Implications of biosimilars for the future

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Biotechnology has a long history. The first known application of biotechnological processes dates back to 4000 BCE, when yeast fermentation was used to produce ethanol for consumption. The many beer products commercially available today, for example, have distinct differences despite the use of the same basic manufacturing process.

Establishing standards by which to differentiate drug products produced through biotechnology is a challenge. The molecules tend to be large and complex, unlike the small molecules of conventional chemical drugs, which are more readily characterized.

The medical and therapeutic applications of biotechnology have a long history, and the pace of new applications has accelerated in recent decades (Table 1). The first documented therapeutic application of biotechnology was in 500 BCE, when an antibiotic derived from moldy soy was used for the treatment of boils in China. A vaccine against smallpox was invented in the late 18th century, representing a remarkable accomplishment for the time. Human growth hormone was synthesized and penicillin was discovered in the 1920s.

The first automatic protein sequencer was developed in the 1960s, with gene synthesis and DNA manipulation following in the 1970s. Although the technology for biopharmaceutical synthesis through recombinant DNA technology was developed several decades ago, clinicians and lawmakers are only now wrestling with issues related to the equivalence and interchangeability of biosimilar and innovator drug products.

Biotechnology is defined by the Food and Drug Administration...
(FDA) as the collection of industrial processes (including genetic engineering) that involve the use of biological systems (i.e., bacteria, yeast, or human cells) to identify, sequence, and manipulate DNA, aimed at producing therapeutic and medical diagnostic products.\(^1\) The U.S. Pharmacopeia (USP), the official public standards-setting authority for the identity, strength (potency), quality, and purity of medications, has not yet established standards for macromolecular drug products (e.g., biotechnology products). However, the first steps have been taken by USP in establishing compendial standards for the two biotechnology products (human growth hormone and interferon) that were approved for marketing in the United States more than 20 years ago.

### Terminology

The terms used to describe genetic factors that influence drug response can be confusing. Pharmacogenetics is the study of how an individual’s genotype can influence drug use and dosing. Genetic variations may influence drug metabolism, especially genetic variation in the expression of cytochrome P-450 drug-metabolizing enzymes. The phenotype is the manifestation of one or more genotypes in an individual, and rapid or slow drug metabolism and drug toxicity or failure may reflect phenotype variance.

Pharmacogenomics is the individualization of medicine (also known as personalized care), with rational prescribing based on an individual’s genetic makeup. Single-nucleotide polymorphisms (SNPs) are variations in DNA sequence that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered. The discovery of SNPs represents a major breakthrough, because their presence in patients with disease can provide a therapeutic target. The rate at which SNPs occur is roughly 1 in 1000 bases among the 3 billion bases in the human genome.\(^2\) Subtle differences between individuals in susceptibility to disease and response to treatment have been attributed to SNPs.\(^3\) For example, the difference between erythropoietin and darbepoetin alfa is attributed to two SNPs.

Proteomics involves the cataloging of human proteins and the DNA sequences driving protein production, with the goal of understanding how genes and the proteins they encode cause the body to function properly or improperly. The study of proteomics provides insight into complex biochemical and physiological mechanisms, which helps identify targets for new drug regimens.

The terminology used for biotechnology drug products also is confusing. Biosimilars were defined in a legislative bill for consideration by the U.S. Senate as biotechnology products that are highly similar to the reference product, notwithstanding minor differences. These products usually are referred to by FDA as follow-on biologics. A variety of other terms, including follow-on proteins, biogenerics, generic biopharmaceuticals, and comparable biologicals, also have been used. Standardized terminology and a definition of what constitutes similarity have not been established.

### Biotechnology benefits

The use of biotechnology provides new approaches to the discovery, design, and production of drug products. It facilitates the prevention, cure, and treatment of diseases and the creation of targeted therapies with greater efficacy and less toxicity than previously available therapies. Advances achieved through the use of biotechnology may enable clinicians and patients to adopt a proactive instead of a reactive approach to disease management.

Replacement of endogenous human proteins that are dysfunctional or absent may be feasible through biotechnology. Biotechnology has allowed the production of drugs that are not contaminated with pathogens from human or animal sources (e.g., recombinant human insulin instead of the insulin from beef or pork sources that was used in the past).

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### Table 1. History of Medical Applications of Biotechnology

<table>
<thead>
<tr>
<th>Year or Decade</th>
<th>Milestone</th>
</tr>
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<tbody>
<tr>
<td>500 BCE</td>
<td>Antibiotic from moldy soy used for treatment of boils in China</td>
</tr>
<tr>
<td>1590</td>
<td>Janssen invents the microscope</td>
</tr>
<tr>
<td>1675</td>
<td>Leeuwenhoek discovers bacteria</td>
</tr>
<tr>
<td>1797</td>
<td>Jenner invents smallpox vaccine</td>
</tr>
<tr>
<td>1833</td>
<td>First proteins and enzymes discovered</td>
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<tr>
<td>1902</td>
<td>Terms “immunology” and “genetics” first documented in the literature</td>
</tr>
<tr>
<td>1920s</td>
<td>Human growth hormone synthesized, penicillin discovered</td>
</tr>
<tr>
<td>1940s</td>
<td>Fields of “molecular biology” and “genetic engineering” first mentioned in the literature</td>
</tr>
<tr>
<td>1950s</td>
<td>Interferon identified, DNA discovered by Watson and Crick</td>
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<tr>
<td>1960s</td>
<td>First automatic protein sequencer developed</td>
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<tr>
<td>1970s</td>
<td>Gene synthesized, DNA manipulated</td>
</tr>
<tr>
<td>1980s</td>
<td>Recombinant vaccine developed</td>
</tr>
<tr>
<td>2000</td>
<td>Human genome mapped</td>
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Biotechnology applications

Various applications of biotechnology have been used to develop biopharmaceuticals. Pharmacists need to be concerned with how biopharmaceuticals are produced, because the production processes have implications for therapeutic use.

Recombinant DNA (rDNA) technology plays a major role in biopharmaceutical production. Transgenic animals (e.g., pigs, goats) have been created by inserting a foreign gene into the animal genome, and these genetically altered animals have been used to produce biopharmaceuticals in their milk.

Fusion proteins (e.g., the botulinum neurotoxin complex in type A and type B products) have been created for therapeutic purposes. The rheumatoid arthritis drug etanercept is formed by fusing two molecules of part of the tumor necrosis factor (TNF) receptor to the Fc portion of human immunoglobulin G1.4

Etanercept interferes with the biological activity of TNF, which is thought to play a key role in the pathogenesis of the disease.

Nucleic acid modulation is a major focus of research. Antisense nucleotides that block gene expression have been explored for the treatment of human immunodeficiency virus (HIV) infection, cytomegalovirus retinitis, and multiple myeloma. The use of ribozymes (RNA molecules that function as enzymes to catalyze the cleavage of other RNA molecules) may have applications in the treatment of cancer and the acquired immune deficiency syndrome (AIDS). The drug approval pipeline at FDA contains several DNA vaccines that recognize and target cancer cells.

Other biotechnology processes include monoclonal antibody production, gene therapy, and enabling technology. The applications for enabling technology are primarily industrial (e.g., bacterial cell surface display screening and other high-throughput technology to facilitate the processing of large numbers of samples in drug discovery laboratories). Pegylation and ligand technology and glycosylation are enabling technologies with applications to drug development.

rDNA technology

Recombinant DNA technology is used to cause a cell to produce a protein that it does not normally make or to make a protein that it ordinarily makes in normal quantities. This technology has applications for individuals lacking vital protein substances (e.g., insulin). The drugs produced through rDNA technology are safer and more effective than drugs obtained from animal or human sources because they are not viewed as foreign by the body, as can occur with animal products, and they are not contaminated with infectious organisms.

Various types of cells may be used as host cells for biopharmaceutical production through rDNA technology (Table 2). Bacteria and yeasts both are easy and inexpensive to grow, but they are not suitable for the production of complex proteins. Mammalian cells may be used to produce stable, complex proteins with low antigenicity, but they are costly to use and may require additional steps for purification.

The type of host cell used for biosynthesis is a factor to consider in evaluating the equivalence of biosimilar and innovator drug products. Certain toxicities, such as antigenicity and problems caused by the

Table 2.
Comparison of Host Cell Types for Recombinant DNA Production of Biopharmaceuticals

<table>
<thead>
<tr>
<th>Type of Host Cell</th>
<th>Advantages</th>
<th>Disadvantages</th>
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</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Ease of growth</td>
<td>Synthesis of biologically inactive products</td>
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<tr>
<td></td>
<td>Well-characterized genetics</td>
<td>Inability to produce large complex proteins, such as glycoproteins</td>
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<tr>
<td></td>
<td>High product yield</td>
<td>Proteins can be difficult to harvest and purify</td>
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<tr>
<td></td>
<td>Large-scale fermentation capability</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td></td>
</tr>
<tr>
<td>Yeasts</td>
<td>Ease of growth</td>
<td>Proteolysis (breakdown of proteins) may result in low product yield</td>
</tr>
<tr>
<td></td>
<td>Large-scale fermentation capability</td>
<td>Inability to produce some sophisticated proteins</td>
</tr>
<tr>
<td></td>
<td>Ease of purification</td>
<td>Additional steps may be required to ensure proper protein folding for biological activity</td>
</tr>
<tr>
<td></td>
<td>Low cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ability to produce some large complex proteins</td>
<td></td>
</tr>
<tr>
<td>Mammalian cells</td>
<td>Ability to produce sophisticated proteins</td>
<td>Low product yield</td>
</tr>
<tr>
<td></td>
<td>Proteins produced may exhibit high stability and low antigenic properties</td>
<td>High cost</td>
</tr>
<tr>
<td></td>
<td>Large-scale fermentation capability</td>
<td>Additional product testing required by regulatory agencies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Additional steps may be required to ensure purification</td>
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</tbody>
</table>
presence of impurities, may be traced to the type of host cell used.

Glycosylation of rDNA entails the addition of carbohydrates to proteins in a host cell. Bacteria cannot add carbohydrates to proteins, and yeasts can glycosylate proteins to a limited extent. However, mammalian cells can fully glycosylate proteins. Lack of glycosylation does not influence the activity of some molecules produced through rDNA technology (e.g., granulocyte colony-stimulating factor), but other molecules created using rDNA technology (e.g., erythropoietin) require glycosylation for activity. Therefore, the host cell and production method selected can be important considerations in producing biopharmaceuticals and establishing the equivalence of biosimilar and innovator products.

Pharmacologically active substances (e.g., vasoactive polypeptide fragments) are produced in the rDNA technology process. Residues of chemicals used in the process (e.g., acid precipitants, separation column debris) may remain in the final product after fermentation and purification, especially if manufacturing processes are not rigorously controlled. Both living and dead microorganisms may be present, and living organisms can produce toxic byproducts or endotoxins. Therefore, purity testing is essential, although it adds to the cost of the product. Product contamination could be minimized by adhering to national standards, but manufacturing and purity standards have not yet been developed for biopharmaceuticals.

A variety of drugs created through rDNA technology have been marketed, including human insulin, interferon alfa, interferon beta, interferon gamma, epoetin alfa, darbepoetin alfa, alteplase, filgrastim, pegfilgrastim, sargramostim, oprelvekin (human interleukin-11), and anakinra (interleukin-1 receptor antagonist). The drug approval pipeline at FDA contains many drugs produced through rDNA technology (e.g., various interleukins).

Monoclonal antibodies

Monoclonal antibodies are synthetic immunoglobulins with specificity for certain antigens that serve as therapeutic targets. Monoclonal antibodies may be unconjugated or conjugated with toxins or radioisotopes. The process for producing monoclonal antibodies involves several steps, including growth in a host cell, harvesting, and purification. A large yield of monoclonal antibodies is feasible with current production processes.

The nomenclature used for monoclonal antibodies reflects the source, with the suffixes -omab for murine, -ximab for chimeric (mixed murine and human), -zumab for humanized, and -umab for fully human products. Muromonab-CD3 (OKT3) was the first monoclonal antibody approved by FDA; it was approved in 1986 for the treatment of acute allograft rejection. Other monoclonal antibody products since approved by FDA for various indications include abciximab, trastuzumab, rituximab, gemtuzumab, ibritumomab tiuxetan, infliximab, cetuximab, alemtuzumab, bortezomib, and bevacizumab. Bevacizumab is a monoclonal antibody that binds to human vascular endothelial growth factor (VEGF). It is approved by FDA for the treatment of metastatic colorectal cancer and non-small-cell lung cancer. Approximately 40 monoclonal antibody products that target VEGF receptors are in the research and development pipeline, and determining whether these products are equivalent to bevacizumab will pose a challenge.

Gene therapy

Gene therapy involves the introduction of genetic material into cells of the body to achieve desired therapeutic effects. The U.S. Human Genome Project has accelerated growth in the use of gene therapy for medical purposes. The project was begun in 1990 to identify all of the approximately 20,000–25,000 genes in human DNA, determine the sequences of the 3 billion chemical base pairs that make up human DNA, store this information in databases, improve tools for data analysis, transfer related technologies to the private sector, and address ethical, legal, and social issues arising from this work. More than 6000 single-gene disorders (e.g., cystic fibrosis, sickle cell anemia, Marfan syndrome, Huntington’s disease) have been identified. The number of gene abnormalities identified as contributors to disease continually increases. There are 20,000 gene patents and 25,000 gene patents pending for gene therapies.

Gene therapy may be used to correct an inherited genetic defect (e.g., cystic fibrosis) or an acquired genetic defect, such as mutations that lead to cancer. Other potential benefits of gene therapy include providing a novel function to certain cells (e.g., insulin production by cells other than pancreatic β cells). Inducing cells to replace defective tissues or growing a new organ or limb may someday be feasible through gene therapy.

Barriers to the use of gene therapy include difficulty identifying the genetic causes of disease and determining and producing the correct DNA sequence needed to correct a genetic defect. Providing a safe means for delivering genetic material may be a challenge because introducing genes into cells requires the use of vectors, which often are viruses. Most viral vectors are attenuated, but mouse retroviruses are the primary source of vectors, and toxicity often is associated with these vectors.

Orchestrating the appropriate expression of a gene to produce the desired therapeutic effect can present a challenge, because effects may vary among patients and may be difficult to predict. Genetic defects often are acquired through mutation, and gene therapy in theory could cause addi-
tional mutations that have adverse effects. Monitoring for unintended effects of gene therapy is necessary. There is a trend toward the use of patient-specific gene therapies, which may help overcome these problems.

Ethical concerns surrounding gene therapy may present barriers to its use. Licensing, patent, and exclusivity issues also may pose challenges.

**Future products**

Biotechnology products are in development for a wide variety of diseases, including HIV infection (Vax Syn HIV-1, a vaccine), heart failure (an adenosine A1 receptor antagonist), asthma (very-late antigen-4 inhibitor), anemia (novel erythropoiesis-stimulating protein), and stroke (enlimomab).9–12 A chimeric protein has been formed from globe spider silk protein and silica.13,14

The engineered protein mimics the strength and rigidity of the natural materials. This biomimicry has potential applications in orthopedic surgery for use in replacement tendons and ligaments.

**Pharmacy considerations**

Pharmacy staff need to be concerned with the storage, handling, preparation, and administration of biotechnology drugs, and training should be provided to address these products’ unique requirements. Many biotechnology drug products are proteins, and proteins degrade when they are administered orally. Therefore, these drugs usually are administered by injection. Protein drug products usually are formulated as liquids or lyophilized powders that must be constituted before administration. The products often do not contain preservatives because of the risk of protein degradation by the preservative.

Protein drug products are relatively unstable. Most products are sensitive to temperature extremes and require refrigeration, although freezing should be avoided because it can destroy the protein structure. Vigorous agitation of protein solutions should be avoided because it can cause froth or foam formation.

Specific diluents and intravenous (i.v.) admixture solutions that are free of preservatives may be needed to ensure product stability. The type of i.v. infusion container and administration set also may need to be considered, because proteins may adhere to the materials (e.g., polyvinyl chloride).

Environmental safety issues are associated with some biotechnology drug products that contain viral vectors or genetically altered material. These products may need to be handled as hazardous materials, with special training provided to protect staff and the environment from exposure. The Environmental Protection Agency may issue regulations for handling and disposal of these products.

The availability of compatibility data for biopharmaceuticals is limited, so administration procedures (e.g., flushing of i.v. tubing) will need to be established to avoid incompatibility problems. Special infusion pumps that differ from the standardized pumps used for conventional drugs in a health system may be needed for biotechnology products. Filtration to remove contaminants (e.g., particulates and pathogens) will not be feasible for many biotechnology products because of the large size of macromolecules.

Education of patients who self-administer biotechnology products will need to address the unique requirements of the products and the risk for and signs and symptoms of hypersensitivity reactions. Close monitoring of patients for such reactions is warranted.

Many biotechnology products can elicit an immunologic response with neutralizing antibody formation (especially human anti-mouse antibodies when murine monoclonal antibodies are used) or a hypersensitivity reaction.15 The immunogenicity of a biotechnology product increases with increases in the extent to which the amino acid sequence of the protein is changed (i.e., the extent to which the protein is viewed as foreign by the body). Desensitization processes involving the administration of serial dilutions (similar to testing for common allergens) have been used to allow patients to receive immunogenic biotechnology products, but these processes are costly and time consuming.

Immune reactions from exposure to biotechnology products ideally would be documented in a lifetime patient medical record, as is done for drug allergies. This documentation could be useful for predicting response to subsequent treatments. The information might become part of the medication reconciliation process when a patient passes from one health care setting to another.

**Classification**

Biotechnology drugs are classified by FDA as biologicals, but they may be regulated as drugs by the FDA Center for Biologics Evaluation and Research or the Center for Drug Evaluation and Research. According to FDA, biologicals are derived from living sources (e.g., humans, animals, microorganisms) and are not easily identified or characterized.16

In its Approved Drug Products with Therapeutic Equivalence Evaluations (commonly referred to as the Orange Book), FDA stipulates that pharmaceutically equivalent drug products must be formulated to contain the same amount of active ingredient in the same dosage form and meet the same compendial or other applicable standards (i.e., strength, quality, purity, and identity).17 Drugs are considered therapeutic equivalents by FDA only if they are pharmaceutical equivalents and they can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.17
New biotechnology products that are similar to the innovator product could infringe on one or more patents. The new product may not be therapeutically equivalent to the innovator product if the FDA definition of therapeutic equivalence is used. However, in practice, drugs in the same therapeutic category with equivalent outcomes often are considered therapeutically equivalent, especially by government agencies and insurance companies that pay for the products. FDA has not defined or developed a pathway for establishing therapeutic equivalence of biosimilar and innovator products. Decisions about the therapeutic equivalence of biopharmaceuticals (i.e., biosimilars and innovator products) will probably be made by payers in the absence of guidance from FDA, and these decisions will be based primarily on cost. Payers have already made such decisions and established therapeutic equivalence for interferon alfa-2a and interferon alfa-2b, epoetin alfa and darbepoetin alfa, the luteinizing hormone-releasing hormones leuprolide acetate and goserelin acetate, granulocyte colony-stimulating factor and granulocyte–macrophage colony-stimulating factor, and various antibiotics. Some taxanes are considered therapeutic equivalents by payers in other countries.

The Biotechnology Industry Organization is a biotechnology product manufacturer association. Many of the members are involved in the agricultural industry, not the pharmaceutical industry. The organization’s position statement about follow-on biologicals is pertinent to a discussion of biotechnology drug products. A portion of this position statement follows:18

Currently, the science does not exist to provide an alternative to a full complement of data, including clinical evidence, to demonstrate safety and effectiveness for follow-on biotechnology products. As FDA has frequently acknowledged, biotechnology products can be difficult to fully characterize. Also, due to differences in the composition of a biotechnology product or differences in how the product is manufactured, different versions of the same biotechnology product produced by companies other than the innovator will inevitably differ in certain respects from the innovator product. Experience shows that even small product differences can result in significant safety or efficacy differences. Therefore, in the current state of scientific knowledge and technique, a clinical trial remains a fundamental principle for evaluating the safety and effectiveness of a follow-on biotechnology product.

Unresolved questions

Generic biotechnology products are commonly recognized throughout the world, but whether the substitution of biosimilars for innovator biological products will be widely accepted in the United States remains to be seen. If substitution is inevitable, pharmacists might best be advised to prepare for it. One might argue that equivalence is warranted for two products with different molecular structures if they target the same receptor site, although the two products might have different properties that translate into different toxicities. Similar therapeutic outcomes may be required.

Currently, therapeutic equivalence of biosimilars and innovator products cannot be demonstrated, and FDA requires a new drug application with clinical efficacy and safety studies for product approval. To provide definitive answers about the equivalence of biosimilar and innovator products, switching studies are required. These studies involve assays for neutralizing antibodies and collection of clinical efficacy and safety data in subjects receiving one biological product followed by one or more similar products before switching back to the first product, for the purpose of determining whether an immunologic response is generated and efficacy and safety are affected by the change in products. These studies are costly and time consuming.

Pressure from payers to establish therapeutic equivalence and reduce costs will continue. The Centers for Medicare and Medicaid Services (CMS) tried and failed to establish functional equivalence and dose conversions for erythropoietic agents, but the agency will likely continue in its efforts to reduce the cost of these and other biological therapies.

Pharmacists might ask themselves why they should support the use of innovator products; the pharmacist stands to lose money when payers limit the amount of reimbursement to the lower cost of biosimilars that are deemed therapeutically equivalent. This question might be pertinent in the hospital inpatient setting, where CMS reimbursement is based on a diagnosis-related group or per diem rate. However, there currently is no incentive to use a lower-cost biosimilar in the outpatient setting, where CMS reimbursement is based on average sale price plus 6%. Use of a lower-cost equivalent would reduce reimbursement.

Whether prescribers of biosimilars that are deemed therapeutically equivalent to the innovator product will be able to write “dispense as written” is an unresolved question. The answer probably will hinge on the framework that FDA creates for establishing equivalence. The arrangement will not be the same as the one currently used for generic small-molecule chemical drugs, because of the complexity of biopharmaceuticals.

The considerations surrounding biopharmaceuticals are complex and will become even more so. A growing percentage of new drug approvals in the future will involve biopharmaceuticals.19

Conclusion

The confusion surrounding biosimilars presents a challenge and an
opportunity for pharmacists. Advising lawmakers and decision-makers in health systems (e.g., members of the pharmacy and therapeutics committee) about the scientific differences between biosimilars and innovator products and the possible clinical implications of using these products as therapeutic equivalents are among the roles pharmacists can play in resolving the confusion and preparing for the future.

References