The Emerging Role of Biologics

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Development and Support
This activity was developed by the American Pharmacists Association and supported in part by an independent educational grant from Amgen.

This webinar is intended to be a primer for Update on Biologics and the Emerging Classifications of Biosimilars, a 2-hour live session on Friday, March 27, 2015, 3:30PM-5:30PM PT, at the APhA Annual Meeting and Exposition.

To register for APhA2015, held March 27-30, 2015, in San Diego, go to aphameeting.org

Other biologics webinars located at pharmacist.com:
Biologic Pharmacovigilance: Key Considerations for Pharmacists
March 12, 2015 2:00pm-3:00pm ET

The Emerging Role of Biosimilars
Archived webinar from March 4, 2015 broadcast – Coming Soon!
Attendance Code

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Initial Release Date: March 5, 2015
Target Audience: Pharmacists
ACPE Activity Type: Knowledge-based
Learning Level: 2
Fee: There is no fee for this activity

Disclosures

- Edward Li, PharmD, MPH, BCOP has received honoraria from Hospira, Sandoz, and Merck for serving on advisory boards and from Pfizer and Amgen for speaking services.
- APhA's editorial staff declares no conflicts of interest or financial interests in any product or service mentioned in this activity, including grants, employment, gifts, stock holdings, and honoraria. For complete staff disclosures, please see the Education and Accreditation Information section at www.pharmacist.com/education.
Learning Objectives

- Describe the importance of biologics and their development.
- Discuss the impact of biologics for patient care and disease management.
- Identify key governing bodies responsible for approving and evaluating biologics.

Which of the following statements about biologics is true?

- Biologics are derived or manufactured from living organisms
- While biologics have a high acquisition cost, they do not impact overall expenditures because of low utilization
- Biologics improve patient outcomes in various diseases, for example cancer and psoriasis
- A and C

Because of more biologic drug approvals, which of the following is likely to occur?

- Administration of injectable agents in the clinic will increase
- Distribution channels will shift from specialty pharmacy to retail
- Overall drug expenditures will decrease
- All of the above
Biologic products in the U.S. are licensed under which Act?

a. Biologics Price Competition and Innovation Act  
b. Drug Price Competition and Patent Term Restoration Act  
c. Food, Drug, and Cosmetic Act  
d. Public Health Service Act

Biological (Biologic) Definition

“Biological product” means:

– A virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsenamine or derivative of arsenamine (or any other trivalent organic arsenic compound) 
– Applicable to the prevention, treatment, or cure of a disease or condition of human beings (Public Health Service Act Section 351(i))
– Biological products also meet the definition of either a drug or device under Sections 201(g) and (h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Biologic Agents: Examples

- Monoclonal antibodies
- Complex sugars
- Blood derivatives
- Vaccines
- Recombinant or purified proteins
  – Cytokines
  – Thrombolytic agents
  – Enzymes
### Differences Between Chemical (Small-Molecule) Drugs and Biologicals

<table>
<thead>
<tr>
<th></th>
<th>Chemical Drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>Small, low molecular weight</td>
<td>Large, high molecular weight</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple, well-defined</td>
<td>Complex, heterogeneous</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>• Reproducible chemical reactions</td>
<td>• Living cells or organisms</td>
</tr>
<tr>
<td></td>
<td>• Identical copies can be made</td>
<td>• Impossoble to ensure identical copies</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Completely characterized</td>
<td>Impossible to fully characterize molecular composition</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>Stable</td>
<td>Unstable, sensitive to external conditions</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Mostly non-immunogenic</td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>


### Biologics vs. Small Molecule Drugs

- **Human EPO**
  - 165 amino acids
  - MW ~ 34,000 Da

- **Cisplatin**
  - (NH$_3$)$_2$PtCl$_2$
  - MW ~ 300 Da

- **Monoclonal Ab**
  - MW ~ 150,000 Da

Courtesy of: Olgun Guvench, MD, PhD, University of New England College of Pharmacy

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Biologics Span Many Therapeutic Categories

- Oncology
  - Active treatment
  - Supportive Care (e.g., erythropoiesis stimulating agents)
- Rheumatology
- Immunology
- Neurology
- Cardiovascular
- Pulmonary
- Gastroenterology
- Dermatology
Therapeutic Uses of Biologics

Analysis of 5% Sample of CMS Claims, 2008 Outpatient Procedures BSA PUF

Excluded: ESAs (1.4 million claims), vaccines, IVIG

Impact on Cancer Outcomes

Impact of Biologics in Treating Moderate to Severe Psoriasis

Fig. 2. Hospital resource use: 17 months before and 17 months after initiation of biologics. Mean resource units (SE) per patient in the 17 months before biologics initiation. *P-value: mean resource units (SE) per patient in the 17 months after biologics initiation. **P-value: panel signed rate.

Biologics included adalimumab, efalizumab, etanercept, or infliximab


Impact of Biologics in Treating Moderate to Severe Psoriasis

Trends in FDA Approval


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Impact of Biologics on Cost

Median Monthly Costs of Cancer Drugs are Rising

Approval dates from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

AWP data from: Redbook Online

Impact of Biologics on Cost

Median Monthly Costs of Cancer Drugs are Rising
Clinical Concerns with Biologics

- All biologics confer a risk of immunogenicity
  - The body can detect and attack foreign proteins
  - Neutralizing antibodies can be developed
  - The more similar a therapeutic protein is to the human protein, the less chance of immunogenicity
  - Scientific tools for detecting immunogenicity exist, but they are not precise

- Changes to the structure of the protein increase variation in immunogenicity
  - Lot-to-lot and between manufacturers
  - Variations in manufacturing must be minimized

- Case reports of rare but serious adverse reactions have been reported

Impact of Biologics on Pharmacy Practice

<table>
<thead>
<tr>
<th>Sector</th>
<th>Expenditures (in Millions)</th>
<th>Percent of Total Expenditures</th>
<th>Growth (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retail pharmacies</td>
<td>166,172</td>
<td>31.9</td>
<td>-0.8</td>
</tr>
<tr>
<td>Mail-order pharmacies</td>
<td>65,940</td>
<td>20.2</td>
<td>-5.5</td>
</tr>
<tr>
<td>Clinics</td>
<td>39,320</td>
<td>12.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Nonfederal hospitals</td>
<td>27,913</td>
<td>8.6</td>
<td>-0.4</td>
</tr>
<tr>
<td>Long-term care</td>
<td>14,340</td>
<td>4.4</td>
<td>-4.7</td>
</tr>
<tr>
<td>Federal facilities</td>
<td>4,333</td>
<td>1.3</td>
<td>4.1</td>
</tr>
<tr>
<td>Staff-model HMO</td>
<td>2,063</td>
<td>0.6</td>
<td>3.8</td>
</tr>
<tr>
<td>Home health care</td>
<td>2,269</td>
<td>0.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Other</td>
<td>873</td>
<td>0.3</td>
<td>-6.4</td>
</tr>
<tr>
<td>Total</td>
<td>326,013</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Impact of Biologics on Pharmacy Practice

Likelihood of a 50% increase in administration of injectable medications in ambulatory clinics and infusion centers:

Investment in Biologics

Biologic Pipeline

REGULATORY APPROVAL PATHWAYS FOR BIOLOGICS

FDA Regulation: Biologic License Application

- Two federal laws for the approval of pharmaceuticals in the United States: safety and efficacy
  - Food, Drug, and Cosmetic Act (FDCA)
    - New drug application (NDA)
  - Public Health Service Act (PHSA) – 351(a)
    - Biologics license application (BLA)
- What about “generics?”
  - Drug Price Competition and Patent Term Restoration Act (informally known as Hatch-Waxman Act) of 1984 allows for an abbreviated pathway (ANDA) for generic small molecules
  - The Biologics Price Competition and Innovation Act allows for a 351(k) abbreviated pathway for biosimilars

Manufacturing Process for Biologics

- Cloning into DNA Vector
- Transferring into Host Cell
- Expression
- Screening / Selection
- Cell Expansion
- Cell Production in Bioreactors
- Recovery through Purification or Centrifugation
- Characterization and Stability
- Purified Bulk Drug
Changes in Manufacturing Can Have Real Consequences

- Differences in manufacturing can lead to differences in structure, stability, and impurities as well as excipients
- Changes in the manufacturing of an epoetin alfa resulted in a small change in formulation
  - Decreased protein stability and increased aggregate formation
  - Resulted in cases of pure red-cell aplasia
- Excessive host cell protein contamination increased immunogenicity with somatropin
  - Resolved with additional purification


Do Changes in Process Lead to Changes in Clinical Activity?

Rituximab: ADCC
Epoetin alfa: Pure red cell aplasia

Biologic Manufacturing Changes

INTRA-manufacturer

Guidance for Industry
QSX Comparability of Biotechnological Biological Products Subject to Changes in Their Manufacturing Process
June 2005


INTER-manufacturer

Guidance for Industry
Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
Feb 2012


June 2005
Feb 2012
Demonstrating Biosimilarity: Things to Keep in Mind

- The clinical efficacy and safety of the biologic molecule has already been demonstrated (i.e., by the innovator)
- The biosimilar sponsor only requires evidence that the candidate biosimilar is not significantly different from the reference product
  - Goal is not to replicate unnecessary clinical trials
  - Smaller-scale direct comparisons and extrapolation
- When a biosimilar is approved, there should not be an expectation that there will be differences in safety and efficacy


Biosimilar Development Approach

There Will Be Many Types of Biologic Products

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Depth of data submitted to the FDA</th>
<th>Compared to originator?</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Originator</strong></td>
<td>First-to-mkt biologic molecule; will likely be the reference product;</td>
<td>Yes</td>
<td>Yes</td>
<td>Biologics similar; safety and efficacy on its own merit; automatic substitution</td>
</tr>
<tr>
<td><strong>Biosimilar</strong></td>
<td>Highly similar to reference product; approved via biosimilar pathway;</td>
<td>Abbreviated data package</td>
<td>Yes or no</td>
<td>New entity; pricing; automatic substitution issues</td>
</tr>
<tr>
<td><strong>Interchangeable Biosimilar</strong></td>
<td>A biosimilar deemed that can be substituted for the reference without permission from prescriber</td>
<td>Abbreviated data package, more information on efficacy and safety</td>
<td>Yes</td>
<td>Different pricing structure; automatic substitution issues</td>
</tr>
<tr>
<td><strong>Non-originator biologic</strong></td>
<td>It is &quot;another brand name&quot; of an already approved biologic</td>
<td>&quot;Standard&quot; data package; efficacy and safety on its own merit</td>
<td>Yes</td>
<td>New entity</td>
</tr>
<tr>
<td><strong>Next-generation “Bio-better”</strong></td>
<td>Biologic that has been altered to achieve improved clinical outcomes</td>
<td>&quot;Standard&quot; data package; efficacy and safety on its own merit</td>
<td>Yes</td>
<td>New entity</td>
</tr>
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**FDA Breakthrough Designation**

- FDA Safety and Innovation Act of 2012 (FDASIA)
- FDA works closely with manufacturer and accelerates timeline for approval
- Criteria for designation
  - Serious/life-threatening disease
  - Preliminary data indicate substantial improvement
- Examples: PD-1 inhibitors, blinatumomab

**Data for FDA Approval**

- **Phase I**
  - Purposes: PK/PD, Dose-finding (MTD)
  - "Efficacy" Outcomes: Response rate, PFS/OS possible, but unlikely
- **Phase II**
  - Purposes: Initial efficacy/toxicity, Dose-optimization
  - "Efficacy" Outcomes: Response rate, PFS/OS possible
- **Phase III**
  - Purposes: Efficacy
  - Efficacy Outcomes: PFS and OS, Response rate
Conclusion

- Biologics are used in a wide array of disease states (mainly in cancer, rheumatology, immunology)
- While effective, these agents are contributing to increased drug expenditures
- The manufacturing of biologics is relatively complex compared to small-molecule drugs
- Government bodies regulate biologics for safety and efficacy, paying close attention to immunogenicity concerns

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