proposed Biosimilar vs Reference Biologic</th>
<th>Supports Biosimilarity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior</td>
<td>No</td>
</tr>
<tr>
<td>Equivalent or noninferior</td>
<td>Yes</td>
</tr>
<tr>
<td>Inferior</td>
<td>No</td>
</tr>
</tbody>
</table>

FDA. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. 2015.
WHAT IS THE REGULATORY AND APPROVAL PATHWAY FOR BIOSIMILARS IN THE US?

At each step, FDA evaluates *totality of evidence* to determine if further studies are required to eliminate residual uncertainty between biosimilar and reference biologic.

- **Analytical studies** of structure and function
- **Animal studies** including assessment of toxicity
- **Clinical studies** of PK/PD and immunogenicity
- **Comparative clinical studies** to determine equivalence

*(If uncertainty remains)*
CLINICAL TRIALS OF NEW BIOLOGICS VS BIOSIMILARS

### New Biologics

- Clinical trials aim to *independently* establish efficacy, safety of biologic\(^1\)
  - Emphasis on large, late-phase clinical trials

### Biosimilars

- Clinical trials aim to demonstrate *similarity* to an already-approved reference biologic\(^2\)
  - Stronger emphasis on analytical data\(^3\)
  - Often compared with reference biologics from both US and Europe

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### HOW DO CLINICAL DEVELOPMENT PATHWAYS FOR NEW BIOLOGICS VS BIOSIMILARS COMPARE?

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>New Biologic – 351(a)(^1)</th>
<th>Biosimilar – 351(k)(^{2,3})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical and animal toxicology studies</td>
<td>▪ Defines pharmacologic, toxicologic effects prior to human studies</td>
<td>▪ Structural/functional analyses</td>
</tr>
<tr>
<td></td>
<td>▪ Dose and schedule determined; immunogenicity assessed</td>
<td>▪ Animal studies including assessment of toxicity</td>
</tr>
<tr>
<td></td>
<td>▪ Clinical activity and safety evaluated in given pt population</td>
<td>▪ Human PK, PD, immunogenicity compared to reference biologic</td>
</tr>
<tr>
<td>Phase I and II</td>
<td>All studies required by FDA</td>
<td>At each step, FDA determines if further studies are needed</td>
</tr>
<tr>
<td>Phase III</td>
<td>▪ Assessed in large population to confirm therapeutic benefit</td>
<td>▪ If requested by FDA because of residual uncertainty, typically designed to demonstrate equivalence or noninferiority to reference biologic</td>
</tr>
</tbody>
</table>

BIOSIMILARS REPRESENT PARADIGM SHIFT IN PRODUCT DEVELOPMENT

CONCERNS WITH BIOSIMILARS

- Efficacy
- Safety
- Biologic variability
- Immunogenicity
- Extrapolation
- Interchangeability
Sources of Biological Variability

Cloning and Protein Expression

- Target DNA
- Cloning into DNA vector
- Transfer into host cell expression screening/selection
- Possibly different vector
- Possibly same gene sequence
- Different cell expression system

Protein Production, Purification, and Validation

- Cell expansion
  - Different cell line, growth media, method of expansion
- Cell production in bioreactors
  - Different cell line, growth media, bioreactor conditions
- Recovery through filtration or centrifugation
- Purification through chromatography
  - Different binding and elution conditions
  - Different methods, reagents, reference standards
- Characterization and stability
  - Purified bulk drug

SOURCES OF BIOLOGIC VARIABILITY

- Expression system (plasmid, cells)
- Fermentation conditions, raw materials
- Protein purification (method, scale, reagents)
- Final purity
- Potency/activity
- Concentration
- Packaging (container, excipients)
- Sterility
VARIABILITY AND DRIFT

- Significant differences in drug products (variability and drift) can arise due to:
  - Production at different sites
  - Changes to manufacturing processes after initial approval
    - FDA or EMA approval required for changes in manufacturing process
- Manufacturers need to be vigilant for any changes in production and must always assume that they can result in clinically significant issues

Both biologics and biosimilars are subject to product variability and drift!

Slide credit: clinicaloptions.com
CONCERNS WITH BIOSIMILARS

- Efficacy
- Safety
- Biologic variability
- Immunogenicity
- Extrapolation
- Interchangeability
IMMUNOGENICITY

- Concern for all biologics (not just biosimilars)[1,2]
- Consequences[1,2]
  - Loss of efficacy
  - Neutralization of endogenous protein and administered biologic agent
  - General immune responses (eg, allergy, anaphylaxis)
- FDA guidance regarding immunogenicity assessment[3]
  - Comparative parallel design (ie, head-to-head study)

CONCERNS WITH BIOSIMILARS

• Efficacy
• Safety
• Biologic variability
• Immunogenicity
• Extrapolation
• Interchangeability
**Extrapolation to Additional Indications Possible with Scientific Justification**

Extrapolation: extending conclusions from studies in one pt population to make inferences in another population\(^1\)

- Convincing evidence to support extrapolation to a reference biologic’s approved indications\(^2\)

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1. EMA. Concept paper on extrapolation of efficacy and safety in medicine development. 2012.
Reference biologics have inherent variability

- Biologic agents are likely to be modified throughout their life cycle with changes in their manufacturing process and are, therefore, unlikely to be identical to the original approved version.

- Regulatory pre- and postchange “comparability exercises” of physicochemical and functional characteristics are accepted as a way to ensure efficacy, safety, and quality of biologics after these changes.

- The approved “new” version is considered to have the same safety and efficacy in all indications as its earlier version.

This thinking also applies to biosimilars, in which the active substance of the biosimilar can be viewed as another version of the active substance of the originator product.
Extrapolation is a familiar concept for regulators. Aims to avoid unnecessary studies in the target population for ethical reasons, for efficiency, and to allocate resources where needed [1].

FDA guidance states that extrapolation of indications for a biosimilar is possible given sufficient scientific justification [2].

“Totality-of-evidence” approach supported by extensive experience in Europe.

- Approved biosimilars have shown similar safety and efficacy profiles as the reference biologic for extrapolated indications [3-5].

1. EMA. Concept paper on extrapolation of efficacy and safety in medicine development. 2012.
2. FDA. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. 2015.
Extrapolation is an unfamiliar concept for clinicians.

Traditionally, clinicians have relied on clinical trial data to judge the safety and efficacy of therapeutic agents.

By definition, approval of a biosimilar for one indication may be based on extrapolation from the biosimilar to the reference biologic.

Therefore, no specific clinical trials with a biosimilar may have been performed in the approved indication/population.

Thus, the paradigm shift in biosimilar development also requires a paradigm shift in evaluation and use of biosimilars in the clinical setting.

CONCERNS WITH BIOSIMILARIS

• Efficacy
• Safety
• Biologic variability
• Immunogenicity
• Extrapolation
• Interchangeability
INTERCHANGEABILITY OF BIOSIMILARS

- A biosimilar may also be designated as “interchangeable” if there is proof that:
  
  - **Switching or alternating** between the biosimilar and the reference product does not affect safety or efficacy any more than using the reference product more than once without such alternating or switching

The designation of “interchangeability” requires higher standards than “biosimilarity” alone

HIGHER STANDARDS FOR BIOSIMILARS DESIGNATED AS INTERCHANGEABLE

Biosimilar

- Same clinical result as reference product

Interchangeable

- Same clinical result as reference product
- Same clinical result when switched or alternated with reference product

FIRST FDA-APPROVED BIOSIMILAR: FILGRASTIM-SNDZ—ANALYTICS, PK/PD, SAFETY

• Approved March 6, 2015; first FDA-approved oncology-related biosimilar
• Structural and functional studies demonstrated same amino acid sequence as US-licensed filgrastim
• Biological activity, receptor binding and physiochemical properties, product-related substances and impurities, and stability profile are highly similar to US-licensed filgrastim, notwithstanding minor differences in clinically inactive components
• 5 studies in healthy subjects evaluating ANC, $C_{\text{max}}$, and CD34+ cell counts demonstrated PK/PD similarity with US-licensed and EU-approved filgrastim
• Phase 3 PIONEER trial involving 204 healthy subjects and 214 pts with breast cancer equivalent to US-licensed and EU-approved filgrastim

Slide credit: clinicaloptions.com
Pegfilgrastim, filgrastim, tbo-filgrastim, as well as filgrastim-sndz and other biosimilars, as they become available, can be used for the prevention of treatment-related febrile neutropenia.

The choice of agent depends on convenience, cost, and the clinical situation.
BIOSIMILARS APPROVED TILL DATE IN US

- Herceptin (trastuzumab) Biosimilars
  - Ogivri (trastuzumab-dkst)
  - Herzuma (trastuzumab-pkrb)
  - Ontruzant (trastuzumab-dttb)
- Rituxan (rituximab) Biosimilars
  - Truxima (rituximab-abbs)
- Neulasta (pegfilgrastim) Biosimilars
  - Fulphila (pegfilgrastim-jmdb)
  - Udenyca (pegfilgrastim-cbqv)
- Humira (adalimumab) Biosimilars
  - Amjevita (adalimumab-atto)
  - Cyltezo (adalimumab-adbm)
  - Hyrimoz (adalimumab-adaz)
- Neupogen (filgrastim) Biosimilars
  - Zarxio (filgrastim-sndz)
  - Nivestym (filgrastim-aafi)
- Epogen / Procrit (epoetin alfa) Biosimilars
  - Retacrit (epoetin alfa-epbx)
- Remicade (infliximab) Biosimilars
  - Inflectra (infliximab-dyyb)
  - Renflexis (infliximab-abda)
  - Ixifi (infliximab-qbttx)
- Avastin (bevacizumab) Biosimilars
  - Mvasi (bevacizumab-awwb)
- Enbrel (etanercept) Biosimilars
  - Erelzi (etanercept-szzs)
POTENTIAL BENEFITS OF BIOSIMILARS TO THE US HEALTHCARE SYSTEM

<table>
<thead>
<tr>
<th>Greater Patient Access</th>
<th>1. Due to improved affordability, a greater proportion of eligible patients should be able to benefit from biologic treatment[1-4]</th>
</tr>
</thead>
</table>
| Greater Competition    | 2. Introduces competition and may drive down biologic costs[5,6]  
                         3. Biosimilar manufacturers can take advantage of the latest technology[5,6] |
| Foster Innovation      | 4. Incentive for investment in the development of innovative new biologic products by originator companies[6,7]  
                         5. Provides budgetary relief enabling the use of new treatments and therapies[7] |

ESTIMATED COST SAVINGS OF BIOSIMILARS

Express Scripts

- Project potentially $250 billion in savings over next 10 years if 11 of the likeliest biosimilars enter the market

Congressional Budget Office

- Estimate 10 year savings to be only $25 billion

http://americanactionforum.org/research/the-new-frontier-of-pharmaceuticals-biosimilars
SUCCESS OF BIOSIMILARS: DEPENDENT VARIABLES

❖ Acceptance of prescribers and patients

❖ Reference product push-back

❖ Final FDA mandates

❖ Acceptance of Extrapolation and Interchangeability

CLINICIAN PERSPECTIVE: FINDING THE RIGHT BALANCE

Biosimilar Approval Process Requires Too Large Amount of Data

Benefits
- Greater healthcare provider confidence in biosimilar product
- Great acceptance and uptake of biosimilar?
- Fewer safety concerns

Risks
- Higher development costs
- Lower pharmacoeconomic benefit over innovator product

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CLINICIAN PERSPECTIVE: ADDRESSING CONCERNS

- Physicians skeptical of efficacy, safety, impact on reimbursement; concerned that use will be forced upon them
- Physician perception will be that cost is the main issue
- Strong clinical data will be important for acceptance
- Education essential to accelerate uptake after approval
  - Unbiased experts, focused on clinical data
  - National meetings and online education

INTEGRATING BIOSIMILARS INTO ONCOLOGY/CLINICAL PRACTICE: CHALLENGES AND OPPORTUNITIES

- Approval based on limited clinical data vs reference
- Biologic variability, drift, and immunogenicity
- Extrapolation of biosimilar indications to indications for which the reference product was approved
- Interchangeability and automatic substitution
- Reduce unsustainable increase in healthcare costs and increase pt access to biologic agents
- Need for pharmacovigilance and physician and patient education
• Biologics are complex molecules and therefore identical ‘generic’ copies are not possible
  • Lot-to-lot variation of innovator drugs is inevitable and is closely regulated
• Regulations to enable the development of biosimilars were created to improve access to essential medications
• Biosimilars are biological similar copies of an innovator with no meaningful differences in safety and efficacy
• The development of biosimilars is the inverse of innovator molecules, with the preclinical development being the key to success
• Clinical trials to compare to the innovator are not aimed at establishing safety and efficacy in an indication – this was accomplished by the innovator
  • The goal is to establish equivalence in PK and PD endpoints and show clinical activity within an accepted equivalence margin
• Major cost saving in the development of biosimilars comes from extrapolation to scientifically and clinically justified indications already approved for the innovator
THANK YOU!!!

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