As with any new category, science must lead the U.S. introduction of biosimilars. In the U.S. healthcare landscape, experts in therapeutic areas who currently use biologics (e.g., rheumatology, gastroenterology, hematology) will likely take a central role in evaluating the potential impact of biosimilars in their field, as the National Comprehensive Cancer Network (NCCN) work group already has done in oncology.1 In most instances, the processes for evaluating these new biologic entities and establishing sound medical and reimbursement policy may match the complexity of the products themselves. All stakeholders will need to be prepared for the expansion in biologic medicine:

- Manufacturers must understand risk and optimize quality and consistency;
- Physicians and pharmacists will need to make clinical decisions based more closely on the science and a patient’s medical or biologic treatment history; and
- Regulators and payers must make economic and medical policy decisions as biosimilars come into their purview, based both on an extrapolation of data and direct clinical trial data.

Recent U.S. experience with the launch of Omnitrope® – under the 505(b)(2) pathway of the Federal Food, Drug and Cosmetic Act (FFDCA) allowing use of data from studies not conducted by or for the applicant – has been seen by some as the first instance of biosimilar-like competition in the U.S. market.2 However, this is similar but not identical to the new U.S. Food and Drug Administration’s (FDA) pathway for biosimilars. Looking abroad, the EU market experience with biosimilars is still preliminary. Ex-U.S. experience to-date suggests little room for generalization, indicating that each biosimilar should be evaluated on a case-by-case basis given each category’s unique characteristics.

Introduction

The Trends in Biologic Medicine Report provides a compilation of trend information related to the U.S. market with specific focus on biosimilars. This report is intended to give reimbursement thought leaders a guide to the topics, trends and issues pertinent to biosimilar introduction and adoption in the U.S.

The implementation of the Biologics Price Competition and Innovation Act of 2009 deepened the complexity of the U.S. healthcare market, which will begin to adopt the next logical step in biologic medicine, the introduction of biosimilars. While clinical experience with follow-on biologics exists outside the U.S., that experience, both clinically and operationally, has had limited impact on the perception of biosimilars in the U.S. market. Here, the debate has focused more on downstream issues, such as substitution and traceability, which has taken attention away from the regulatory pathways required for approvability and the demand for guidance around the clinical utility of biosimilars that payers, providers and patients need to understand to establish how these products will be used and reimbursed in the future.
Characteristics shaping U.S. perceptions of biosimilars
The U.S. market has its own set of characteristics that are shaping perceptions and decisions related to the introduction of biosimilars:

No Two Biologics Are Alike
Due to processes associated with translating biologics from living cells in the laboratory to mass production molecules, including variability related to manufacturing, biosimilars can only be highly similar to the innovative biologic medicines (or “reference products”) they are designed to resemble: there is no way to make identical copies of biologics.3

Approvability of Biosimilars = Comparability
Due to the lack of clarity around each biosimilar’s exact structure and clinical profile, the decision to approve a biosimilar is likely to be based largely on head-to-head clinical trials that demonstrate the product profile is comparable to its reference product.4

Interchangeability – Setting A Higher Standard
The FDA has designed a pathway for sponsors to apply to have a biosimilar product designated as “interchangeable” with its reference product, meaning that the biosimilar can be substituted for the reference product without consulting a patient’s healthcare provider.2 However, individual state pharmacy acts will be responsible for allowing substitution to occur.3
Since the 1970s, a revolution in biotechnology has resulted in a new class of medicine: the biologic. A biologic medicine is a large molecule typically derived from living cells and used in the treatment, diagnosis or prevention of disease. Biologic medicines include therapeutic proteins, DNA vaccines, monoclonal antibodies (i.e., MABs) and fusion proteins. Biologic medicines are up to a thousand times the size of a small-molecule drug and are far more complex structurally. They are also highly sensitive, making them more difficult to characterize and produce. Due to both their size and sensitivity, biologic medicines are almost always injected into a patient’s body.

How are biologic medicines developed?
A biologic is manufactured in a living system such as a microorganism, plant or animal cells. Most biologics are very large, complex molecules or mixtures of molecules. Many biologics are produced using recombinant DNA technology, which often is used to insert or remove specific genes within a cell or via a vector such as a virus, prompting a specific function, such as the production of a protein to treat disease. This relatively new advance in biotechnology has led to the development of many of today’s most important medicines, including monoclonal antibodies for cancer, human insulin for diabetes and the cloning of the naturally occurring protein, erythropoietin for chronic anemia.

Facts About Biologics
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The genetic code of a chosen protein, such as human insulin or an immune-system antibody, is identified and replicated by combining segments of DNA to build a functional DNA sequence. The sequence is introduced into the host cell of a living organism, such as bacteria, yeast or mammal cells, altering the cell’s genetic makeup and coding it to produce the chosen protein. Genetically modified cell lines are carefully selected and cultured in large bioreactors before the biologic medicine is extracted through complex and lengthy purification processes. Each step is intricate, sensitive and often specific to a particular medicine, requiring significant skill and expertise. Even minor alterations may lead to changes in cell behavior and differences in the structure, stability or other aspects of the end product. Any of these differences have the potential to affect the treatment’s safety, efficacy and shelf life, and to increase the risk of an unwanted immune response.

Biologic medicines are made in living organisms by genetically engineering DNA. DNA is inserted into living cells, such as bacteria, yeast or cultured animal cells, to code for the production of a particular protein.

The biologic is modified to ensure it functions as intended. Specific chemicals are added to control the function of the biologic.

The most effective cell line is selected for expansion. During selection, the cells that can produce the biologic most effectively are identified and expanded to manufacture the medicine. This cell line is unique to each manufacturer and is the source of all future product.

The unique cell line is grown in bioreactors and carefully monitored. The biologic drug is then isolated and purified using sophisticated technology.

By understanding the mechanisms of diseases biologic medicines can be developed to target and modify underlying causes of disease, potentially altering the course of disease rather than simply treating symptoms.
Biosimilars ≠ Generics

Key Considerations for U.S. Payers:

1. **Biosimilars are not generic medicines**.

2. **All biosimilars may not be approved as interchangeable with their reference product**.

3. **Biosimilars may have all, some or only one of the indications of their reference product**.

4. **Physician perceptions regarding interchangeability and substitution will be a considerable factor in driving use of a biosimilar**.

Highly similar, but still unique biologic entities

The FDA defines a biosimilar as:

A biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biosimilar and the approved biological product in terms of the safety, purity, and potency.

Some originator product characteristics cannot be replicated

Each step of the biologics manufacturing process is intricate and requires significant expertise to protect the protein while producing a therapeutically useful treatment. Certain steps are specially designed to cultivate a single therapeutic protein and may be proprietary to the manufacturer, as they have been established through extensive biologic testing and manufacturing experience. Even with tightly controlled processes, there is some batch-to-batch variability in the end product. Since the specific processes and product standards differ by company and are not disclosed in public labels, biologics cannot be identically reproduced by another manufacturer.
Today, generic drugs are frequently substituted by the pharmacist without the involvement of the prescriber. This is due to the fact that small molecule generics are considered interchangeable with one another and are often automatically substituted. Such substitution is permitted by select state laws because the active ingredient of the generic drug has been deemed chemically identical to the active ingredient of the medicine it has copied.3

Biosimilarity and interchangeability standards
The 2010 law that allows the FDA to approve biosimilars established two distinct standards related to these medicines: “biosimilarity,” which is common to other jurisdictions, and the designation of “interchangeability.”5

Once a product has met the first standard, biosimilarity, it may be considered for a determination of interchangeability with the reference product. This designation carries the expectation that the product will produce the same clinical result in any given patient and that no additional risk to safety or efficacy will result from switching between the biosimilar and the reference product.1 If a biosimilar is determined to be interchangeable, it may be substituted for the reference product without the intervention of the prescriber.3

Receiving the FDA “interchangeable” designation marks substantial progress for manufacturers: in addition to achieving substitution, the product receives 12 months of exclusivity. In this period, the FDA may still approve other biosimilars, but those products cannot be substituted by pharmacists.3 However, interchangeability poses potential risks. For example, if an applicant fails to receive the interchangeability designation through the FDA for one or more indications, it could undermine provider and patient confidence in the product or in other biosimilars.11

According to the market research done by Decision Resources Group Company, physicians may be less willing to prescribe a biosimilar without specific clinical data in that indication despite the FDA allowance for biosimilar extrapolation. According to an analysis published by McKinsey and Company in February 2013, most of the currently marketed “large” biologics have 55 percent to 65 percent of sales within their primary indication, with the second-largest indication typically accounting for another 15 percent to 25 percent of sales.11

At this time, it is reasonable to expect that interchangeability requirements will vary by class. In addition, because clinical data requirements remain unknown, interchangeability designations are unlikely in the short term.13

Another consideration for payers (as well as for providers) is to understand what the FDA will allow for indication extrapolation for biosimilars. Indication extrapolation may be allowed assuming the biosimilar sponsor has considered potential differences in each indication with respect to the mechanism of action, pharmacokinetics, biodistribution, and toxicities.13

This is also an important issue for biosimilars manufacturers, because adding regulatory requirements related to clinical development programs for each indication would increase the costs of development. Increased development costs may limit the potential savings from these medicines, and may impact the number of market entrants.11

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U.S. – FDA
The FDA can designate a biosimilar as an interchangeable biologic when the following criteria are met:

1. The biologic product is biosimilar to the reference biologic product
2. The biologic product can be expected to produce the same clinical results as the reference product in any given patient
3. For a biological product 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 no greater than the risk of using the reference product without such alternation or switch.3

Europe – EMA
Decisions on substitution are made at the national level. In many EU countries, automatic substitution of biologics is officially prohibited or not recommended.1

World Health Organization
The WHO does not define standards on interchangeability for biologic medicines.
It recognizes that a number of issues associated with the use of biologics should be defined by the national authorities.12

Substitution and interchangeability at a glance
Manufacturing Biologics Requires Planning for and Managing Variability

Key Considerations for U.S. Payers:

1. **Biotech manufacturing is a constantly evolving science**

2. **Cell-line selection and manufacturing processes are proprietary in nature, so biosimilars can never be identical copies of the originator medicine**

3. **How a biologic is manufactured can have important clinical outcomes**

4. **Understand the steps manufacturers should take to ensure reliable supply**

Biologic medicines are manufactured using living cells that have been engineered to produce therapeutic proteins in large quantities. These proteins are very sensitive to their conditions of synthesis and handling, and a series of critical culturing and purification steps is required to produce a consistent, high-quality active ingredient. The complexity, precision and controls associated with this process require careful design and strict adherence since any changes can potentially influence the quality of the final product, including the structure, function and purity of the active ingredient.

The complexities of manufacturing biologic medicines also apply to biosimilars, which are approved on the basis of demonstrating similar quality, safety and efficacy to originator biologic medicines. In attempting to copy the originator product, biosimilar manufacturers must independently design their own cell cultures and production steps, which are considered proprietary knowledge. It is therefore impossible for biosimilar manufacturers to precisely replicate the manufacturing process of the original biologic or the active ingredient of the protein product.
Clinically meaningful differences

While many structural differences have no clinical relevance, it is possible that differences in protein folding, structural modifications (such as glycosylation), batch composition and even the product container may, among others, have unexpected impact on the safety or efficacy of the product. For example:

A product container contributed to a trend in immunogenicity for erythropoietin-stimulating agents (sold in the EU) starting in 1998. This manifested as a sharp increase in the incidence of pure red cell aplasia (PRCA) in patients with chronic kidney disease and was ultimately traced to the effects of organic compounds leaching into the pre-filled syringes from uncoated rubber stoppers used by the manufacturer. Due to the subtlety of the effect and the latency of the onset of PRCA (in some cases up to nine months after initiation of treatment), it took several years to identify and mitigate the effect of the organic leachate.14

More recently, a clinical trial of the European Medicines Agency (EMA)-approved ESA biosimilar HX575 being studied for label expansion to the subcutaneous route of administration, resulted in neutralizing antibodies in two of 174 patients treated with it, with one confirmed case of PRCA.15 The manufacturer evaluated product quality in the relevant batches and identified individual pre-filled syringes with elevated levels of aggregated protein. As aggregated protein was considered a likely contributor to immunogenicity, the root cause investigation focused on parameters that could result in variable aggregate levels. Shipping and handling as well as chemicals that had leached from the drug product container were evaluated; HX575 manufacturer ultimately traced the issue to the interaction of its medicine with tungsten residuals from the drug product container. The manufacturer of the syringes subsequently converted to low-tungsten components.16

In both examples, neither routine quality control tests nor additional analytical testing required for regulatory approvals of the respective drug products detected the underlying product quality issues. Only after actively monitoring for and ultimately receiving unexpected safety signals could the companies embark on the exhaustive investigations that revealed the root causes and triggered mitigations to improve product quality and safety.15,16

Importance of high-quality manufacturing to prevent shortages

Manufacturing and quality control issues can impact patient safety and result in a loss of confidence in the quality of biologics. In addition, these issues may also impact other products manufactured in the facility and lead to product recalls and drug shortages, any of which can have profound effects on the company, customers, the biotech industry, providers and patients.14

Officials from the FDA published an article in January 2013 describing quality management failures as a factor in sterile injectable drug shortages:

‘… drug shortages are first and foremost driven by the inability of various firms to maintain production because of the failure of quality management in facilities that produce the finished dosage form of the drug … ’

J Woodcock and M Wosinska
Center for Drug Evaluation and Research for the U.S. Food and Drug Administration17

Although FDA authors address the relationship of quality management to shortages of sterile injectable drugs, the issues cited are similar to the manufacture of biologics. These products share some quality control issues with sterile injectables in that the final products are filled in facilities subject to similar stringent controls. But biologics are, if anything, more susceptible to quality issues due to their relatively high sensitivity to multiple manufacturing steps. The rapidly increasing array of innovative biologics and biosimilars could increase the chances of unexpected quality issues.16
These risks can be mitigated with investments in process and facility design, quality control systems and management oversight, all of which can increase manufacturing reliability. While current market forces may not reward investments in quality and reliability, the FDA may explore mechanisms to change this dynamic:

‘FDA could support the buyers and payers in their purchase and reimbursement decisions by providing them with meaningful manufacturing quality metrics. This general approach has been successfully used in many other settings where quality is difficult to observe or quality signals are difficult to interpret. Restaurant grades, HMO scorecards or even a U.S. Pharmacopeia stamp on vitamins are just a few among many tools that utilize this concept.’

J Woodcock and M Wosinska

Shortages have forced healthcare providers to ration drugs, delay critical treatments, substitute drugs with less efficacious or more expensive medications or even use alternative suppliers. In oncology practice, shortages have forced physicians to prioritize patients, substitute drugs in standard chemotherapy regimens and choose unproven treatment options for patients with curable disease. Alternative drugs may be less efficacious and less tolerable, and conversion factors and dose adjustments may be unknown.

Biologic products have also been affected by shortages. The Office of Compliance and Biologics Quality (OCBQ) at the FDA’s Center for Biologics Evaluation and Research (CBER) tracks these shortages, and as of September 2013, ongoing biological shortages include proteins immune globulin (Human) and a number of vaccines. Past biologic shortages have included essential medicines such as factor VIII, several vaccines and the biotechnology products agalsidase beta (Fabrazyme®) for Fabry disease and imiglucerase for injection (Cerezyme®) for Type 1 Gaucher disease.

At the time of the shortages of Fabrazyme® and Cerezyme®, alternative therapies were unavailable, and patients were subject to rationing. It is noteworthy that the manufacturer experienced concurrent issues with viral contamination at a drug substance facility, and with control of particulates in a drug product facility, illustrating the particular susceptibility of biologics to supply disruptions.

High reliability organizations (HRO)

High Reliability Organizations exist where high performance is needed despite overwhelming potential for error and disaster.

HROs invest in continuous monitoring, learning, and improvement to ensure the resilience of their operations. In the context of worldwide drug shortages and their impact on healthcare, providers may gain awareness of the capabilities and commitment of biologics manufacturers through publications, public information about regulatory observations and actions, and through other evidence about the reliability of supply. Therefore, when evaluating drugs for formulary inclusion and coverage decisions, payers should have an understanding of those manufacturers that can be classified as an HRO.
Pharmacovigilance
Monitoring biologics in real-life settings

Key Considerations for U.S. Payers:

1. **Biologic medicines have the potential to stimulate an unwanted immune response.**

2. **There is a compelling need to develop accurate, consistent reporting and tracing of adverse events.**

3. **Promoting identification and resolution of product issues will enable manufacturer accountability.**

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**The importance of pharmacovigilance**

All biologic medicines carry similar risks as small molecule compounds based on the patient’s reaction to proteins in the medicine, which would affect their efficacy or safety. As such, the ability to track and trace all biologic medicines throughout the product lifecycle is critical to help ensure patient safety.

Adverse event (AE) reporting is collected from a variety of sources based on currently accepted pharmasurveillance practices with manufacturers. This reporting process depends on the voluntary participation of prescribers, patients and others, which is not always consistent and often results in underreporting. Further, the quality of reports varies and the medication suspected of causing the AE is not always identified, delaying efforts to prevent further harm.

**Biologics and pharmacovigilance**

Tracing AEs associated with biologics is challenging because the occurrence may not manifest as an acute episode and reporting may occur weeks or months after administration and most likely after the product packaging has been discarded. Under these circumstances, AE reporting likely depends on the reporter’s memory or the patient’s medical record. User-friendly drug identifiers that are easily remembered, are frequently included in accessible electronic medical records, and effectively distinguish products may help facilitate more accurate AE reporting and tracing.

Biosimilars are not anticipated to exhibit any clinically meaningful differences from the reference product in terms of safety, purity, and potency, and the FDA is recommending clinical efficacy/safety studies of biosimilars prior to approval. It is important to note that clinical studies may not detect infrequent but potentially serious AEs. Therefore, the robust post-approval surveillance of all biologics is an important aspect of how these medicines are utilized in the clinical setting.

**Inconsistencies in current identification**

Unfortunately, there are inconsistencies in the identification of biologics in the U.S. pharmacovigilance system that limit accurate tracing of reported AEs. The need to rapidly and accurately identify the precise product implicated in a post-marketing safety investigation is exemplified by a case study of 246 fatal allergic-type reactions in patients on hemodialysis who received contaminated heparin. In this case, the lack of manufacturer information and lot numbers in some AE reports were noted as hampering identification of the responsible heparin manufacturer.
Although heparins are not complex biologics or biosimilars, this example underscores:

- The importance of distinguishable identifiers;
- Recognition and support throughout the healthcare community for the need for accurate biologic product identification for AE reporting; and
- The need for national pharmacovigilance systems that accurately and reliably collect this information.

Generic names may inhibit accurate traceability

The nonproprietary name (international nonproprietary name [INN]/U.S. adopted name [USAN]) is commonly used to identify the product in an AE report and may be the only identifier recorded in some hospital or healthcare databases. In current practice, if a biosimilar was assigned the same INN/USAN as its reference product, AEs could not be clearly traced to the correct product. Additionally, a shared INN/USAN would not allow for prescriber awareness of biosimilar substitutions at the pharmacy level. A shared INN/USAN would identify a therapeutic class rather than the specific administered biologic, unless it were complemented with additional information (e.g., brand name or manufacturer). Moreover, shared INNs/USANs could imply interchangeability, a designation that requires meeting FDA-specified criteria. Whether a biosimilar should receive the same USAN as its reference product will ultimately be determined by the FDA. There is growing debate on this topic. Some parties believe that the FDA does not need to require a different USAN for a biosimilar because the current system of AE reporting, including the use of National Drug Codes (NDCs), is an adequate way to identify and track suspected AEs. Moreover, requiring a biosimilar medicine to have a different USAN from its reference product (such as a common shared root but a distinguishable pre-fix or suffix) could create potential confusion among prescribing physicians, and thus limit the commercial viability of biosimilars. Conversely at least one declared biosimilars manufacturer has announced it intends to seek distinguishable USANs for its biosimilar medicine to help improve the quality of suspected adverse event report investigations.

National drug codes are simple, but not the solution

NDCs provide detailed information about a medication and, if accurately included in an AE report, would provide a reliable means of product identification; however, NDCs have significant limitations for biologic identification. Here’s why:

- Although all approved drugs receive a NDC, it may not always appear on the packaging because inclusion in the labeling is determined by state law.
- NDCs are a 10-digit number making them susceptible to transcription errors.
- In current practice, AE reports are unlikely to contain the NDC. Physicians and patients are often unfamiliar with the NDC, and most AEs are reported without access to primary packaging that may contain this code.
- It has been suggested that NDCs could be recovered from other databases (e.g., payer systems); however, the NDC is inconsistently collected and access to such databases is neither simple nor quick.
- For example, if the FDA wishes to investigate a series of AEs, there is no mechanism for immediate access to private, federal, or state systems or uniform system structures.
- Additionally, patients are anonymous in AE reports; queries to payer systems would be futile without first identifying each patient in the AE reports.
Future Trends

Biologics have a large presence in the global healthcare landscape today. In the U.S., these products continue to capture a greater portion of the total health-related spending, with biologics now representing four to five percent of the total commercial healthcare spend. The average cost of a biologic is estimated at about 40 times that of traditional small molecule drugs. In parallel, sales have continued to rise as more biologics become available around the world, particularly in the U.S., Japan, and much of Western Europe. The biologic medicines market is expected to grow to $190-200 billion by 2015, and their overall market share is expected to double by 2020. When comparing the top therapeutic categories responsible for increases in global healthcare spending, seven of the top areas are primarily treated with specialty medicines, as they offer novel mechanisms and improved efficacy to treat patients with serious cancers or genetic diseases. With an increasing focus on cost containment, markets are considering a range of pricing strategies to help manage the steep trajectory of spending on this segment of the healthcare market.
Emerging opportunities in biosimilars

Biosimilars are an area of strong interest to pharmacy and medical directors as they continuously explore opportunities to recognize cost savings related to prescription drugs. By 2020, biologic medicines worth an estimated $81 billion globally are expected to experience patent expiry, paving the way for the next generation of biologic medicine – biosimilars. Among these new alternatives, there is likely to be a range of fusion proteins and monoclonal antibodies currently used in cancer and autoimmune diseases.

Biosimilars have had limited exposure to date in the U.S. However, in Europe, since 2006, eight unique medicines have been approved (currently marketed as 15 different brands), while several product applications have been withdrawn and one product was rejected. One product was approved by the EMA and has been since withdrawn from the market by its manufacturer. Until 2013, these medicines had been limited to just a few categories (such as human growth hormones and erythropoietins), but in September 2013 the European Commission authorized the approval of the first monoclonal antibody, a TNF-inhibitor.

Between 2006 and 2012, sales of these molecules were $1.2 billion (USD) but the penetration rate of these biosimilars compared to the innovator (reference) brands have not matched those of traditional small-molecule generics. In 2012, the European Commission sponsored a review of the biosimilars market and determined biosimilars market share varied between 7-18 percent of the accessible market.

Reimbursement authorities in Europe are not yet experiencing the level of cost savings for biosimilars compared to traditional small-molecule generic medicines. This is partly driven by the varied level of pricing offered by manufacturers. The former head of the European Generics Medicines Association has publicly stated, “It is important the authorities realize that biosimilars will never have generic-type pricing.” and the European Commission has noted, “Compared to chemical molecules, the savings expected are less prominent due to the high costs involved in the development of biosimilars.” Further, in its sector review, the European Commission has noted that biosimilars “may” be a less costly alternative to an established product, as the availability of biosimilars enhances existing market competition. An example of this price competition can be found in Germany, which is the largest sales market for biosimilars in Europe. “Health insurers have to ask ‘does this make sense for us?’ ‘Will we save money?’ Our feeling is that we don’t always save money with biosimilars,” said Ann Marini, GKV-Spitzenverband.
Despite this, the market has experienced swift growth and is predicted to have significant future potential as approval pathways become better defined and as markets gain experience with these advancements. As of March 2012, there were 73 biosimilar monoclonal antibodies in development\(^\text{11}\) and estimates suggest that by 2015, biosimilars sales around the world may reach up to $2.5B.\(^\text{41}\)

The list of companies planning entrants in the biosimilars market is small due to the capabilities and expertise required, and in the short term, the list of products that will be targeted for competition is also limited, based on the manufacturing challenges and patent issues/expiry. But as the biosimilar market segment matures, risks will reduce and competition will rise.\(^\text{42}\)

**Restructuring the value definition:**

What should payers consider for biosimilars

The complexity of biosimilar production plays a significant role in defining their value compared with traditional small molecule generics, so cost savings may not be the only value indicator for this emerging market. The total development costs for biosimilars are estimated to be between $75 and $250 million for registration and approval. As with traditional molecules, companies will be looking to realize a return on those investments through sales.\(^\text{43}\) Current pricing assumptions indicate that biosimilars may be marketed at roughly a 20-30 percent discount from the innovator price, compared to a 75-80 percent discount for generic equivalents to traditional drugs.\(^\text{44}\) Assuming a 30 percent savings delivered by a biosimilar, a 2011 analysis by Milliman, Inc., projected the overall saving as a percentage of total healthcare costs for a patient resulting from biosimilars is likely to be small (i.e., roughly 1.2-1.5%).\(^\text{45}\)

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As biologics grow and continue to have an impact on healthcare spending over the next five years, estimates suggest the impact of cost savings from biosimilar introduction could be relatively small. Biosimilars have strong market potential but given the relatively small number of differentiated benefits from innovator products, patients may be less likely to receive these types of treatments until more experience is gained by providers, payers and patients. Due to these factors, there is some debate whether employers will consider coverage policies that encourage biosimilar usage.\(^\text{46}\)

Given this landscape, a primary risk in this debate is that cost becomes the sole focal point. When concerns about cost supersede the interest of patients, there is potential negative impact both in terms of effectiveness and safety of biosimilars.\(^\text{55}\)

Instead, the challenge to all stakeholders should be to create a holistic view of how these alternative products can fit into global healthcare models in a way that meets the needs of healthcare systems while providing benefit to patients. Clinical evaluation as well as the relative value of biosimilars versus the originator biologics is of primary importance to reimbursement decision makers. Through this type of analysis, reimbursement decision makers will understand how to develop the appropriate clinical and economic modeling to support their population health management strategies.\(^\text{56}\)

Key issues remain in the path toward biosimilars:\(^\text{14}\)

- Pricing models/analysis
- Experience with the category and familiarity with the originator product
- Acute vs. chronic treatment
- Nomenclature and pharmacovigilance
- The “unknowns” of coverage tiers and switching/substitution
- And patient choice

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Biosimilars have a large presence in the global healthcare landscape today. In the U.S., these products represent four to five percent of the total commercial healthcare spend. The *Trends in Biologic Medicine Report* explores the emerging biosimilars field in the U.S., with specific discussion on issues that will be relevant for the payer community as these alternative biologic products are evaluated for adoption in the U.S. market.

### Biosimilars ≠ Generics

1. **Biosimilars are not generic medicines**
2. **All biosimilars may not be approved as interchangeable with their reference product**
3. **Biosimilars may have all, some or only one of the indications of their reference product**
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### Manufacturing Biologics Requires Planning for and Managing Variability

1. **Biotech manufacturing is a constantly evolving science**
2. **Cell-line selection and manufacturing processes are proprietary in nature, so biosimilars can never be identical copies of the originator medicine**
3. **How a biologic is manufactured can have important clinical outcomes**
4. **Understand the steps manufacturers should take to ensure reliable supply**

### Pharmacovigilance: Monitoring biologics in real-life settings

1. **Biologic medicines have the potential to stimulate an unwanted immune response**
2. **There is a compelling need to develop accurate, consistent reporting and tracing of adverse events**
3. **Promoting identification and resolution of product issues will enable manufacturer accountability**