SUPPLEMENT TO
MANAGED Care

Regulation of Follow-On Biologics: Ensuring Quality and Patient Safety

A Policy Forum held in Washington, D.C.
April 2009

HIGHLIGHTS

- Getting Past the Exclusivity Debate
- Current Regulatory Review and Approval Processes
- Legislation Update
- Is Interchangeability Possible?
- Panel Discussion

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EDITORIAL

ARTICLE

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Regulation of Follow-on Biologics: The Case for Science over Bureaucratic Expediency

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In the wake of health care reform legislation, there continues to be widespread concern about the upward spiral of the cost of prescription pharmaceuticals, particularly for biologic products used to treat patients with debilitating conditions that are unresponsive to traditional therapies. We in the medical community share this concern and have taken a keen interest in The Patient Protection and Affordable Care Act (PPACA 2009) with respect to generic biologics, also called follow-on biologics (FOBs) or biosimilars.

Although the PPACA is clear about periods of exclusivity for innovator biologics and the first-approved FOB products, it is less prescriptive about the regulatory pathways and approval criteria for these agents. In fact, the U.S. Food and Drug Administration (FDA) has been given considerable latitude and flexibility in fashioning these processes; for example, the PPACA has no requirement for the publication of guidance (i.e., serious scientific review) with respect to the interchangeability of biosimilar products.

Moreover, although the PPACA requires FDA applications to demonstrate the similarity of FOBs with reference products in terms of safety, purity, and potency in treating one or more of the conditions for which the reference product is licensed, it permits the Secretary of Health and Human Services to determine that elements in the application, such as clinical studies, are unnecessary. Given the myriad unresolved scientific issues (e.g., therapeutic equivalence, bioequivalence, pharmaceutical equivalence, immunogenicity) surrounding these very complex products, these potential loopholes raise some concerns.

Uncharacteristically, the United States lags behind the rest of the world in the regulation of FOBs. There are already some excellent prototypes. The European Medicines Agency (EMEA) is the front-runner, and its approach makes a great deal of sense. The EMEA has adopted a set of general guidelines and developed specific criteria for each distinct biologic class as opposed to a single FOB process. All guidelines and criteria are disseminated for public comment before rulings are issued. The EMEA has produced guidance for five to six specific product classes that are currently approved in the United States as drugs (e.g., insulin, epoetin alfa, low-molecular-weight heparin). Rather than "reinvent the wheel," the FDA would be wise to give the EMEA model serious consideration as it hammers out the details of processes in the United States.

From my standpoint as a physician, the most important caveat for any regulation concerning FOBs is that patient safety must always be the top priority. Since biologic drugs are extremely complex, making them difficult (and, in some cases, impossible) to replicate, isn't it in everyone's best interest — especially patients' — to require that all FOBs be clinically tested for safety before introducing them to the marketplace?

I believe that the FDA should commit to focusing on the science of FOBs as opposed to seeking bureaucratic expediency. In keeping with its responsibilities for patient safety and public health, the FDA must ensure that the approval process for FOBs is science-based and transparent, with reasonable input from stakeholders in the scientific, clinical, consumer, payer, and health policy arenas. My advice would fall into three general domains:

- Avoid overly prescriptive regulations
- Ask everything that needs to be asked
- Make certain that the criteria adopted are appropriate for the specific type of therapeutic class (i.e., requiring clinical trials for safety and efficacy of FOBs in recognition that these products are not really substitutable or interchangeable)

In late April 2009, I had the privilege of facilitating a policy forum at the National Press Club in Washington, D.C., entitled "Regulation of Follow-on Biologics: Ensuring Quality and Patient Safety." The forum, sponsored by the Jefferson School of Population Health, brought together an impressive group of experts from the fields of medicine, science, economics, and health policy to discuss the quality and safety issues involved in creating a regulatory pathway to bring FOBs to market in the United States. Several of the forum speakers participated in a follow-up congressional briefing on the topic in November 2009.

This forum is what first convinced me that, although

there is broad support for improving access to biologics and for producing lower cost FOBs, there also is an appropriate level of concern when it comes to patient safety. The FDA would be well served to exercise great care as it finalizes regulations and approval processes for FOBs and to learn from the good (and bad) examples of its European and Canadian counterparts.

The presentations at the forum — as timely today as they were before the PPACA was enacted — are summarized in this supplement. They provide various perspectives and valuable insights into this very important topic. I hope that the material will stimulate discussion and spur positive action toward assuring that the dual goals of lower costs and patient safety can be met. Lower cost at the expense of patient safety is no bargain.

As always, I welcome your feedback. I can be reached at «david.nash@jefferson.edu».

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ARTICLE

Regulation of Follow-On Biologics: Ensuring Quality and Patient Safety

Transcribed and adapted for publication by Janice L. Clarke, RN
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Introduction

Biologics are a "hot topic" today, not only within the health care industry but also in the business/finance and political arenas. These agents are highly valued by physicians as treatments for the symptoms and underlying causes of debilitating conditions for patients whose illnesses are unresponsive to traditional drugs and therapies. The downside in the value equation is that these products are extremely expensive per prescription and, thus, unaffordable for many of the Americans who stand to benefit from them the most. The logical question raised by policy makers and consumers alike is, "Why aren't there 'biogenerics' just as there are other generic drugs?"

It is relatively easy to achieve equivalent chemical composition to traditional drugs with simple chemical structures. In contrast, biologic products present difficult scientific challenges. Narrowly defined, biologic products share two traits that differentiate them from their chemical counterparts: 1) they can be produced only from living cells/systems, and 2) they are relatively large molecules with inherently heterogeneous structures that may contain hundreds of amino acids (Morrow 2004).

It is these attributes that lead scientists to believe biologic products are very difficult — some would say impossible — to replicate. More importantly, studies have shown that even minuscule differences in a product's structure and manufacturing process can produce different clinical outcomes.

The Patient Protection and Affordable Care Act (PPACA 2009) establishes a new regulatory authority within the U. S. Food and Drug Administration (FDA) by creating a licensure pathway for follow-on biologics (FOBs). The mission of the FDA, stated clearly on its Web site, is as follows:

> *"The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.*
>
> *The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health."*

In light of the existing scientific evidence, the regulatory standards and approval pathways for FOBs will have to go beyond mere cost-effectiveness to protect the public health. It is clear that other critical elements in the value equation — namely quality and patient safety — must be given equal consideration.

At a policy forum held at the National Press Club in Washington, D.C., in April 2009, a group of knowledgeable speakers and interested participants addressed this multifaceted topic, striving to understand the intricate interaction of scientific, business, and legislative implications. The proceedings of that policy forum are summarized in this supplement.

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Follow-on Biologics: Getting Past the Exclusivity Debate

MICHAEL MCCAUGHAN
Editor-in-Chief, The Pink Sheet, FDA-Windhover's Biopharma Group

The View From 30,000 Feet

> *"Follow-on biologics (FOBs) provide a perfect vantage point for exploring the important intersection between public policy, science, and business."*

Prior to the passage of legislation, exclusivity dominated the legislative debate. Rep. Henry Waxman (D-Calif.) and Sen. Ted Kennedy (D-Mass.), until his death, agreed on most of the important aspects, but on the topic of biologic products, the period of exclusivity became an uncharacteristic point of contention. Sen. Kennedy supported a longer period of exclusivity to pro-

tect the innovators of biologic products from competitive follow-on products, while Rep. Waxman argued for less time. The compromise came down to these two legislative points of view.

As it turns out, the period of exclusivity may have been a "red herring," because it does not reflect the direction in which the industry is heading. Over the past decade, attitudes toward biologics have evolved from perceived threat to potential opportunity. *"As the blockbuster model to which we have become accustomed evolves, 'Big Pharma' companies may end up being the biggest beneficiaries of [follow-on biologics] FOBs."*

Business models are concerned with what happens *after* legislation has become law. Unlike chemical generics legislation, an immediate flow of products into the marketplace could not take place on the day that FOBs legislation was signed. The U.S. Food and Drug Administration (FDA) will have to develop regulations, and ongoing resource constraints could delay implementation. Because it will take time for FDA approvals under any new regulation, FOBs are not a near-term commercial option.

The approval process for existing FOBs is lengthy, and a more cautious FDA will want to assure that the spotlight remains focused on drug safety. Although all versions of FOBs legislation encouraged clinical studies, some permitted the FDA to waive trials if it deems them unnecessary. Therapeutic substitution is the ideal; however, it likely will remain a long-term goal.

Not since proof of efficacy was put into effect as a result of the Kefauver-Harris Amendments in 1962 (Kefauver 1962) has there been a magnitude of change comparable to the FDA Amendments Act (FDA 2007). This new regulatory model for all drugs emphasizes safety, first and foremost. Risk evaluation and mitigation strategies increase the ability of the FDA to control which patients receive a drug and also to build in time lines for reassessments. Mandatory post-marketing trials will assure that questions arising from real-world use will be answered.

Such issues as contaminated heparin have underscored Congress' sense that the FDA's credibility is at stake. In essence, Congress is backing away from the blockbuster model (i.e., chemical products that help as many people as possible with placebo-like safety) and moving toward a biotechnology model (i.e., very active medicines that target rarer diseases/smaller populations and require more careful regulation). The FDA's response to the new law will change the drug launch model in fundamental ways. *"We are in the era of the 'mini-buster' or 'progressive blockbuster'."*

The Obama Administration has acted with urgency to fill key FDA positions. Members of the team assembled to implement biologics are knowledgeable and have been vetted to assure independence from the pharmaceutical industry.

Follow-on Biologics and Innovation

Innovation requires ideas and money in sufficient quantities to produce new medicines. Three sources of funding are critical to the biotech industry but not equally at all stages:

1. Government funding via direct research investment, tax incentives, and purchase agreements. Government funding agencies view FOBs as a cost-saving opportunity. Policy priorities drive investment rather than return on investment (ROI).

2. Industry research and development (R&D) budgets. Money for funding comes from sales of existing products. Companies develop some of their own ideas and products, and buy others. A majority of large pharmaceutical companies missed the biotech revolution and, consequently, relatively small portions of their portfolios are at risk with respect to FOBs. *"While industry R&D spending is driven by ROI, innovation is life, so a decrease in R&D spending is unlikely."*

3. The classic biotech model involves direct investment from Wall Street via venture capitalists, private equity, and institutional investors. Generally, these large investors are not tied to the pharmaceutical or health care industry. *"Capital will chase the highest return. In 2007, more opportunity than threat was perceived in the FOB space."*

The Orphan Drug Act (1983), enacted to bring molecules to market to treat diseases or conditions affecting fewer than 200,000 persons in the United States, contains an exclusivity clause to protect developers against the introduction of competing products for 7 years. Since the Act's passage, 7 years of exclusivity has become a valuable asset for biotech companies in terms of additional time to raise necessary capital. Whatever the exclusivity period, it is helpful in obtaining investors and it has worked to bring products for rare diseases to the market.

In the decade after the Hatch-Waxman legislation (1984) was enacted, output of new molecules mushroomed until, in 1996, R&D trended downward. This may have been an early indication that industry R&D was not paying off in the conventional drug arena. The legislation itself may have triggered a change in how drug development is viewed.

The life cycle of biologics is relatively attractive, and substitutable biologics are not likely attainable in the near term. Generic-style price competition is unlikely. Biotech development is seen as faster and less risky than chemical development, with fewer dropouts and a less costly sales infrastructure. There are more disease targets from which to choose, and technological advancements in pro-

duction and drug delivery minimize the disadvantages. Because they focus on process rather than product, patent estates for biologics are generally more robust than those for chemicals. Even payers have demonstrated a willingness to pay for small product improvements for certain diseases. "*The future is in high-value, personalized medicine, and there is plenty of room for pricing discounts.*" Also, there are many acquisition opportunities among start-up platform technology companies.

Business plans based on FOBs might steer innovation toward FOB-proof products; for example, vaccines. New vaccines are already experiencing significant growth but, once the population is immunized, growth ceases, and there is no incentive for FOBs.

Line extensions (e.g., nifedipine (Procardia XL), zolpidem tartrate (Ambien CR) and combination medications are common in drug delivery. The real issue for FOBs lies on the fine line between what is follow-on ("Me Too") and what is innovation ("Me Better"). Making a copy of a biologic is infinitely more difficult than making a copy of a conventional drug. It stands to reason that pharmaceutical companies are positioning themselves to enter the "Me Better" space by developing better versions of currently available molecules. Price and regulatory pathway issues may also make "Me Better" products more attractive to pharmaceutical companies. The downside risks for manufacturers are highly saturated markets, intellectual property issues (patent litigations), and manufacturing issues (different processes and manufacturing plants may be needed for different products).

Conclusion

Given their experience with small molecules, the pharmaceutical industry is the most likely source of capital for the biotech industry. The slowing of the R&D pipeline signals that the wave of blockbuster patent expirations will crest early in the next decade. Acquiring biotech companies will improve the pharmaceutical industry's opportunity to deliver attractive products to the market.

Regulatory Review and Approval Process Under Current U.S. Guidelines and Across the Globe

Part 1: U.S. Regulatory Review and Approval Process and the Potential Impact on Follow-On Biologics

BRIAN HARVEY, MD, PHD
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Congress charges the U.S. Food and Drug Administration (FDA) with a dual mission. Since its inception, the agency has been responsible for *public health safety* (protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation). More recently, Congress added the element of *public health advancement* (helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate science-based information they need to use medicines and foods to improve their health). "*The problem is that, at times, protection and promotion can be conflicting goals.*"

As defined under Section 351 of the Public Health Service Act (PHSA 1944), a biologic product is "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product or analogous product." Hence, products derived from viruses, bacteria, or blood are biological products, *and* products made from cells — including those derived from biotechnology methods — are considered biological products.

Under existing regulations, molecules that appear to be similar are regulated under different processes and pathways, not because of their individual indications but by happenstance. A memo of understanding laid the foundation for this pathway. Prior to 1997, there were two separate applications for new molecular entities: the Biologics License Application (BLA) for the product and the New Drug Application (NDA) for the process.

Pre-PPACA Follow-On Product Regulations and Biologics

With respect to follow-on products, the Food, Drug and Cosmetic Act (FD&C), Section 505(b)(2), allows applicants to create innovative medicines using currently available products without performing a full complement of safety and efficacy studies. It permits an applicant to base approval of a drug on information from published scientific literature or on the "finding" that the FDA has determined a similar drug to be safe and effective. The applicant must demonstrate that reliance on previous safety and efficacy data is justifiable, and must submit whatever additional nonclinical and clinical data are necessary to establish that the proposed product is safe and effective.

Under generic approval in the FD&C Act, Section 505(j) (Abbreviated New Drug Applications [ANDA]), generic drugs must contain the same active ingredient as the innovator product. The drug must be bioequivalent to the innovator product and must have the same dosage form, strength, route of administration, labeling, and conditions of use. Generic manufacturers can rely solely on the FDA's finding of safety and efficacy for the approved innovator product. Most generic drugs approved under Section 505(j) are therapeutically equivalent to the approved innovator drug.

For more detail on these regulations, see Guidance for Industry at: «http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf».

Potential Regulatory Concerns for Follow-on Biologics

When these processes were considered with respect to biologics, there was a problem. Enzyme mixtures from animal material are not well characterized and activity cannot be accurately assessed. The FDA decided to regulate biologics under Section 505(b)(2) rather than 505(j). Why not 506 (insulin)? Given the complex nature of some antibiotic and insulin products and issues related to purity and potency, perhaps biologic-like products do not fit the traditional generics model.

The FDA considers drug products to be bioequivalent if they are pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions. This may be demonstrated through in vivo or in vitro test methods, comparative clinical trials, or pharmacodynamic studies. This definition is suitable for products that can be measured in the patient's bloodstream. However, if the drug remains primarily on the skin or in the gastrointestinal tract, such as certain drugs for treating ulcerative colitis, rather than in the bloodstream, a different or expanded definition is needed.

Drugs vs. Biologic Products. A product can be characterized as biologic in one country and as a drug in another. Even within the United States, classification is ambiguous. Some natural source biological products and recombinant forms have been regulated as drugs under the FD&C Act (e.g., human growth hormone [hGH]). Certain biological recombinant proteins (e.g., monoclonal antibodies, clotting factors) are regulated under the Public Health Service Act. Therapeutic proteins (e.g., monoclonal antibodies, inborn error of metabolism replacement enzymes), formerly regulated by the Center for Biologics Evaluation and Research, were transferred in 2003 to the Center for Drug Evaluation and Research, but without a change to the regulatory pathway. The "protein only" approach provides the best case for a well-characterized product. Proteins, lipids, carbohydrates, and combinations can be classified as biological products. Complex carbohydrate mixtures are more difficult to characterize — the most difficult component of "glycoprotein" to characterize is the carbohydrate.

Immunogenicity with Biologics. Antibody formation can result in loss of efficacy (neutralizing antibodies) and serious adverse events, such as anaphylaxis. The presence or absence of antibodies also is associated with the quality of the in vitro diagnostic assay used to measure these antibodies. The presence of antibodies in patients receiving biologic-like products does not necessarily indicate that the product is "bad." Science has yet to determine what their presence means. The FDA regulates the drug enoxaparin as a biologic product. Enoxaparin is biologic-like in that each low-molecular-weight heparin (LMWH) manufacturing process affects different structural features on the heparin macromolecule. Even though it is approved for many indications (e.g., deep venous thrombosis, pulmonary embolism, myocardial infarction), it is difficult to characterize; for example, we do not understand which of its components treats venous clots versus arterial clots.

Other Regulatory Issues

Currently, 40 to 50 products fall into the category of "biologic-like." The FDA has authority to approve generic versions of these "biologic-like" products under the 505(j) pathway if the innovator products were approved as drugs under NDA by the FDA. For example, enoxaparin was approved by the FDA as a drug under NDA because unfractionated heparins were regulated as drugs under NDA rather than as biologics under BLA.

Another potential regulatory concern is that current standards of bioequivalence do not ensure therapeutic equivalence of products that contain complex mixtures. To illustrate the potential safety issues, we need look no further than Vioxx and Celebrex. Researchers were aware of structural differences between these COX-2 products, but there was no way to predict the observed clinical differences on the basis of the molecules' structures. The differences in rates of cardiovascular events, including "heart attacks," were discovered after a 3-year cancer prevention clinical trial that involved thousands of patients.

Conclusion

Key issues include the scope of reference products, approval standards, data requirements, FDA approval pathways, interchangeability, product naming, data exclusivity, patent provisions, and post-market surveillance. The FDA regulatory system is in great need of an upgrade. Creating a new pathway for follow-on biologics under the Public Health Service Act affords an opportunity to make corrections to the current system and to make appropriate changes to the post-market surveillance system for adequate patient safety monitoring of the products approved through the new abbreviated regulatory pathway. "*We must never forget the patient…safety is a critical issue.*"

Part 2: International Perspective on Follow-On Biologics

GUNDU H. R. RAO, PHD

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"Biosimilars are shaking up the biologics market on a worldwide scale."

There is a sense of urgency among biopharmaceutical manufacturers — they must take action or risk being left behind. These companies cannot afford to sit back and wait for guidance.

Without appropriate guidance on a global scale, each country will develop its own unique guidance documents pertaining to biologics and biosimilar products. The European Medicines Agency (EMEA) was the first to set a standard and many other countries have based their standards on these guidelines.

And without such clear-cut definitions and uniform processes, serious problems may arise. We need only consider the fact that Chinese and Indian manufacturers currently produce 40 percent of the world's blood products without clinical studies and in unregulated facilities.

Globally, we are moving toward "generic" biologics. For instance, Health Canada recently published draft approval guidelines for biosimilars, making it likely that Canada will have less expensive copies of biotech products on the market earlier than the United States. In the European Union (EU), EMEA guidelines address comparability when companies introduce changes in their manufacturing processes, and two biosimilar recombinant hGH products have already been brought to the market.

The issue is what further testing should be required for biosimilar products. The EMEA approval structure for biosimilar products is significantly more comprehensive than that of the FDA. Original legislation in the EU, in 2003, did not require toxicological, pharmacological, or clinical trials to demonstrate safety and efficacy for biosimilars. Since that time, the EMEA has issued a number of guidance documents to improve safety and efficacy. European law now requires preclinical and clinical data to support the approval of biosimilar products. Aisling Burnar, former chief executive of the UK BioIndustry Association in London, stated, "*The ultimate goal of the guidelines should be to ensure patient safety.*" This is a concern for all countries.

Only a few of the world's 150 countries — the regulatory authorities of Canada, the EU, South Korea, Japan, Australia, Belgium, Poland, and the United States — were represented at a World Health Organization (WHO) meeting to discuss a global policy for biosimilars. Conspicuous by their absence were the countries that produce a substantial percentage of the world's active pharmaceutical ingredients: China and India. The WHO's global regulatory guidelines for biosimilars would serve to license the manufacture of these products in member nations; however, guidelines developed by an organization with no regulatory power over member nations are not likely to have much impact.

The intent of the 2008 draft WHO guideline is to provide a general set of principles for the evaluation and licensing of biotherapeutics on the basis of a reduced clinical data package without compromising the quality, safety, and efficacy of these products. There are two approval pathways: biosimilar or clinical comparability. The question remains, how can this be accomplished without clinical trials?

Global Industry Overview of Biosimilar Development

- **Japan** manufactures a number of biosimilars that are sold as drugs (e.g., gamma globulin). The country is unlikely to produce more than a handful of biosimilars domestically in the near future. Regulatory guidelines will be necessary for Japanese developers to plan and initiate production of biosimilars. Recent draft guidance contains definitions similar to those in the EMEA Guidelines (2008) on the "quality, safety, and efficacy" of follow-on biologics:

  "A 'follow-on biologic' is a drug to be developed by a different marketing approval holder as a drug that is bio-equivalent/quality-equivalent to a biotechnology derived drug already approved domestically. A follow-on biologic must be developed on the basis of data obtained from a comparison with the comparator bio-drug demonstrating bio-equivalence/quality-equivalence in respect of quality, safety, and efficacy; or similar data."

- **Argentina** has a guidance document for registration and registry modification of biological medicinal products that contains the following description:

  "A 'similar biological medicinal product' is a medicinal product that has been shown, by similarity studies, to be similar in terms of quality, safety, and efficacy to a biological medicinal product taken as reference which has already been authorized by the health authority."

  This definition is applicable to products that may be broadly characterized, such as proteins obtained by recombinant DNA techniques, polypeptides, and highly purified natural proteins.

- **Malaysia's** guidance document and guidelines for registration of biosimilars was finalized in August 2008. It states: "*The information in the guidance is adopted from the EMEA guidelines, in particular the guidelines on similar biological medicinal products containing biotechnology-derived proteins as active substances, with some adaptations for Malaysian applications.*"

- **India** makes and markets blood and recombinant products in factories operated by a number of generic drug companies. Today, India produces 30–40 percent of the world's vaccines at WHO-approved facilities. Dr. Reddy's Laboratories, the country's third-largest drug maker, is seeking joint ventures with world biotech companies to manufacture biosimilars, and Ranbaxy of India recently announced a joint venture with Zenotech Laboratories for the first biosimilar product in India (granulocyte-colony stimulating factor [G-CSF]).

  Existing drug regulations are less stringent than those developed by other countries. Products are sold in a largely unregulated market without proof of safety or efficacy. In order to compete globally, India's greatest challenge may be to meet regulatory requests for additional clinical trials and preclinical data to prove that the biosimilars are as safe as the original product.

Global Challenges

The lack of uniform guidelines and processes is creating problems throughout the world. The few listed below are illustrative.

- Both Australia and Croatia have approved the drug Omnitrope (somatropin), and Swiss drug manufacturer Novartis, wants to sell the drug in the United States. The Urbana Court ruled that the FDA has not presented a compelling reason for delaying approval of this drug. At the heart of the problem is the lack of a process to verify the safety and efficacy of copies of biotech drugs without the benefit of data from clinical trials.
- Using WHO guidelines, India produces and sells large quantities of vaccines and other biosimilars in non-U.S. markets without performing any clinical tests.
- The EMEA has put in place abbreviated approval guidelines for four categories of biosimilars: human growth hormone (somatropin), recombinant G-CSF, insulin, and erythropoietin.
- Under the approval process in the Biologics Price Competition and Innovation Act of 2007 (BPCIA 2007), a biosimilar applicant will be required to demonstrate that there are no clinically significant differences in the safety, purity, and potency between the biosimilar product and the branded product by using analytical, animal, *and* human testing.
- The Standardization Subcommittee (SSC) of the International Society on Thrombosis and Hemostasis (ISTH) USA has made the following collective recommendation for one biologic with a very complex molecule: the generic version of low-molecular-weight heparin (LMWH). "*Efficacy and safety of a biosimilar LMWH must be demonstrated in clinical trials for every indication to be approved by the regulatory authorities. Based on the heterogeneity of the LMWHs, all biosimilar LMWHs must demonstrate their non-inferiority, compared to the originator products, in preclinical and clinical investigations.*" Experts from different countries met in Boston (under the North American Thrombosis Forum platform) and in New Delhi, India, (under the South Asian Society for Atherosclerosis and Thrombosis platform) to draft editorials and white papers on the subject. These experts reached the same conclusion as that of experts from SSC of ISTH and EMEA: *Clinical and preclinical trials are essential for the approval of biosimilars.*

Conclusion

Many of the world's countries are pursuing this very lucrative platform. Everyone wants cost-effective biologics, biogenerics, biosimilars, follow-on biologics, and cheaper copies of biotech products; however, regulatory processes are different in each country. To ensure quality and patient safety in a global market, there must be uniform global regulatory review and a global approval process. In view of World Trade Organization agreements, globalization of economy, and marketing efforts, it is critical to devise a global review and approval process with clear consensus definitions.

Q&A Discussion Points

- Ideally, the FDA should develop a clear definition and delineate a process that could serve as the model for a global process. Unfortunately, the FDA cannot agree on simple questions.
- Consider the alternative — other countries will act independently. For example, over 1,000 factories and manufacturing plants in China are approved by the FDA, and 50 percent of these will not be visited or inspected by the agency. India processed aspirin differently from the United States for many years because of such laxity in regulatory oversight and lack of commitment to safety.
- In 1995, FDA efforts were directed toward international harmonization of regulations, but these efforts decreased under the Bush Administration. The

hope is that we will begin to refocus on harmonization of regulations relating to safety and efficacy.

- With biologic agents, it is critical to look at the process, as well as the end product. Process specifications must be defined and followed at every step. A change in manufacturing of a biologic produces a changed drug.

Comparison of Legislative Proposals and Implications: Legislation Update

ANN WITT, JD

Counselor to the Deputy Commissioner for Policy at the U.S. Food and Drug Administration

(At the time this paper was written, Ms. Witt was Health Counsel for the House Committee on Energy and Commerce.)

> "*There is a huge amount of interest in the topic of FOBs on both sides of the debate... also it may have been the most heavily lobbied bill I have seen.*"

Why do manufacturers, payers, and policy makers care so much? In Rep. Waxman's view, it boils down to the fact that the price of biologics has become unsustainable for individual patients and payers.

According to Centers for Medicare and Medicaid Services (CMS) data, the top six drugs (in terms of cost) are all biologics, a huge share of the budget. The cost of biologics has risen so high in less than five years that some state payers are forced to consider drastic increases in copayments or, worse, stop coverage for the class.

We cannot permit the future drug supply of the United States to be priced out of range for our citizens. Within the next couple of years, the U.S. Food and Drug Administration (FDA) must have an approval process in place for follow-on biologics (FOBs). When the original Hatch-Waxman bill passed in 1984, there were no biologics. As science evolved, the FDA was comfortable with approving applications for simple proteins, some of which are regulated as drugs (e.g., human growth hormone, insulin) under Hatch-Waxman. Science is at the point where biosimilars require new processes.

A biosimilar product is one that is "not identical but highly similar in chemical structure" to a branded biologic product. Rep. Waxman advocates a system wherein the FDA *could* approve a biosimilar product *if* reviewers were convinced of the science. Under such a system, the FDA would have complete discretion to determine what additional data and/or studies are necessary in order to approve a biosimilar product. The biotech industry has expressed concern that the FDA is too conservative with innovators and will be too lax with biosimilars.

A form of competition that will lower prices requires *interchangeable* versions of biologic products. Rep. Waxman argues that biosimilar products must show interchangeability with the branded product. Switch studies should be conducted in order to demonstrate a reduced risk of adverse reactions, such as new immunogenetic responses. In reality, interchangeable versions will take more time, and the less complex biologics will probably be the first to have approved biosimilar products.

In 1984, the pharmaceutical industry raised concerns about generic forms of traditional drugs, noting that they would be unsafe, clinically inferior, and produce no cost savings. The concerns were unfounded because of guidelines already in place. Rep. Waxman would like these principles to be part of any regulatory processes:

1. ***Assurance of safety and effectiveness.*** There must be a guarantee that any FOB is high quality, as safe as the innovator, and (ideally) interchangeable with it.

2. ***A process that allows for improvement in safety and technology.*** All *necessary* tests must be conducted. As science improves, some simple molecules may not require new clinical trials. The approval process should anticipate scientific/analytic advances that may eliminate the need for clinical trials.

3. ***Avoid excessive and/or duplicative procedures for FDA applications.***

4. ***Early resolution of patent disputes.*** Issues need to be resolved regarding patent infringement litigation delays.

5. ***Adequate incentives for innovation without delaying competition.*** At issue is determining how much intellectual property protection is needed to assure continued innovation (over and above patent protections).

Biotech companies benefit from ample protection in the form of patent extensions of up to 14 years. Current patents may be insufficient to protect innovators from competition because they do not cover "highly similar" drugs. This could be rectified by draft patents that cover "minor variations." "*There is a great deal of patent litigation and, hence, substantial case law to use as evidence.*" For example, Roche has been trying to get an Epogen-like (epoetin alpha) product to market since 1989. Via patent litigation, Amgen (manufacturer of Epogen) has succeeded in protecting its patent until 2015.

Conclusion

Decisions must always be based on adequate evidence. The one thing that remains clear is that we need to be vigilant in assuring that these important drugs do not become inaccessible.

Is Interchangeability Possible? Understanding and Evaluating the Evidence Base: Implications for Quality and Safety

Geno Merli, MD

Chief Medical Officer, Thomas Jefferson University Hospital, Philadelphia

> *"When treating patients with actual or potential clotting disorders, clinicians need assurance that the drugs they use are safe and effective."*

Most cardiovascular deaths in the United States are related to clotting and bleeding disorders. The complex anticoagulant drugs used to treat critical clotting disorders (e.g., deep vein thrombosis, pulmonary embolism [PE], acute coronary syndrome, stroke, atrial fibrillation) must be safe and effective; for instance, the clotting process must be stopped to prevent a stroke in a patient with a left atrial thrombus that is causing atrial fibrillation.

Common orthopedic procedures, such as total hip replacement and fractured hip repair, are associated with a high risk of stroke and PE, and clotting is a likely occurrence in heart valve replacement, one of the most frequent cardiac surgery procedures. In all instances, there is a need for safe and effective drugs to prevent clotting without causing the patient to bleed excessively.

Safety considerations related to anticoagulant drugs include bleeding, allergic reactions, thrombocytopenia, skin necrosis, liver toxicity, vascular reactions, rebound thrombosis, anticoagulant resistance, drug interactions, and population-specific variations; for example, risk of bleeding varies with patient age.

Of the anticoagulant drugs prescribed, 75 percent are generics (identical or bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use). Although these traditional chemical generics are assumed to be equally efficacious, this is not necessarily so.

The first oral anticoagulant drug (warfarin/Coumadin) and its derivatives have been used for over 50 years. Generic compounds rated as bioequivalent with warfarin were introduced by six different manufacturers. To obtain this rating, manufacturers merely had to demonstrate that the pharmacokinetics were the same. Clinical trials were not required, nor were trials comparing the generic with Coumadin. After the six generic versions were on the market for some time, significant differences were observed, leading to the realization that qualifiers were needed for generic forms of Coumadin. The National Anticoagulation Forum generated the following key points regarding warfarin:

- It has a narrow therapeutic index and a varying pharmacodynamic response
- Close monitoring is needed when patients are switched from brand name to generic product, or vice versa, or from one generic to another generic, to avoid underdosing or overdosing
- The generic interchange of warfarin should be avoided in elderly patients and in patients with liver disease and gastric resection
- All anticoagulants are critical drugs. In the case of warfarin, small changes can result in large pharmacodynamic variations.

Unlike warfarin, biosimilar drugs or follow-on biologics (FOBs) — proteins, antibodies, glycosylated proteins, polysaccharides, and polynucleotides — are not single molecule agents. They are highly complex and differ substantially in safety and efficaciousness. The Heparin Incident illustrates this point.

Lessons from the Heparin Incident

The biologic agent in unfractionated heparin (UFH) is derived from porcine (pig) intestine. On February 29, 2008, a contaminant that caused an increase in allergic-type reactions was discovered in a UFH product produced by Baxter Laboratories.

On that date, the entire heparin supply at Thomas Jefferson University Hospital had come from this manufacturer, necessitating a massive conversion at this 900-bed hospital in a single day. There were no deaths in the hospital, but two patients experienced allergic reactions.

In addition to the United States, the contaminated UFH affected large supplies in Canada, France, Netherlands, Italy, Germany Australia, New Zealand, Japan, and China.

Venous Thromboembolism Prophylaxis

For a product to be classified as "biosimilar," the manufacturing process must be the same. Currently, there are four branded low-molecular-weight heparin (LMWH) products, each of which is produced using a different manufacturing process. When each was compared with

placebo in clinical trials, the four LMWHs were shown to be safe and efficacious when used for prophylaxis in patients at high risk for venous thrombo-embolism (VTE). No difference in efficacy was observed in clinical trials comparing unfractionated heparin (UFH) with LMWHs for VTE prophylaxis in hospitalized patients.

A recent meta-analysis of anticoagulant VTE prophylaxis in 19,958 at-risk hospitalized medical patients (nine studies) revealed a 62 percent reduction in fatal PE, a 57 percent reduction in fatal or nonfatal PE, and a 53 percent reduction in DVT, with a nonsignificant increase in bleeding. Clearly, anticoagulant VTE prophylaxis is effective and at-risk patients in U.S. hospitals must be treated with one of the available agents.

In a classic study comparing the efficacy and safety of three LMWHs versus UFH, all patients had bilateral leg venography and lung scanning on days 1 and 10, and warfarin was not started until day 11. Even though each LMWH had a different structure, safety and efficacy profiles were the same for all products. Nevertheless, the three LMWHs demonstrated three different degrees of VTE prevention. The current American College of Chest Physicians guidelines recommend initial treatment with LMWH (subcutaneously) once or twice daily as an outpatient or an inpatient rather than UFH.

Acute Coronary Syndrome

In U.S. hospitals, 5.3 million emergency department visits due to chest pain result in 1.4 million hospitalizations per year. Of these, 15 percent of patients die or have recurrent myocardial infraction (MI) within 30 days, and 41 percent of patients die, have recurrent MI, or experience severe ischemia requiring hospitalization within two weeks of initial presentation. In addition, 85 percent of patients presenting with unstable angina/non-ST segment elevation MI are sent for cardiac catheterization.

A study looking at the endpoints of death, MI, recurrent ischemia, and +/- revascularization showed marked differences among four LMWHs. Initial results (up to 30 days) and one-year follow-up of the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-wave Coronary Events (ESSENCE) study showed a difference in effectiveness with respect to prevention.

Cost-Effectiveness

If LMWH performs only as well as the less expensive UFH, why not use UFH? Another marked difference between UFH and LMWH is the incidence of *heparin induced thrombocytopenia* (HIT), an immunogenic response to the product (UFH), which is derived from pig intestine. In cases of HIT, clot formation is *stimulated* by the anticoagulant — the opposite of the desired effect — sometimes resulting in the loss of hands, feet, and legs in affected patients. A comparison study revealed that 4.8 percent of patients receiving UFH developed HIT compared with 0.6 percent of patients receiving a LMWH (Enoxaparin). A meta-analysis of five studies suggested that LMWHs decrease the risk of this immunogenic response.

Impact of Follow-on Biologics

Regulatory bodies in the United States and Europe may allow "generic" versions of LMWHs in the near future and apply the same guidelines used for other biologics. Additional requirements in the form of supplementary chemical and biological data may be needed to support these filings. Some stipulations from the citizen petition may be considered. Clinical trials may or may not be required for specific products for approved indications depending upon the filing material review.

Such steps are important but insufficient. Follow-on LMWH products must be *interchangeable*, and additional requirements will be necessary to achieve this. Biosimilar products vary in potency, response, and immunogenicity (i.e., glycosylation, contamination, changes to the three-dimensional structure). The human immune system can detect even small changes in protein structure between an introduced molecule versus the original. Chemical characterization of branded LMWH is insufficient to assure pharmacodynamic equivalence.

"*LMWHs are hybrid products of biologic origin with chemical modifications. The starting material is more important to characterize for product consistency. Biosimilar drugs are derived from living cells; therefore, they cannot be copied or duplicated. Two biologics can result in significantly different immune responses.*"

Conclusion

We lack scientific evidence to guarantee a safe interchange between biologics. Difficulties exist in molecular characterization and in the depth of knowledge regarding the mechanism of action. The clinical consequences include severe allergic or anaphylactic reactions and immune responses leading to autoimmunity to the patient's own endogenous proteins.

PANEL DISCUSSION

The Interplay of Economic and Clinical Issues

JUDITH K. JONES, MD, PHD
President and CEO, Degge Group, Ltd.

Assessing the safety of biologics and biosimilars presents many challenges. "*For nonphysicians, it might be impossible to envision the diversity among biologic agents.*" Glycoproteins are composed of hundreds of amino acids

that fold over in various ways and act differently with different receptors in the body. They are exceedingly complex with many variables that affect everything from study to packaging. They have very little resemblance to one another other than the term "generic."

Some low-molecular-weight heparin biologics and short peptides are amenable to generic development, but one must proceed cautiously with others. When an amino acid is given by injection, it breaks down into peptides depending on the environment and the host. Some of these peptides affect DNA or RNA in cell nuclei, stimulating the production of new proteins in some and stopping production of proteins in others. The effects of biologics are difficult to measure and we do not fully understand the entire process. We do not know how long the effects of biologics last (their half life) and there are serious gaps in our knowledge of protein synthesis.

The pharmacoepidemiological methods used to study patient safety in chemical drugs are not always applicable to biologics. Differences exist in methods for detection; for instance, because of shortcomings in medical claims systems, it is more difficult to detect a person's exposure to biologics. Also, risk management strategies may be difficult to design and effectiveness may be difficult to establish for follow-on biologics (FOBs).

Clinical trials ensure a drug's "efficacy" before it is marketed. A drug's "effectiveness" and safety can be determined only after it is on the market. When drugs are removed from the market, it is usually due to uncommon safety events that do not occur in controlled trials. Given the high degree of clinical variability with biologics, the regulatory process should mandate post-marketing surveillance and include databases to monitor use of these products in different populations.

Terry Hisey

Vice Chairman, U.S. Life Sciences Leader, Deloitte LLP

By the time Congress was debating the Hatch-Waxman Act (1984), the chemical-based pharmaceutical industry was over a century old and represented a stable, mature business system with respect to its basic science, business model, and federal regulatory regime.

Although this Act achieved its objective of generating price competition and savings, it also had some unintended consequences that precipitated different economic models. We witnessed higher pricing and more aggressive marketing as the industry attempted to increase short-term revenues. The industry focused on developing drugs that targeted the largest number of potential indications. Huge numbers of compounds in development are reaching "no man's land" within a few years of patent.

Moving forward, we need to maximize the area under the curve; that is, to identify which products yield the largest returns and become the new "blockbusters." It is important to work through the business system issues, thinking in advance about biosimilar products and trying to understand access and savings expectations in an arena in which more capital and more complexity are involved.

"*Wall Street is not interested in innovation. Large companies are on the edge of a patent cliff and the industry is at a crossroads.*"

The chief barrier to entry is "substitution."

Although there are obvious similarities between the pre-Hatch-Waxman pharmaceutical industry of 1983 and the biotech industry of today, there also are certain clear, structural differences with related scientific, business model, regulatory, and consumer implications. How important are these differences? What unintended consequences would similar legislation have on the biotech industry? Are the objectives of price competition and savings achievable? What will happen to the largest funding sources for innovation, the companies themselves?

Q&A Discussion Points

Generally, biologics are evaluated by biotech committees rather than pharmacy & therapeutics (P&T) committees. In an environment without rules, issues invariably arise regarding access and coverage. The real challenges lie in administrative questions such as diagnosis-related group lump-sum payments and lifetime benefit structure implications.

Laurence Kotlikoff, PhD

Professor of Economics, Boston University

The literature on monopoly protection leads the monopolist to retain protection as a major goal, thereby reducing innovation. It follows that monopolies decrease innovation.

An innovator is one of many companies that could have been first to come up with the innovation. Innovators are the public's "employees." The first innovator to find what we want gets the reward and, in this case, charges whatever price it chooses, which sets up a system whereby it manufactures the product at marginal cost.

Innovators also have the right and responsibility to pass knowledge on to the next innovator to make an even better product.

"*It is like a relay race. You don't want a single runner who slows down before the finish when the goal is to cure disease. You don't want too many, or too few, runners.*"

Hatch-Waxman (1984) resulted in increased research, development, and innovation. Much of today's $2 trillion health care industry spend is for prescription medications. At a cost of 22 times more per dose than

chemical products, biologics account for $40 billion per year.

"*The innovators are being paid handsomely, but it shouldn't be forever.*"

The concept of exclusivity is unique to pharmaceutical manufacturers in the United States. Other industries with similar considerations in terms of innovation and research and development costs have no such protection; jet engine manufacturers, for instance. Patent restoration is universally available to give innovators extra protection, such as additional time to make up for getting approvals. Exclusivity delays the passing of the baton. It is potentially damaging to the next generation of innovators. Exclusivity also contributes to high prices. Manufacturers cite huge costs, but there are also huge returns. Grabowski's often cited economic analysis (Grabowski H, 2008) is flawed. Cumulative cash flows are not indicative of present value. "*Exclusivity is not about safety. It is about money.*" As the pace of innovation slows, the incentive for monopolists grows.

Q&A Discussion Points

- Participants' opinions vary regarding risk in the biotech industry. A few believe that a higher number of compounds fail. Others agreed that although biotech is riskier than some industries, it is not riskier than chemicals.
- Rather than arguing over economic models, we should concern ourselves with safety, efficacy, and effectiveness, as no post-market surveillance system currently assures these. There must be follow-up, including surrogate endpoints, for *all* products.
- It is important to consider employers, unions, and municipalities. We must seek better ways to manage health in different care settings, stages of illness, and catastrophic cases. Current insurance and benefit designs will be unable to accommodate branded biologics or personalized medicine. We need new models that recognize the important relationship between cost and accessibility.

Randy Vogenberg, RPh, PhD

Chief Strategic Officer, EPS, LLC, and Executive Director, Biologic Finance and Access Council (BFAC)

Dr. Vogenberg examined biologics and FOBs from a risk management and benefit design perspective. The biologic marketplace has grown rapidly over the past seven years from 1 percent of overall drug spend in 2002 to 10 percent in 2007. Today, biologics are managed by specialty pharmacy programs for the most part and constitute 14 percent of overall pharmacy expenditure.

The Centers for Medicare and Medicaid Services (CMS) reports that 90 percent of individuals covered under the Part D Pharmacy Program who were on biologic drugs hit the "doughnut hole." The average cost for an individual receiving biologics is $5,000 per month. "*The financial pain for patients required to pay 12 percent out of pocket is much greater with biologics.*"

Generic drugs generally are accepted in the traditional marketplace and represent considerable cost savings over branded chemical products. The cost savings realized from price reductions with biosimilars are not expected to be as significant. From an insurance/risk management standpoint, no savings have been realized to date. The important question is, "Will patients be able to afford biologics?"

A further complication related to biologics is the issue of multiple or cross settings. There has been enormous growth in combination therapies that need to be administered in a variety of settings, such as physician offices and patient homes. New guidelines and tools are emerging. Step therapy is becoming a common spending management technique for biologics.

A unique aspect of biologics is that they possess both medical and pharmacy components, and coverage may fall under either the medical insurance or the pharmacy insurance program. Despite recent efforts to have biologics managed under pharmacy benefits, such a shift was not observed in 2008–2009.

Looking at biologics from a real-world perspective, there are layers of confusion. One message is clear: We need a new insurance model. Current insurance benefit designs are seriously outdated. They do not reflect biologic products and services.

Summary and Highlights

This national policy forum, with speakers and participants representing a broad range of perspectives, presented a comprehensive overview of follow-on biologics (FOBs) and shed light on what are, and must remain, the overarching goals of any new legislation and U.S. Food and Drug Administration (FDA) regulation. Major themes that emerged were:

- ***Patient safety must be our number one priority.*** This requires that FOBs undergo adequate safety testing before approval.
- ***The United States should consider adopting some proven provisions of European regulations***, such as clarity with respect to the circumstances and extent of testing required for FOBs.
- ***A comprehensive FOB-approval pathway*** must recognize the complex nature of all biologic medications, including proteins and polysaccharides.
- ***We must resolve the issue of access to biologics.*** Based

on the best available evidence, we must do our best to get appropriate drugs to appropriate patients.

- ***The FDA must move toward safety and effectiveness in real-world settings*** and call for post-marketing surveillance.

For more detail, readers are encouraged to view the webcast and PowerPoint presentations from the policy forum on the Jefferson Digital Commons at «http://jdc.jefferson.edu/jsph_biologics_quality_and_patient_safety/2009/».

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