As cost considerations continue to play a bigger role in healthcare delivery, consumers and payers have increasingly looked to generic medications as a viable alternative to expensive branded drugs. In principle, if generics and their comparators contain the same active ingredients, their safety and efficacy ought to be equivalent; if they are therefore interchangeable, then the lower price option should be preferable.

Market preference for generic drugs has been strong over the previous two decades, and although the price of generic drugs have generally risen since the passage of the Patient Protection and Affordable Care Act (PPACA), cost containment is nonetheless more important because of the law. The safety and efficacy of a given medication are still paramount; however, financial considerations have been given greater weight as commercial and government insurance programs have been afforded greater latitude under PPACA to dictate formularies. Thus, it is really no surprise that according to the FDA, nearly 80 percent of prescriptions filled in 2015 were for a generic drug, and that the number is expected to increase in the coming years.

The modern generic drug market has its origins in the passage of the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act), which was ratified by a rare unanimous vote in the House of Representatives. That law, which amended the Federal Food, Drug and Cosmetic Act (FDCA) and the Patent Act, created the abbreviated new drug application (ANDA) process and, in effect, set the standards for what could be considered bioequivalent. Much of the language used in generic drug discussions today follows from the Hatch-Waxman Act and the FDA’s subsequent actions to formalize its intent.

The success of the generic drug market has now given rise to a new trend in drug manufacturing as drug makers seek to make equivalent copies of branded biologic agents.

The looming availability of biosimilar medications raises important clinical and regulatory questions.

**BY BRYAN BECHTEL, SPECIAL CONTRIBUTOR**

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**Biosimilars: Generic Biologics or Something Much More Complex?**

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**Biosimilars: Study Design Considerations**

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offer them at considerably lower prices. On the one hand, so-called biosimilars borrow the concepts developed in generic drug manufacturing and apply them to expensive but highly effective biologic agents. As patent expiry dates approach on popular biologic agents, drug manufacturers are hoping that market and consumer preferences for lower priced options coupled with a favorable regulatory environment and popular support will drive demand for biosimilars, in turn creating potential for massive profits.

Yet, although the market availability of biosimilar agents seems more a matter of when and not if, researchers are quick to point out that although there is a conceptual similarity in generics and biosimilars, there are critically important differences that clinicians will have to be aware of before prescribing a biosimilar agent.

COMING SOON

During a session held during the recent Maui Derm for Dermatologists Meeting in Maui, Jashin J. Wu, MD, a researcher and clinician with Kaiser Permanente, pointed out that the very real cost savings represented by biosimilars may be too enormous for payers to ignore. Whereas it takes about 10 years and about $1 billion investment to develop an innovator biologic, a biosimilar takes about eight years and about $100 million to develop.3

But potential savings are not just on the supply side. The Congressional Budget office estimated in 2008 that biosimilars would reduce costs by about $25 billion over 10 years and could save the federal government about $6 billion dollars. A report by the Rand Foundation found that the widespread introduction of biosimilars could save anywhere from $13 billion to $66 billion between 2014 and 2024, with physicians and hospital seeing the greatest benefit in the short term, and patients and taxpayers winning in the long run.4

Manufacturers are already clamoring for entrance to the potentially lucrative biosimilar market. In March 2014, Celltrion filed a lawsuit claiming that Janssen’s remaining patents on Remicade are invalid. A short five months later, Celltrion and partner Hospira submitted a Biologics License Application (BLA) for its biosimilar infliximab, the first monoclonal antibody biosimilar submitted to the FDA and the second biosimilar to appear on the FDA’s radar. However, in May 2015, Johnson & Johnson blocked Celltrion/Hospira with a court-ordered injunction. The various legal maneuvers continue to this day.

Then, in October 2015, Sandoz announced that the FDA had accepted its BLA for its biosimilar etanercept, making it the first company to reach that status. A month later, Amgen submitted a BLA for a biosimilar adalimumab, which was expected to come off patent in December 2016 but has recently been extended.

“We should be ready, because the first biosimilars may be here in the next year or two potentially,” said Dr. Wu.

BIOSIMILARS: HOW SIMILAR ARE THEY?

Although a biosimilar and a biologic share the same analogous relationship as a generic and its branded reference, the similarities between the two classes of medications really stop there. According to Andrew Blauvelt, MD, MBA, of the Oregon Research Center and Head of the International Psoriasis Council Working Group, the terms biosimilar and generic come from regulatory definitions and are intended to convey very different things.

“The term generic means it is the same chemically, so 100 percent the same chemical compound. The chemical process is the same from one manufacturer to another, so you would be able to reproduce the drug. Biologics, however, are made from living systems and living cells, and that cannot be replicated, and so we cannot call them generics,” said
Some states are now requiring pharmacies to inform physicians when they intend to switch patients to generics; but tightly applied standards for generics may not even apply to biosimilars. Furthermore, many states still permit pharmacy switches without prior consent from the physician, and many states permit pharmacists to be incentivized to dole out cheaper alternates.

Dr. Blauvelt during the Biosimilar Session at Maui Derm for Dermatologists Meeting.

The technical definition of a biosimilar according to the FDA, Dr. Blauvelt said, is twofold:

A biologic product that is highly similar to a reference product, notwithstanding minor differences in clinically inactive components.

No clinically meaningful differences in terms of safety, purity, and potency.

That wording, Dr. Blauvelt added, although tightly constructed, is actually vague, as there is no set standard for what constitutes “highly similar,” “minor differences,” and “clinically meaningful differences.” In fact, biosimilars are manufactured by a completely dissimilar process than generic medications are in reference to their comparators, and so even achieving similarity is complex.

Biosimilars are manufactured by first reverse engineering the amino acid sequence of the intended biologic product to create a reference DNA sequence; that sequence then becomes the blueprint for creating the biosimilar. However, while biologic processes are similar between drug manufacturers, they are never identical. Each manufacturer has unique steps for cell expansion, cell production, recovery through filtration, chromatography purification, and characterization and stability. Moreover, drug companies change manufacturing processes over time, and even small changes can change the nature of a biologic drug—as such, a reference product for a biosimilar evolves, and although a biosimilar may be similar to the original biologic, it may not be similar to the same biologic produced 10 years after the original.

One aspect adding further complexity is that biologics induce an immune response. “All biologics have immunogenic potential, some more than others,” Dr. Blauvelt said. However, protein biochemistry is a complex science, much more so than the chemistry processes used to manufacture drugs, and a lot of them are proprietary. In particular, glycosylation is vital for developing a functional protein and has potential to affect the end product’s mechanism of action, drug clearance, and its immunogenicity. Yet, glycosylation is sensitive to the cell type and cell line used, the raw materials, culture conditions, and purification process.

Further complicating matters is that multiple manufacturers of the same biosimilar will not produce similar products relative to the reference. In other words, biosimilar B is not the same as biosimilar C even if they are both based on reference biologic X. According to Dr. Blauvelt, the FDA has not made it clear how wide open the biosimilar field will be and whether multiple companies will be permitted to produce the same type biosimilar. Meanwhile, the potential for multiple biosimilars based on the same reference engender concerns about whether formulary constraints dictated by payers could override the potentially significant differences between competing biosimilars.

And so, for myriad reasons, creating a biologic, and in turn, a biosimilar, is an incredibly complicated and sensitive process. Dr. Blauvelt pointed to an analogy to help explain why generic drugs and biosimilars, after all is said and done, may not be analogous products after all:

“If aspirin is like a bike and if human growth hormone is like a car, then a biologic is like a jet plane. It might be relatively simple to copy a bike, but remaking a jet plane is very sophisticated,” he said.

PATHWAY TO APPROVAL

It is obvious that biologics are highly effective treatments. Adalimumab (Humira, Abbvie), approved for treatment of arthritis, plaque psoriasis, ankylosing spondylitis, Crohn’s disease, and ulcerative colitis, is arguably the top selling drug in the world. Potential safety concerns aside, the only real downside to the biologic class of medications is the expensive price tag, an issue that drug and law makers hope to correct as biosimilars move toward market.

“The promise of biosimilars is to reduce costs of and increase access to biologic drugs for patients who most need them,” said Dr. Blauvelt.

Biosimilars are cheaper to produce because they go through different development and regulatory pathways than their reference drug; that reduced cost due to reduced clinical trial program requirements is intended to allow makers to offer lower prices to the market.

Such efforts are good for costs but leave many experts
Residual Uncertainty About Biosimilarity

- Complexity of larger proteins
  - Unlikely to be shown to be structurally identical

- Manufacturing process considerations
  - Different manufacturing processes and changes to processes may alter a protein product

- Some amount of clinical data may be needed to address residual uncertainty

Biosimilars, he said, are most often tested in a switch study design, wherein one group is maintained throughout the entire study on the reference, while the other group is switched from reference to biosimilar at some predetermined time point; a variation on this is to have the active group split and randomized to start on either reference or biosimilar and to have the two groups cross over, with results compared against a group maintained on the reference drug for the duration of the trial.

Clinical trials of biosimilars have, so far, yielded favorable results, Dr. Strober said. A clinical trial of Inflectra (CT-P13, Hospira/Celltrion) versus Remicade (infliximab, Janssen Biotech) showed similar efficacy through 30 weeks of follow-up, with a two percent difference in ACR50 and ACR70 rates. Furthermore, 25.4 percent and 25.8 percent of patients in the CT-P13 and infliximab groups, respectively, developed antibodies to infliximab by week 14, and 48.4 percent and 48.2 percent, respectively, by week 30.

A trial of adalimumab in psoriasis showed no statistically significant differences in groups of patients on reference or biosimilar drugs through week 16 with successful demonstration of efficacy, and no discernable differences in safety.

Although the lack of a placebo arm may lead to an inflated sense of efficacy, “biosimilars need not be identical, only comparable,” Dr. Strober said. “Importantly, biosimilars should neither be better or worse” than the reference drug.

Once a biosimilar is approved, its indications can be expanded through a process called extrapolation. If the sponsor can demonstrate that pharmacokinetics, pharmacodynamics, and immunogenicity in different patient populations are similar; that the toxicity should not be different in different patient populations; that the mechanism of action is the same; and that any other factor that may affect safety and efficacy for each indication is not a consideration, then the biosimilar sponsor can apply for any indication that the reference product is licensed, if appropriate scientific justification is provided,” said Dr. Strober.

In other words, “a proposed biosimilar product may be licensed in one or more additional indications for which the reference product is licensed, if appropriate scientific justification is provided,” said Dr. Strober.

Where assumptions of equivalence may become sticky is with another principle known as interchangability, or that “the biosimilar can be expected to produce the same clinical result as the reference product in any given patient,” Dr. Strober said.

If a biosimilar is granted status as interchangeable, its effects are seen as no different than the reference, thus establishing a rationale for a clinical or pharmacy switch.

“(According to the principle of interchangeability) If the biosimilar is administered more than once to an individual, (Continued on page 50)
CONCLUSION
The biosimilar world is, in fact, entirely dissimilar to that of generic medications. Although generic drugs provide a convenient analogy to understand the rationale for and potential cost benefits of biosimilars, significant differences in manufacturing principles and requirements for drugs and biologics (and the resulting complexity of the products) yield vast potential differences in terms of equivalence.

Nonetheless, many experts feel that despite the myriad clinical and regulatory questions yet to be resolved, the emergence of the biosimilar class is a frank inevitability. The potential cost savings are too great. The expiry of patents on market-leading biologics is looming. The regulatory climate is set with precedent established in the admittedly dissimilar generic market. But, perhaps most important, the market is demanding cheaper alternates and greater patient access, and law makers have shown willingness to exercise power to clear the hurdles that would otherwise limit the potential for commercial and government payers to dictate treatment choices in the clinic.

“A lot of what you can do with biosimilars may not be your choice. The payers are going to dictate a lot of what goes on in the clinic,” said Dr. Strober