Several follow-on biologics, including biosimilars, have become available over the past few years, with many more in the development pipeline and ready to enter the marketplace. These drugs should play an increasing role as part of an overall strategy to reduce drug prices as they find their way onto contracts and formularies.

Diabetes educators need to have a good understanding of how these products are to be used in patient care, the differences in these types of drugs, and how they fit into different therapies in order to clarify and answer questions about their use from patients and providers alike. A better understanding of biosimilars can help prescribers and their patients maximize the benefits of these drugs.

As prescribers attempt to change therapies or initiate biologics to save patients money, they may not fully understand the differences between using a biosimilar and the reference licensed biologic product or, in many cases, how they can be used in place of one another. Being able to explain the differences in these drugs to patients as well as providers attempting to prescribe or switch patients to biosimilars will become a part of the role of diabetes educators in the near future.

This article is intended to provide educators with the basic definitions, comparisons, and use of biologics and follow-on drugs. Contracting, formulary, and the more complex financial aspects of these drugs are beyond the scope of this document.
Biologics, Biosimilars, and Generics

It’s easy for confusion to occur when discussing the field of biologics, biosimilars, and generics. A clarification of the terminology may help to understand the roles these products play in today’s health care.

The use of biologics and biological medications is not new to patient treatment. They have been with us for decades in the form of antivirals, antitoxins, antirheumatics, blood products, therapeutic proteins, and therapeutic hormones. All drugs in the biologic class have one thing in common: They are derived from living organisms using genetic engineering. They are manufactured in living systems, such as yeast or bacteria, or in other plant or animal cells. Many biologics are produced using recombinant DNA technology. Because of the process of producing biologics in these living cells, it’s impossible to make an exact replica of a product unless the manufacturer follows the same exacting procedure as the company producing the brand name drug. As this process is proprietary, other routes of manufacturing the biologic must be used.

The first drug approval for a genetically engineered biologic product was Humulin R (recombinant human insulin) by Eli Lilly and Company in 1982 utilizing a nonpathogenic laboratory strain of Escherichia coli. Another example of a genetically engineered product created using recombinant DNA technology is Epoetin alfa (Procrit, Epogen), approved in 1989 and widely used to replace erythropoietin, which occurs naturally in the body and is essential for the formation of red blood cells to prevent anemia.

To address the manufacturing procedures involved in working with biologics, a new term was created to describe a process of creating a product that was very close but not identical to the brand name product. These drugs are now called biosimilars because changes in cell lines, growing conditions, expression times, purification processes, and other variables can result in minor changes to the product.

Biosimilars are similar—but not identical—to the brand name drug, also known as the reference drug or product. A biosimilar or a “follow on biologic” is a biological product that is approved based on demonstrating that it is highly similar to the FDA-approved reference product concerning safety, potency, and purity and that there are no clinically meaningful differences in terms of safety and effectiveness from the reference product. The new process of manufacture can lead to minor differences in structure, stability, excipients, and impurities that are compared with the reference biologic and are allowable if they are not clinically significant. Biosimilars produce the same results using the same mechanism of action as the reference product at the same dose.

What Biosimilars Are Not

Biosimilars are always compared to the referenced biological medication already approved by the FDA. However, it’s important to remember that biosimilars are not biological generics of a brand name drug. Generic drugs consist of simple, small molecule, well-defined products. Biosimilars, in comparison, are large complex molecules or mixtures of molecules defined entirely by an exacting manufacturing process. So, “the process is the product.”

Comparing biosimilar products is not the same thing as comparing a generic drug to a brand name pharmaceutical, as in comparing metformin to Glucophage. When a generic drug is submitted for approval, it is required to be chemically identical in structure to the brand name it is comparing itself to. It must have the same active ingredient, chemical structure, and strength, and it must also be bioequivalent, acting the same way in the body as the referenced drug in areas such as absorption and dispersion. The generic and brand name drug are considered interchangeable. Even when the manufacturing process is changed, if the chemical...
The new approval pathways allow that the process of development for a biosimilar might create minor changes in structure, stability, impurities, and excipients compared with the reference biological.

components and end product remain the same, the generic drug is considered the same product.

With biosimilars, the process is much more complex. Small process differences in the source, processing, and handling of cultures of living organisms can significantly affect the nature of the finished product and how closely it resembles the referenced brand name product and in the way it affects bodily functions. This process of manufacturing is extremely complex and labor intensive, as is submitting the human and animal studies and laboratory controls assuring the FDA of a reliable reproducible product.

A New Path to Approval
To address the difference in complexity and process, the FDA created other methods of approval for biosimilars that are entirely different than those for generic drugs applying for a copy of an approved brand name product. These new approval pathways, known as 351(k) or 505(b)(2) pathways, allow for the avoidance of unnecessarily repeating studies of referenced drugs in the areas of safety and efficacy, thus shortening the development time to bring biosimilar products to market in hopes of creating low-cost alternatives to already approved biologics.

The new approval pathways allow that the process of development for a biosimilar might create minor changes in structure, stability, impurities, and excipients compared with the reference biological. To gain approval, these changes must not result in clinically significant changes in the drug. Basaglar (insulin glargine injection) was approved and filed through the 505(b)(2) pathway with no differentiation in the nonproprietary name associated with Lantus (Sanofi). However, because it used this route of approval, even though it has been cleared for use, it is not considered a true biosimilar in the United States.

Approval of biosimilars has one overall goal for the health care marketplace: to reduce health care costs. Biosimilars are expected to reduce overall drug costs by 20% to 30% as competition in the marketplace develops. While the cost is not expected to be as great as the 100% to 400% savings seen in the generic versus brand name model developed over the past several decades, the result of incorporating biosimilars has the potential to produce billions in savings to the health care system while also possibly improving health due to better adherence via savings for patients, especially concerning out-of-pocket expenses. One estimate places the savings to the health care system by using biosimilars at over $44 billion.
An area that does require some consideration and vigilance when dealing with biological products is the immune response that all biologics trigger in a patient to one degree or another.

As payers move forward in an attempt to save money, they are likely to be in the position to dictate what access patients and providers have to biosimilar products and which ones may be used in place of another for savings benefits.

**Conclusion**

Although the concept of biosimilars is relatively new to diabetes care, products coming off patent and the need for savings will drive the market quickly and elicit questions that will need to be addressed by all members of the diabetes care team. These drugs will continue to play a greater role in patient treatment as newer products in the pipeline are brought to market. The diabetes educator can help with the transition by becoming educated in the roles and processes of this new drug class.

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**REFERENCES**

