



Institute for Policy Innovation

Biosimilars and Safety:

Experts Weigh In on the FDA's Approval Process

Edited by Merrill Matthews, Ph.D

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Forward

Advancements in medical technology are rapidly progressing and propelling us into a future of targeted treatments specifically engineered for an individual patient's needs. The advancement of biological therapies today mirror the progress of pharmaceutical developments at the turn of the 20th century. Discoveries such as penicillin have shaped treatments for nearly a century and stimulated discovery and ingenuity while forging the way for modern medicine. I can only imagine the potential biologics hold for the next 100 years.

When I took the Hippocratic Oath in 1977, I vowed to “respect the hard-won scientific gains of those physicians in whose steps I walk.” Through my 25 years of medical practice, I relied on the discoveries of previous scientists who laid the foundation for treatments which were once considered unfathomable. I worked alongside doctors whose discoveries carried us into a new realm of medicine, and I dreamed of future generations who would find cures to the most devastating diseases. The future is now. Technological advancements, such as those in biologics, have opened the doors to possible treatments that could have previously only been described as science fiction.

This progression has also yielded biosimilars, which are protein drugs that are similar but not identical to an existing product. I have previously supported an amendment brought before my committee and later incorporated into the Patient Protection and Affordable Care Act by Representative Eshoo and Representative Barton to create a pathway for drug companies to manufacture and market biosimilars. As a country we have always been on the forefront of medicine. As interchangeable products are created, their testing and research needs to be done here, in America, to foster economic growth while we strive for the safest product possible while keeping the promise they hold moving forward.

As we progress into this new era of medical innovation, it is essential we remain vigilant in the pursuit of ensuring the safety of our patients. I want to make certain that when patients receive a biosimilar drug, this treatment will deliver the same results as the biologic and safety will not be compromised. FDA regulation is the essential aspect to ensure there is a procedural mechanism to add this level of oversight to the process. As a doctor, my number one priority was the well-being of my patient, and although my occupation may have changed, my unwavering commitment to their health has remained the same.

I am frequently asked by medical school students, if I were given the choice to enter the medical profession today, would I do it? The answer is yes. I believe we are on the brink of making breakthroughs in curing some of the deadliest diseases thanks to rapid scientific progress and technological innovations. Biologics and biosimilars are helping achieve these goals, and I look forward to seeing the progress that will be made in the near future.

Dr. Michael C. Burgess
Member of Congress TX-26

Introduction

by Merrill Matthews, Ph.D

THE EMERGENCE OF BIOLOGICS

The nature of the market for medicines is changing. Most prescription drugs that consumers are familiar with come from the pharmacy in pill form. They are considered “small molecules” and are relatively simple to manufacture or duplicate through chemistry. But a new class of drugs, generally referred to as “biologics,” is emerging from the innovator drug companies.

They are called biologics because they are derived from complex organic sources, such as proteins, sugars or nucleic acids, and living cells or tissues. The Public Health Service defines a “biological product” as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”ⁱ

Biologics include products the public is widely familiar with such as vaccines and insulin, but they also include newer and more esoteric medicines such as human growth hormone. And rather than a pill, biologics typically come in a liquid form that must be injected.

Although biologics have been around for more than a century, there has been an explosion of innovative activity in biologics over the past few decades, with some 600 biologics currently in clinical trials.ⁱⁱ According to a 2009 report from EvaluatePharma, by 2014 six of the top 10 selling drugs will be biologics and could represent up to 75 percent of drug company revenues, targeting cancers, arthritis and many other chronic and debilitating diseases.ⁱⁱⁱ

Because biologics are “large molecules” and very complex, manufacturing them is difficult and even slight variations can substantially change the outcome of the medicine, including its effectiveness and safety. Plus, both administration and handling of biologics are more complicated than traditional drugs. Pills can be left alone in a medicine cabinet for years and may still be potent; biologics’ shelf life is much shorter and they usually must be refrigerated and handled with care.

THE CHALLENGE OF BIOSIMILARS

Some biologics, as innovative products, can also be expensive. Yet at a time of rapidly rising health care costs people want lower-cost alternatives to many of the expensive procedures and medicines available today. But until recently, there was no clearly defined, abbreviated pathway for drug manufacturers to create generic versions of brand name biologics—usually referred to as “biosimilars” or “follow-on biologics”—and get them approved by the U.S. Food and Drug Administration (FDA).

What was needed, almost everyone agreed, was legislation that created a pathway establishing the ground rules for biosimilars so that both brand name and generic drug manufacturers would know what was required of them, much like the Hatch-Waxman Act did for traditional small-molecule drugs.

THE HATCH-WAXMAN PATHWAY

The Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as the Hatch-Waxman Act, established a pathway for generic pharmaceuticals to pursue FDA approval and move to market. The legislation tried to balance both the innovator companies' need for sufficient intellectual property protections to ensure they would continue to innovate and create new drugs and the public's desire to eventually have access to less-expensive generic versions of brand name drugs.

Generics manufacturers were allowed to piggyback off of the research and clinical trials of a brand name drug. As long as the generics manufacturer could demonstrate that its follow-on drug was "bioequivalent" with the brand name drug, meaning the molecule was virtually identical, the drug could be approved based on the brand name company's research, which saves generics manufacturers both money and time to market. Demonstrating bioequivalence has been fairly simple with small-molecule drugs, and so we have a plethora of generic versions of drugs used by the public. While issues have arisen over Hatch-Waxman over the past 25 years, most people agree that it has done a reasonable job of balancing the needs and interests of both the drug industry and the public.

But what about the biologics market? Because biosimilars are much more complex than generic pharmaceuticals, how do we set the ground rules for FDA approval? Do we need a Hatch-Waxman-type of bill for biosimilars?

THE PATIENT PROTECTION AND AFFORDABLE CARE ACT

The Patient Protection and Affordable Care Act that passed in March of 2010 incorporated biologics legislation worked out by a number of congressmen and senators, including Sen. Edward Kennedy and Reps. Henry Waxman, Nathan Deal, Anna Eshoo, Jay Inslee and Joe Barton.

The legislation focused primarily on intellectual property protections for biologics, providing a 12-year data exclusivity period—which limits a generics manufacturer from access to the data needed for creating the drug—for brand name biologics. That was an important step in ensuring innovator companies have the ability to profit from their investment in a new biologic. For small-molecule drugs, patent protection is the key issue; for biologics patents are still important, but data exclusivity is critical.

While PPACA does govern biologics under a new pathway, that doesn't happen for 10 years. Until then, the FDA may use its discretion over whether a proposed biosimilar would follow the new biosimilars track or the older generic drug track. For example, after several years of indecision the FDA recently decided to approve a biosimilar version of Lovenox, called enoxaparin, based on an abbreviated generic drug approval process. The decision is controversial. While Lovenox is not a traditional biologic as defined by the new law, because it is not made of proteins, it is still made by using living organisms

THE QUESTIONS OF SAFETY, EFFICACY AND EQUIVALENCE

In order to bring some expert light on this issue, the Institute for Policy Innovation (IPI) began a discussion with several academic medical experts and researchers to get some perspective on the challenges. Their concerns about safety and efficacy are compelling such that IPI is pleased to publish their responses to questions regarding the biosimilar approval process, safety, efficacy and bioequivalence.

THIS RESEARCH PAPER

We presented a series of 18 questions to each of six experts, and present an edited version of their responses in this paper. Our goal is to inform the current debate over biosimilars by sharing the experts' thinking and concerns, which result from both academic research and practical clinical experience. In some cases, when there was a clear consensus, we may not have included all responses.

Prior to the question-and-answer section, we include a short biography of each participant. These experts provided their answers prior to the recent FDA approval of a biosimilar version of Lovenox. Their concerns raise real questions about whether the FDA made the right decision.

Because the PPACA gives the FDA 10 years of discretion over how to approve biosimilars, contributions from experts may help the agency craft a more thoughtful procedure in the future.

THE EUROPEAN MEDICINES AGENCY MODEL

What might a “more thoughtful” procedure be? Perhaps the FDA should consider the European Medicines Agency as a model. The EMA has established guidelines for class-specific biologics and requires at least some clinical evidence—albeit incorporating a more limited trial than required for a brand name drug—before potential approval. The EMA's approach attempts to balance the needs of the public to have access to lower-cost biologics while still ensuring the safety of the biosimilar.

i. 42 U.S.C. § 262(i) (2006).

ii. Pharmaceutical Research and Manufacturers of America, “Medicines in Development,” *Biotechnology* (2008), August 17, 2009.

iii. Patent Docs, “Future Drug Sales Predictions Highlight Importance of Follow-on Biologics Legislation,” June 21, 2009.

About Our Contributors



Dr. Henry I. Bussey is a professor in the College of Pharmacy at the University of Texas at Austin and president of Genesis Clinical Research in San Antonio, Texas. In addition, Dr. Bussey is co-founder of ClotCare and a consultant to Genesis Advanced Technologies on the development of the ClotFree system for online anticoagulation management.

Dr. Bussey obtained his B.S. in Pharmacy from the University of Georgia and his Pharm.D. (with a concurrent clinical pharmacy residency in Internal Medicine) from the University of Texas at Austin and the University of Texas Health Science Center in San Antonio. He has worked with anticoagulation for 25 years and served for a decade on the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy. He also serves on the Scientific Advisory Board of the North American Thrombosis Forum (NATF). He has authored more than 100 publications, is on the editorial board for *Pharmacotherapy*, and is a reviewer for several pharmacy and medical journals.



Dr. Marc Cohen is Chief of the Division of Cardiology, and Director of Cardiology Fellowship Training at Newark Beth Israel Medical Center in New Jersey. He is also Professor of Medicine at the Mount Sinai School of Medicine in New York.

Dr. Cohen serves on the Council on Clinical Cardiology and the Council on Arteriosclerosis, Thrombosis, and Vascular Biology of the American Heart Association. He has served as a consultant on the Clinical Trial Review Committee of the National Heart, Lung, and Blood Institute, and is a member of the Cardiovascular Health Advisory Panel to the Commissioner of Health of the State of New Jersey.

As a physician/cardiologist, he devoted 25 years to antithrombotic therapy research. He wrote his first paper on antithrombotic therapy in 1982, and participated in the very first National Institutes of Health-sponsored trial using lytic therapy intra-coronary. Since then he has authored or coauthored more than 300 articles including 130 peer-reviewed, original papers.



Dr. Christopher B. Granger is Director of the Coronary Care Unit at Duke University Medical Center. He regularly treats patients with different types of heparin and direct thrombin inhibitors. His primary research interest is in the conduct and methodology of large randomized clinical trials pertaining to heart disease. He has led a number of large, international clinical studies in heart attacks, unstable angina, heart failure, and atrial fibrillation. He has studied the effects of genetic variation on heart disease and worked with the National Institutes of Health and the FDA on evaluation of heart disease and of new drugs.

Dr. Granger has been co-director of the Reperfusion of Acute MI in Carolina Emergency Departments (RACE) project that is a North Carolina state-wide program to improve reperfusion care for acute myocardial infarction. He is one of the world's experts on acute myocardial infarction care with more than 300 publications to his credit.



Dr. William R. Hiatt is currently the Novartis Foundation endowed professor for cardiovascular research in the Department of Medicine, University of Colorado, Denver, in cardiology. He is chief of the Section of Vascular Medicine and president of CPC Clinical Research, which is a university-affiliated cardiovascular and clinical trials research organization.

Dr. Hiatt is a Fellow in the American Heart Association. In 2008 he received the Robert W. Schrier Award of Excellence from the Department of Medicine, University of Colorado, Denver, and he received the Julius H. Jacobson II, MD Physician Excellence Award from the Vascular Disease Foundation.

His academic career has focused on the clinical, educational, and research aspects of patients with peripheral arterial disease resulting in over 140 peer-reviewed publications. He served five years on the FDA's Cardiovascular and Renal Drugs Advisory committee (chair for 2.5 years) and remains a Special Government Employee for the FDA with ongoing work for the Endocrine and Metabolism Committee. He is the current chair of the American Heart Association Peripheral Vascular Disease Council



Dr. Craig Kessler is Professor of Medicine and Pathology at the Georgetown University Medical Center, Washington D.C. He is also Chief of the Division of Hematology-Oncology, Director of the Division of Coagulation in the Department of Laboratory Medicine, and Director of the Adult Component, Washington Area Hemophilia Comprehensive Care Center at Georgetown.

Dr. Kessler has been involved in on-going scientific and clinical research, including that for the National Institutes of Health and the Centers for Disease Control and Prevention. He has been published extensively in peer-reviewed journals, edited several textbooks and is the co-editor of *Haemophilia*. He has been named a Fellow of the American College of Internal Medicine and received the Alpha Therapeutic Award for his research and clinical work in bleeding and clotting disorders.

His everyday practice includes the cure of individuals who have clotting disorders, deep venous thrombosis, pulmonary embolisms, stroke and heart attacks.



Dr. Charles Pollack is Professor of Emergency Medicine at the University of Pennsylvania School of Medicine and Chairman of Emergency Medicine at Pennsylvania Hospital in Philadelphia. From 1992-2001, Dr. Pollack served in various positions in the Department of Emergency Medicine at Maricopa Medical Center in Phoenix, Arizona. He was Research Director from 1994 to 2000, and he chaired the department from 1997 to 2001.

He is the only physician to have received the American College of Emergency Physicians' highest national awards in both teaching and research; he also received the national teaching award from the Council of Emergency Medicine Residency Directors. His primary research interests are in the management of cardiopulmonary emergencies, especially acute thrombosis and acutely decompensated heart failure, and infectious disease emergencies. He has written more than 300 original research articles, chapters, and abstracts, and serves on the editorial boards of several journals and on the steering committees of multiple trials.

Tell me about your interest in the development and use of follow-on biologics. What are some of the biologic products used with your patients (if there is patient interface)?

Cohen As a physician/cardiologist who's had a keen research interest in the field of anti-thrombotic therapy, I wrote my first paper on antithrombotic therapy around 1982 or '83. So about a 25-year commitment to antithrombotic therapy research. And I participated in the very first National Institutes of Health-sponsored trial using lytic therapy intra-coronary.

Bussey I've been working with anticoagulation for about 25 years. And the one category that is most within my focus is in the low-molecular-weight heparins.

Granger I've done some clinical research with enoxaparin and dalteparin. And I'm director of a cardiac care unit where we treat a lot of people with different types of heparin and direct thrombin inhibitors, and have all of the complexities in clinical care related to their use.

So I think it is an interesting area where, in my opinion, there's considerable uncertainty as to what the U.S. Food and Drug Administration (FDA) and the clinical community should do with biosimilars, particularly around the issue of enoxaparin going generic. It was a bit frightening about the deaths related to presumably this oversulfated chondroitin sulfate contaminate in heparin a couple of years ago.

I'm nervous about biosimilars in this area of heparins because even modest differences in the way these drugs are manufactured could result in clinically meaningful differences in safety and efficacy that are difficult to measure by ex-vivo or in-vitro testing measures.

Hiatt My perspective would focus on drug safety. I have served five years on the FDA's Cardiovascular and Renal Drugs Advisory committee (chair for 2.5 years) and remain an SGE for the FDA with ongoing work for the Endocrine and Metabolism committee. My experience is with standard small-molecule drugs and the cardiac safety perspective.

Kessler My everyday practice includes the cure of individuals who have clotting disorders, deep venous thrombosis, pulmonary embolisms, stroke, heart attacks, etc. The questions that I'm typically asked are why did people get them when they shouldn't have? Why did they occur in unusual sites and how do we treat them? I've done a large amount of research on the prevention and therapy of these clotting disorders, using the low-molecular-weight heparins and other products.

Pollack In the emergency department it's fairly limited. We're not giving growth hormone; we sometimes give some female hormones for acute control of bleeding. But really, the vast majority of use in our setting is going to be low-molecular-weight heparins.

Most of the debate around biosimilars in the recently passed health care reform legislation has focused on data exclusivity and patent disputes. Are you concerned that there was not more emphasis on review standards and ultimately patient safety?

Kessler The laudable issue of trying to contain costs was buried in what was going on at Capitol Hill, where the emphasis was on patent protection and prolonging the life of the patent for these low-molecular weight heparin drugs. I personally, and my colleagues, did not want to touch that issue. We want to come at it from the patient safety issue, which the patent issue does not really pertain to. And we felt that was most of the emphasis in many of the initiatives coming from Waxman's Committee.

Kennedy only focused on protecting the pharmaceuticals, but somehow missed the patient. I think it was out of their naiveté; these drugs are not really similar, even though they're called biosimilars.

Biologics don't follow the same rules as other kinds of medications, such as generic warfarin, for instance, versus a commercial FDA-approved warfarin. Or making a generic aspirin or a generic molecule like Argatroban, for instance, which is a very small peptide.

These are easy to make because they're very small molecules. They're very easy to characterize, and they should have the same pharmacology and biologic effects. But heparin is completely different.

And when you are trying to compare a low-molecular-weight heparin—as a biologic—to another low-molecular-weight biosimilar, it's almost an incredulous argument because not only is a source material at issue (and essentially the same source material is used for unfractionated heparin as for low-molecular-weight heparin), but you're dealing with a molecule that's only 30 percent characterized. And to suggest that you could actually have a biosimilar with 70 percent of the molecule uncharacterized is really a worrisome issue to me, particular when these biosimilars act differently in a cluster, probably act differently in patients and probably act differently from one another.

So the move on Capitol Hill, through Senator Kennedy's office, was mounted to try to almost force through the FDA approval of biosimilars in the low-molecular-weight heparin area with an approval process that would bypass the initiation of clinical trials for safety purposes, if not for efficacy purposes.

We were very concerned that there might be products that are introduced into pharmacologic armamentarium that might actually produce more harm than good. But if you begin to ferret out all of the details and all of the potential complications that could occur, you're left with an ill-defined biosimilar, a follow-on biosimilar product, that could actually have the reverse affect of increasing the side effects, and perhaps increasing the modality of the individuals who are going to be receiving these drugs.

Cohen I think with regard to the biosimilar issues, there has to be some attention paid to safety. There are certain copy-cat drugs—I'll use the word "copy-cat" just for simplicity—that are easy to measure their clinical effect, and so safety in those areas becomes really very simple.

And then there are other drugs in the biosimilar field, among the biologics, that are not so easy to say, "Okay, what is the clinical effect?" So, for example, take a drug

like Coumadin. Clearly, Coumadin's patent lapsed, and you have all sorts of generic warfarin molecules.

And regardless of whether the warfarin molecules aren't exactly like Coumadin—maybe some are a little stronger, some are a little weaker—all you really need to do is the blood test that measures the clinical effect, which is a simple INR (international normalized ratio) measurement. If the INR is a little low, you don't say, "Oh, my God, this is awful." You just give a little more of the generic on the presumption that the generic is just a little weaker than Coumadin.

But among the heparins and the biologic heparins, what do you measure? With the low-molecular-weight heparins, do you want to measure the anticoagulant effect? Do you do an ACT (activated clotting time)?

The burden, with regard to the biosimilars, and specifically as relates to the low-molecular-weight heparins, is that there is no way around some kind of clinical outcome/patient safety measure, because there are no simple lab tests to gauge the similarity.

The challenge for the low-molecular-weight heparins, and I suspect other biologics, is they're used as anticoagulants. They're blood thinners. And it would be real easy if there were a simple blood test that said, "Tell me how thin my blood is." Well, there is, like the INR for Coumadin, or like the APTT (activated partial thromboplastin time) for traditional unfractionated heparin. Those are blood tests that are incredibly predictable. You give a little more Coumadin, the INR goes up. If you give a little less Coumadin, the INR goes down. You don't need to wait to see how many people are bleeding on Coumadin.

Now, what is the measure that you would apply to all molecular weight heparins?

At the end of the day, there's no shortcut in terms of the clinical outcome that you're measuring. There's no quick and dirty little blood test, or quick and dirty cardiogram.

Coumadin can be measured once a month with INR. But for low-molecular-weight heparins, there's no shortcut measure. You're stuck measuring those very, very complicated things called stroke, myocardial infarction, the need for emergency angioplasty, cardiac death. There is no shortcut that's so clear.

Bussey

I'm concerned about the potential for therapeutic differences and, also, safety differences with any biologic just because of the components and the potential for sort of a composite effect. These products often don't have just a single mechanism of action. They often have several different mechanisms, and which ones are most important and how they vary from one product to another is often not clear.

Granger

I can definitely answer yes. I think it should be ultimately more focused on patient safety.

Hiatt

But the key issues would be ensuring equivalent dosing across preparations (which is a safety issue if doses are not correct).

Pollack I'm terribly concerned about that. I think it's bad medicine. If you look at the hurdles that low-molecular-weight heparins had to overcome to get approved, it really was striking how many thousands of patients were enrolled in clinical trials that were laboriously designed. And I think that approach convinced everybody that they offered a legitimate alternative to heparin anticoagulation, which has its own significant limitations.

So the idea that a drug that structurally, chemically is similar or even identical to one of these agents—or as close to identical as one can get—is going to behave in the same way, just being accepted as a concept without proof of that concept really bothers me. And it concerns me that we might be asked to use something—or even worse, that our pharmacists might without even telling us switch a patient to something—that hasn't been subjected to that same sort of rigorous scientific review.

The law provides the FDA with significant discretion to approve biosimilars as the agency sees fit. It is not required to ask a company to conduct clinical trials, draft product class-specific guidelines in advance of accepting applications for products within that class, or determine whether a biosimilar is interchangeable or not. Does this concern you?

Cohen Yes. You know the FDA at some point in time was under the influence of Congress not to accept the morning after pill. And at another point in time, the winds of fortune changed and now it may be more liberal. That's not how the process should work. Either the law is scientifically valid and the FDA has guidelines, but to leave it up to the FDA, that's not quite right.

Bussey Yes, it concerns me because biosimilars are really not like a single-entity drug like, say, Tylenol. And so since these are derived from biological products to begin with, the initial biological product that you're working with may be different from one product to another. And then, the way in which they were manipulated or purified or extracted or modified may also alter both the therapeutic effect of the product as well as the potential for antigenic or allergic response with the product.

Granger Well, yes and no. It's not realistic to think that each of these biosimilars is going to conduct an outcome trial that's definitive for whether or not this drug has similar effects as the predecessor agent. So ultimately I think what we need is transparency and clear communication to the clinical community about the uncertainty. There needs to be some emphasis on patient safety, and then there needs to be understanding of the uncertainty as to whether or not the new drug is going to have similar benefits and risks as the established drug.

Hiatt Yes. The requirement for new clinical trials is mandated for most small-molecule drugs that undergo formulation changes. It should be applied here as well.

Kessler The fact that there are no guidelines does concern me. If you go to Capitol Hill, as I've done, to try to discuss this with members of Congress, the first thing they say is your fears are totally unjustified because we're allowing the FDA to make its own

decisions about how to approve these drugs. We do not want to interfere or compromise safety.

But the FDA says, “We get inquiries everyday. Why aren’t we approving these drugs? Congress is after us all the time. The manufacturers are after us all the time. And we can’t tell them what our concerns are before they become public in hearings or with their committee structures having various leanings such as the Blood Products Advisory Committee.”

But up until that open meeting, there is a lot of information that the FDA has that it will not divulge publicly. So if a congressman calls up and says, “I want Millennium’s low-molecular-weight heparin approved tomorrow. You’ve been sitting on it for three years. Tell me why you haven’t approved it.” The FDA can’t tell him. Obviously, the FDA is dealing not just with the efficacy of the drug, but also safety and manufacturing-quality control.

And, also, there needs to be an adequately funded Phase IV structure at the FDA. (Phase IV drug approval is post-marketing surveillance.) And I think that all of these drugs should be under post-marketing surveillance. All of the follow-on biologics should be under a longitudinal surveillance program that is not voluntary by the companies.

They’re still going to get fast tracked through it anyway. The FDA can’t demand that a company do clinical trials. The FDA may say, “We may not be able to approve your drug unless you do your clinical trial in X, Y and Z fashion.” That doesn’t mean that the company has to abide by that request. Some do and some don’t. And when it comes time for the approval, the FDA may or may not have that institutional memory to recall why it told the company to do X, Y and Z.

Pollack

Yes. It’s an area where we’re dealing with sick patients who have a lot of bad things happen to them, even in the absence of giving them an anticoagulant. And now we’re looking at, again, being asked to use an agent that hasn’t been fully vetted or fully tested in a systematic way that would convince me of its safety, much less its efficacy.

What issues will you be paying attention to as the FDA reviews biosimilars applications?

Bussey

My main concern is that the therapeutic effect of any new biosimilar product be well defined and, also, that any potential for allergic or antigenic response is thoroughly assessed.

Granger

It’s the rigor for which the biosimilarity is reviewed in terms of the pharmacologic features of the drug that’s at issue. And more importantly, how much of an emphasis there is on issues of patient safety and pharmacodynamic and clinical outcome evidence from clinical trials. So ideally, having clinical trials testing biosimilars is optimal; I just don’t think that’s realistic.

Hiatt

Hiatt: Equivalent dosing will be key. This issue may take more than just monitoring things like factor Xa (a surrogate biological effect marker in the blood) levels.

Pollack

My concern is that they not approve one of these [biosimilar] agents based simply on the chemical nature of the compound. My concern is going to be that the FDA demands, in the interest of patient safety, data from prospective controlled trials demonstrating that safety. And, of course, the efficacy has got to be there as well, but I'm really more concerned about the safety side. And you'll hear from me, and from a lot of other people, howls of protest if they just say, "Well, here's the mass spec image of our compound. Here's the mass spec image of dalteparin or enoxaparin or whatever and look how they overlap here. Let's approve this drug." You know that doesn't even make scientific sense to me, much less clinical sense.

Cohen

In general, I'll be keeping an eye on it. The biggest step forward in cardiology in the last 40 years was TPA, tissue plasminogen activator, which was a biosimilar derived from cloning and mass production of this protein by yeast cells. You can imagine how many potential issues there were with that, with different people saying, "Well, mine is just like yours." It's a complex arena of cloning yeast cells that mass-produce this kind of protein. So, in cardiology, this is an important arena for all of us to be keeping an eye on.

Kessler

What I would be concerned about is safety and efficacy. Efficacy should be equal with the currently available products that consider themselves to be biosimilars. This is a very tricky issue for low-molecular-weight heparins. There are three that are licensed in the U.S. and more around the world. But in the U.S. not every low-molecular-weight heparin has the same number of indications.

For instance, some are FDA approved for the prevention of deep venous thrombosis in orthopedic surgery. There are some that are licensed for the therapy of acute deep venous thrombosis and pulmonary embolism, whereas others aren't. There are some that are licensed for use in cancer patients and some that are licensed for use in the treatment of acute DVT (deep venous thrombosis) pulmonary embolism to prevent recurrence of those complications in cancer patients.

But not any one low-molecular-weight heparin has all of those indications all at once. In addition, numerous low-molecular-weight heparins have been approved for use in arterial thrombotic complications. Some have been approved for use in acute coronary syndrome, some for acute peripheral arterial thrombosis, some for stroke, and some for heart attacks.

On top of that is the fact that the dosing regimens are different on the arterial side versus the venous side. And even on the venous side, there are numerous regimens of dosing that are approved by the FDA. Some dosing is weight based; other dosing is not weight based.

Consequently, when a company says it has a biosimilar that's probably going to be used off label more than it's used on label, then to me it's difficult to approve or accept the fact that they are very similar to all the other low-molecular-weight heparins that will be used in completely different manners without having a good clinical trial.

How similar to the reference product should a biosimilar be to be approved or considered interchangeable?

Bussey I think it's pretty unlikely that any of the biosimilars can be considered interchangeable. Although they may be very similar in terms of effect and, also, and in terms of adverse effects and antigenicity, I think it's next to impossible that one is identical to another. And, indeed, there may be reasons why we don't want to have one that's identical to another because there might be either a therapeutic or safety advantage, and it would be good to know that.

Granger It should be shown to be very similar. But the corollary question is how much confidence can you have with some of these complicated molecules that it is biosimilar? That's one of the key questions.

Kessler From a clinical and statistical perspective it's going to be very difficult, because they're going to have to have clinical trials that are robust enough to really show clinical similarity or bioequivalence or, as I say, non-inferiority studies. Now, the problem with non-inferiority studies is that if you pick the right parameter, then you can become non-inferior. But if you don't pick the right parameter, then you won't be able to consider yourself bioequivalent or non-inferior.

For example, if you're going to say that you're rate of prevention of deep venous thrombosis in the context of a total hip replacements or a certain level of prevention of DVT, then you can probably formulate a trial that would include less than the number of people that were included in the original drug company's license application. But there may be a wider margin of error.

So I think that confidence intervals have to be more loosely defined, but they have to be relatively identical. And in order to maintain a good confidence interval, you have to have a certain number of patients to be able to fall within that confidence interval. So even with an adequate confidence interval on efficacy, that doesn't necessarily mean that there's going to be the same confidence interval for safety.

Cohen Let's say we're debating about whether or not to approve a generic for Synthroid. If you show me the TSH level is plus or minus 15-20 percent, I can live with that. If your drug is routinely a little weaker than Synthroid, no big deal, I'll just use a little more of your drug. But, I'll still be saving money, right?

Or, if you come along with a generic Coumadin and routinely your drug gives me a higher INR — it's a little stronger than regular Coumadin — I'll just use a little less of your drug compared to Coumadin. For those drugs that have simple ways to measure their effects, the 25 percent equivalence margin may be fine. But, what kind of margin do you set on a drug that doesn't have a quick and dirty way of measuring its clinical effect?

Hiatt If you approach this from a non-inferiority perspective then the new formulation should retain at least 50 percent of the reference product benefit (defined not by the point estimate but by the 95 percent confidence interval).

Pollack

The FDA, the World Health Organization, the American College of Cardiology, the American College of Chest Physicians are all on record as saying low-molecular weight heparins as a class is superior to unfractionated heparin, but the agents themselves are not interchangeable. They're made in different ways. They have subtly different chemical properties, and that translates into different behaviors in clinical trials.

So that brings up the question of could a biosimilar also be considered interchangeable. Even the drugs that have gone through this very rigorous approval process I don't think are interchangeable, and so a new agent can't be considered interchangeable unless it is compared to the reference product in a randomized control trial. You have to show me across-the-broad spectrum that the drug behaves in the same way regardless of what its chemical structure looks like.

And I would think you're going to need many thousands of patients to demonstrate that, which means you have to take the time to do it right and protect patients.

Understanding the complexity of these products and that minor differences in structure could potentially mean major differences in safety and/or effectiveness, should some level of clinical testing be mandatory to ensure such differences do not have adverse clinical significance?

Cohen

The answer is categorically, yes. You have to do some level of clinical testing, (A) to ensure efficacy, and (B) to guarantee that there is a minimum of adverse effect.

Kessler

I think there should be clinical trials that are prospective and, again, the Phase IV longitudinal surveillance should be mandatory.

Hiatt

Yes in most cases, but this will pose a financial challenge for sponsors.

Bussey

When I think of differences in structure, to me that's like talking about one chemical compound and that the chemical entity of a molecule may be modified a little bit. And with the follow-on biologics, we're talking about multiple chemical entities. In some cases they're polysaccharides. In other cases they may be peptides or proteins.

But you're dealing not with just one polysaccharide or one peptide, you're actually most likely dealing with several just because of the process of taking the raw biologic material and producing the refined product. So, you end up with a composite of components rather than a single structure that's just been modified.

Granger

I think the answer is yes. There should be some clinical testing. It's probably not going to be large clinical trials, but some clinical testing.

Should comparative studies between a biosimilar and the reference product be required prior to an interchangeability determination?

Kessler Interchangeability is a messy issue for the simple reason that interchangeability implies equal safety and efficacy.

And even if a product is approved for hip surgery, that doesn't mean it's going to be equally effective and safe for acute coronary artery syndrome. So yes, I think there has to be some upfront clinical trial before interchangeability is granted.

Pollack I think there's too much emphasis being placed on chemical similarities. And the first question that has to be answered is, does the drug work the same way? I understand efficacy has to come first, but the next question has got to be, is this drug going to be as safe as the reference product?

Cohen Comparative studies need to be done with these types of biologic agents, relative to "standard drugs," which may or may not be in the exact same family, as long as they have done something and compared themselves to something that all of us would agree is a standard therapy.

At the end of the day, the subliminal message is that there needs to be comparative studies. You can decide what the control group should be, depending on what you want in your label. But, some comparative studies need to be done.

Granger It depends on what you mean by comparative studies. Should there be studies in human beings that look at important parameters of PK and PD (pharmacokinetic and pharmacodynamic)? Yes.

Bussey Again, I think the interchangeability is going to be next to impossible to certify with any real certainty. There are therapeutic interchanges. For example, we have more than one low-molecular-weight heparin now approved for a given indication.

But to me interchangeable means that it has the exact same therapeutic effect, and it has the exact same risk of allergic response or contamination. And I don't think we can say that about [biosimilar] products unless it starts with the same exact raw material and is processed the same, exact way as the other product. Now, it may be therapeutically equivalent, both in terms of efficacy and safety, but I'm not sure I would consider that to be interchangeable.

Would you be comfortable prescribing a biosimilar with no clinical testing being conducted prior to FDA approval?

Pollack I would not prescribe it. Again, my concern would be a background therapeutic interchange that gives my patient something different from what I ordered. And then that would be driven, of course, by cost, perhaps at the expense of patient safety.

Kessler Absolutely not.

Hiatt No

Granger No.

Cohen Not with this family.

Bussey While I don't actually prescribe, I recommend, I would not feel comfortable advocating the use of a biosimilar that had not been through appropriate clinical testing prior to FDA approval just because we don't know what other contaminants may be in there, what differences there may be in allergic responses.

Given that biological products have immunogenic potential, should clinical trials be required to ensure that "minor differences" in structure do not result in dangerous immunogenic effects?

Cohen This is very important because the question is not whether they may have immunologic potential; they do have immunogenic potential. We know that heparin has immunogenic potential. We know that the low-molecular-weight heparins have less immunogenic potential, but it's not zero. So, it's actually just a matter of degree as to whether or not they have this property of triggering an immune response.

I think this question almost necessitates a categorical response, not a complicated response. The answer is, categorically, yes. Given the nature of these drugs and given the known fact—it is a fact that all of the heparins do trigger some degree of an immune response. The safety studies, I think, are indispensable

We're not talking about a theoretical here when it comes to heparin-induced thrombocytopenia. Heparin-induced thrombocytopenia is a real issue, and it didn't go away with Lovenox. It just was cut by about 60 percent, which is great, but it's not zero.

Pollack

Absolutely, and there's another aspect of that. There's been signals for a long time that low-molecular heparins have—particularly enoxaparin but some of the others as well—some antineoplastic potential, not that you would treat cancer with these agents, but frequently cancer patients are anticoagulated, at least for periods of time. There may actually be some beneficial impact on the tumor from those agents.

There are properties of these reference compounds that we still don't understand. So if you accept that, then to ask us to accept the biosimilars that might have a different chemical behavior than the parent compound or reference compound does, to me is very hazardous.

Kessler

I think so. They haven't done any studies to date on the biogenerics and their capacity to produce the same kind of antibodies that low-molecular-weight heparin or unfractionated heparin produce to induce a clinical syndrome known as heparin-induced thrombocytopenia. This is a problem that occurs in about 5 percent of individuals who receive unfractionated heparin and a little less than 1 percent of individuals who get low-molecular-weight heparin.

What we don't know is, again from the interchangeability perspective, that if you give an individual one of these follow-on biologics, will that patient develop antibodies so that the use of any low-molecular-weight heparin will not be useable because of the neutralizing use of antibodies? Or will the patient develop thrombocytopenia and the clotting problems that are associated with the syndrome?

So when you talk about interchangeability, this issue of immunogenicity is key because we don't know whether or not the products are interchangeable from an immunologic perspective.

Granger

I think it really depends on the compound; that's a hard question to answer as a yes or no. So the answer is it depends; but in some situations, yes. I don't think minor differences in low-molecular-weight heparins are likely to result in major differences in immunologic effects. But on other situations it might be more of an issue.

Bussey

There again, I take issue a little bit with talking about structure because we're really talking about differences in a product that has multiple components, that is not a single-chemical structure. But I think the potential to have even fatal immunological differences is bigger, as we saw a year or two ago with the heparin contamination issue.

And so I think that's a real concern. I think it might not only need to be done in the clinical trials. I think there needs to be some post-marketing monitoring or surveillance as well.

Given that unique and sensitive processes are used to develop, manufacture, and store biological products, often derived from animals and other natural sources from around the world, how important is it that the FDA ensures equivalent processes are in place prior to approval of a biosimilar? Prior to an interchangeability determination?

Bussey Bussey: I think interchangeability is going to be next to impossible to determine satisfactorily. And the reference here to natural sources from around the world brings us back to the heparin issue where we had, perhaps intentionally, contaminated forms of heparin being distributed. And if those same products were used to produce low-molecular-weight heparin, then, likely, it would have the same problems.

Kessler Kessler: I don't think it's that critical. I think that even if the FDA required that the biosimilar have exactly the same process that the original reference product went through, it still will require human studies in order to make sure that there aren't any problems.

Hiatt It seems critically important.

Granger I think it's important.

Cohen We can't ask the FDA, realistically, to get so heavily involved in guaranteeing the integrity of the raw materials, or even the processes. I think the FDA has to look at what the molecule is, what the compound is, and focus on the claim.

There is so much possibility and variety. And one day the heparin and the pigs could be coming from state A, and another day from state B. The homework, the legwork, is up to the company. I think the FDA should ensure that the final product does what it's supposed to do and with a frequency of adverse events that doctors and experts in the field view as acceptably low.

All the detail about how the company got to that point is nothing but dilution of the meager resources, so to speak, that the FDA really has in my opinion.

Pollack I think it's critical. Dalteparin, tinzaparin and enoxaparin are all made by chopping up heparin into smaller pieces, but the processes that result in those three different drugs are proprietary and done in a specific way. And even when they're done in that specific way, if you were to analyze the enoxaparin in a syringe labeled Lovenox or analyze the dalteparin in a syringe labeled Fragmin, there's a range of molecular weights and, therefore, biologic activity even within that given syringe.

So to think that the clinical effect of that range of molecules could be reproduced in a lab just by trying to copy one piece of what's inside that syringe to me seems foolhardy. You can't call things interchangeable until you've studied them in the same population.

How important is it that the FDA ensures the integrity of the raw materials and the quality of manufacturing processes?

Pollack I think that's essential in every drug, not just the biologic agents we're talking about. I think that's the FDA's job, and it seems to me that they're making noises like they might be willing to shirk that in the interest of expediting approvals and saving somebody money somewhere, at least in the short-term. I think it's a recipe for disaster.

Bussey I think the equivalent appropriate safeguards need to be put in place to assure that the product—either the natural source or the completed product—doesn't have contaminants or antigenic components that might be dangerous.

Kessler Really critical. But I don't think that the FDA has the capacity to do it now. We know what's happened in the past with the Chinese contamination issue, and this is something that can happen any time for the low-molecular-weight heparins, because there's no way to quality-control the source product and to make sure that the source product is from the same farm, from the same person isolating the impression or anything else. And I don't think that the generic drug companies have been required to perform certain types of testing on their source material to guarantee that it's identical.

Do you feel as though the FDA is equipped to inspect and monitor the global supply chains and manufacturing processes required for biological products? If not, in your opinion what changes need to be made?

Cohen They're not equipped. Even unfractionated heparin was brought into this country and killed people. It's much, much bigger than you and I can even begin to imagine. But, what we can do is say, "Give me a vial of what you're claiming to be the real McCoy, and I'm going to go ahead and test that vial. And you better be able to stand tall with all our testing."

Granger The FDA is definitely not equipped, and in my opinion there do need to be changes. For example, I think we need to have more of an integrated global group of national drug regulatory bodies that have standards in place for assuring quality and that are shared, and therefore can be trusted, across the different agencies.

Bussey Because the raw material comes from outside the U.S. and the processing may also be done outside the U.S., I think that creates a real potential. It's something that needs to be monitored and the quality of the process needs to be assured, but I don't know what the capability is of the FDA to handle that task.

Hiatt Probably not, particularly with foreign sources.

Kessler They're not at this point.

Pollack I think it's patently obvious that they're not, and I don't see where more resources are going to come from. But to me, the sensible thing to do is to shift the burden of demonstration that new products are safe and effective to the researchers who are testing the safety and efficacy of the products in the first place.

What do you think of the expectations of both physicians and patients with regard to the FDA ensuring follow-on biologics are well tested, safe and effective? Do you think either the health care community or the patient community would be surprised to learn that there doesn't appear to be adequate requirements in place, at least not yet?

Cohen I think the latter. I don't think many of us are that sophisticated in terms of our understanding of how thoroughly, or not so thoroughly, a lot of the genetics are vetted.

Hiatt I doubt most physicians and patients are aware of the process or the concerns.

Granger I think in principle that's correct. You know I don't want to be an alarmist about this issue relative to other issues the FDA is up against. But I think there's poor understanding in the clinical community, let alone the general community, where I think 99.9 percent of people wouldn't even know what bioequivalent means.

So I think getting the message out to the public in any type of specific way is simply naïve. But I think even amongst the medical community, the physicians who prescribe these drugs, there's a relatively primitive understanding about this whole issue of what bioequivalence and what regulatory guidelines are in place. And I think people would be surprised and a bit disappointed to know that there's not more rigor.

Bussey Well, I think both the health care community and the patient community were probably very surprised with what happened with heparin. But now we've got a hard and fast example of how we can have harmful products introduced in this country as FDA-approved products

Pollack Oh, I think zero percent of patients and about 1 percent of physicians have ever given this any thought. Patients have a right to think that an agent that has been blessed by the FDA and given a label and a package insert that they can look up on the Internet is safe and, if used the way the label says it should be used, is going to be effective.

Physicians, on the other hand, tend to be a little jaded about what comes out of the FDA. They get tired of waiting for new agents they've heard about. They scoff at some of the limitations that are on the label because they think they don't apply to their practice.

So I think there needs to be a real wake-up call to rank-and-file physicians outside of academics, outside of people who do research in areas related to biologics to let them know that these agents can be approved on the basis of a chemical analysis and not any clinical data whatsoever.

Kessler

I think that it would be great to have follow-on biologics on the marketplace. I just want to make sure that they're safe and effective. If they are deemed safe and effective and I see the clinical trials that indicate so, I'll be the first one to order them. I think that the FDA doesn't feel that it has the tools, and I don't think that the medical community knowledgeable in this area feels that the adequate provisions have been in place to guarantee efficacy and safety.

There have been issues that have disturbed me and my colleagues, looking at it from the patient safety perspective. One was the introduction of a biosimilar Factor VIII concentrate for the treatment of hemophilia. Now, this Factor VIII concentrate, by all the measurements and biochemistry and physiologic parameters, was the same as other plasma-derived Factor VIII concentrates that have been made prior to it.

And in fact, the same source material was being used. And yet, when the hemophilia patients received this brand of Factor VIII, which was supposed to be a follow-on biologic made by the Dutch Red Cross, a large number of individuals developed high titer antibodies against the Factor VIII molecule. Even though the molecule was the same and acted the same in a test tube, obviously, the purification process or the prior accumulation process of the finalized molecule, changed it in some way to make it all of a sudden an immunogenic protein. That sort of proves then that even when something looks like another molecule that's already on the market, you have to test it in humans before you can assume that there's going to be equal safety and efficacy.

How has the contaminated heparin crisis shaped your opinion on this set of issues? Has the FDA adequately addressed this matter?

Cohen

The contaminated heparin crisis didn't shape my opinion; it just proved my opinion that when you deal with complex biologics coming from animals from different parts of the world, you better have a mechanism in place that tests the final products. If you know what these compounds look like and you have some sense of what people have to go through to extract the final product, you will understand that it's just a matter of time before such a complex process can break down somewhere if somebody is not held to the fire in terms of the discipline of the process.

Granger

I think the heparin contamination did highlight the potential risks if there's not adequate oversight and assurance of quality, especially in the heparin manufacturing area.

Hiatt

It is a work in progress.

Bussey

Actually, most of what I've seen and heard in clinical literature, really, has not been FDA-based. It's been more clinical-scientist based, so FDA may have done much more than I'm aware of in the heparin issue. But I haven't really seen or heard the FDA taking a very strong lead in this area.

Pollack

I don't know that it's had that much impact to tell you the truth. I long ago switched away from unfractionated heparin because of its disadvantageous pharmacokinetic and pharmacodynamic properties, not so much because I was concerned about how or where it was made.

Kessler

In my practice, if I had the choice I would never use unfractionated heparin. Here I am in 2010, and I would not have thought that I would be even considering the use of unfractionated heparin except for very specific indications, maybe like in heart bypass on the machines. But, otherwise, I would not have thought I would be sitting here talking about unfractionated heparin being used to flush catheters, to prevent DVTs and PEs (pulmonary embolism) or to treat DVTs and PEs, much less being used in a cardiac catheterization.

But it hasn't changed the landscape in the United States yet because of the reimbursement structure for low-molecular-weight heparin. If you want to send a Medicare patient out of the hospital who's on low-molecular-weight heparin, that patient is probably not going to get reimbursed for the cost because Medicare doesn't cover injectibles.

And many insurance companies don't cover injectibles. So you have to send the patients home on unfractionated heparin, even if they may have been on low-molecular-weight heparin when they were in the hospital. You don't have a choice. So the cost and insurance reimbursement structure have prevented the improvement of the quality of care in the chronic DVT or PE patient, or arterial thrombotic or thrombosis patient.

Has it changed my opinion as to what needs to be done in the future for biosimilars? Absolutely it has. And that's the reason that I'm pushing very hard for clinical trials.

But, also, I'm trying to get the pharmaceutical companies to realize that one of the advantages that they could invoke is by characterizing the other 70 percent of the low-molecular-weight heparin source material that they are using right now to make low-molecular-weight heparin, because they would need to figure out what else is in the product in order to be able to figure out if there are any contaminants in the source product.

And do I think the FDA handled it well? Yes and no. I think it sets a dangerous precedent for Janet Woodcock to go out to one of the companies that is trying to make a generic product for FDA licensure and ask them to help develop a means of characterizing the source material coming into the U.S. I cannot believe that they are the only scientists with pharmaceutical companies that could have done this.

And I think that even though she was exonerated from any impropriety, it sends the wrong signal. I think that they were very slow to recognize what was happening, until over 200 deaths occurred with unfractionated heparin. They're just lucky there was no death associated with low-molecular-weight heparin as far as they can tell.

But they now ought to learn their lesson. For instance, the government of Argentina just mandated the withdrawal of a low-molecular-weight heparin there, and I don't know the details of that. But I think that the FDA ought to find out what the problems were in Chile for them to withdraw a low-molecular-weight heparin product that was similar to enoxaparin.

These products are licensed in other countries, but can we get enough data retrospectively on the number of individuals who have used those products to determine if there are any side effects? Were the surveillance mechanisms set up in an adequate fashion to detect them well before there's an endemic?

The European Medicines Agency (EMA) has issued product class-specific guidelines for a number of biosimilar product classes, including growth hormones, low-molecular-weight heparins and insulin, yet the FDA is not required to issue such guidance. Should the FDA be required to do so?

Pollack I absolutely think they should. It seems to me there should be regular meetings between the EMA and the FDA, which have at their disposal a tremendous amount of clinical and research brain power, ignoring all of the regulatory and logistical abilities and capabilities they have, to think of the science available to those two agencies. It seems to me they should be talking regularly about these things and that when there are differences between policies, if there's a clear impact on patient safety, that is, if one of the agencies has a policy that seems to be more safety-focused than the other, then the other ought to be taking a hard look at changing its own policy. So I think in this case, the FDA should look more like EMA.

Cohen I do think that the FDA should adopt some strategies that at least acknowledge that there are different classes of agents and that some agents may be real easy to check on, and other agents may be really complicated to check on. So, it's not that I would have a recipe for the FDA to say, "Why don't you just do what the EMA is doing because that's so perfect?" But, I do want to hear the FDA saying, "We can't apply square rules to circular compounds, and circular rules to square compounds." They know that, but they just need to act on that in a more public manner.

Granger I think the heparin contamination did highlight the potential risks if there's not adequate oversight and assurance of quality, especially in the heparin manufacturing area.

Bussey I have reviewed the EMA's positions and they seem valid and sound to me. It would seem that we should be following similar standards in this country. And to my knowledge, we don't have the same thoroughness in addressing those issues as the EMA has.

Hiatt Probably, but the process to get there would likely require a policy meeting initiated by the FDA.

Kessler I think they should. At least they should consider it. And I think it would be very helpful because not only should these low-molecular-weight heparins be alike, I suspect there are going to be a lot more follow-on biologics that are going to be similar to some peptide-like antithrombotic agents that are currently being licensed. So I think that it's going to be imperative to have the ground rules set as quickly as possible before these products come into the market.

These product classes, though biologically derived, are currently regulated as drugs in the US so the traditional generic approval pathways are available. While under the legislation most of these products will be deemed biologics in 10 years, and the biosimilars pathway will be required for abbreviated applicants referencing these products, should the FDA approve traditional generics in the meantime?

Cohen The short answer is the FDA definitely should be in the business of trying to save money by approving generics. It just can't apply square rules to circular molecules, and circular rules to square molecules.

Granger Probably not. I'm not so familiar with the details of this particular distinction, but it seems to me with biologics we should be requiring a degree of more sophisticated review that we anticipate we'll be implementing in the future.

Kessler I think they have to.

Bussey No, I think it was a mistake to approve low-molecular heparins as a drug rather than a biologic. And I'm not sure what avenues there are for reversing that process. But to continue to deal with new biologics in the same way that we deal with single-entity chemical products I think is a mistake.

Hiatt Only if the issues discussed earlier are respected.

Pollack No, we're dealing with the repercussions of a bad decision we made a number of years ago with these being considered low-molecular heparins and some of the other biologics being considered drugs instead of biologics. I mean, it seems to me that instead of short-circuiting the system and trying to rush some new approvals out the door, what they ought to be doing instead is correcting the past mistake and reclassifying these drugs.

Omnitrope, a human growth hormone, was approved via the 505(b)(2) pathway and is not interchangeable with its reference product; however, there are pending 505(j) applications for interchangeable versions of Lovenox, a low-molecular-weight heparin. Under this pathway, FDA may not require clinical trials for safety and efficacy. In your opinion, does this raise any patient safety concerns?

Hiatt The appropriate clinical trials should be performed

Cohen The answer is absolutely, yes.

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- Bussey** Absolutely, I think even trying to identify biologic products as interchangeable is difficult even if the clinical trials are done.
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- Kessler** Definitely. It gets back to the question of a peptide versus a large protein.
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- Granger** Yes, but more importantly, even if there are no specific safety concerns, I think that there needs to be clarity about lack of confidence in the assessment of efficacy and safety taking this pathway.

Will a biosimilar be required to have data for all approved uses? If not, how will interchangeability determinations be made?

Granger Good question—and I don't know. I suppose that there should be some data for each situation that is requested for approval for the biosimilar. At least an argument needs to be made that the data that are available from other sources fulfill the needs. I don't know if you need to have a study on each and every indication. If there are some indications that are very similar, probably not, but you should at least have an argument for why it's not needed.

Pollack The concern is for indication creep. And if a biosimilar is approved for, say, treatment of DVT and it's on the market, and let's just say for the sake of argument that it is noticeably cheaper than the reference compounds, then pharmacists are going to start substituting in other indications. Things are going to start happening that are outside that label, and we may have significant safety repercussions because of that.

Cohen I'm not so concerned about indications and uses, because if doctors identify a drug as being effective in its molecular activity, then the market pretty much drives how it's used.

If you convince me, for example, that a generic Lovenox from Argentina is really just that, a generic Lovenox, and I'm comfortable that it provides enough antithrombotic effect and doesn't cause heparin-induced thrombocytopenia, I'm not going to stand on ceremony and say that the comfort that you provide me in this large, acute coronary syndrome study doesn't have any bearing on my patient who has a DVT and pulmonary embolism.

I think most doctors will say that if you show them that the drug does what, molecularly, it's supposed to do, then most of us would feel okay with the general indications and not force you to go one by one by one through each indication.

Bussey I have a hard time accepting the concept of interchangeability of biologic products and I think there should be at least some clinical data to support any indication for a new biologic. It may not need to be a full-scale clinical trial. This would be required for a new drug that's first in class, but I still think we need to have clinical data to reassure us that these agents work the way that we anticipate they will.

Hiatt The extent of evaluation will depend on the current label.

Kessler One biosimilar can't be equated with all the others that have different indications. And even if they've had one study, what's to say that the efficacy for arterial disease is the same as for venous disease, and how do you dose them? Enoxaparin has a specific dosing regimen for acute coronary syndrome, which is weight based. But using dalteparin is not a weight-based dosage schedule for acute coronary syndrome. So how do you equate a drug that's weight based for dosing versus one that has the indication that you want, but it isn't even weight based?

To sum up, is the FDA generally on the right path with regard to biosimilar approval and why?

Cohen No, I think the FDA is not on the right path. I think that the FDA should publically acknowledge that all of its methodologies addressing bringing generics to market quickly to reduce the cost of medicine a little bit, that those methodologies cannot be boilerplate methodologies, and they have to be somewhat relative to the individual class of drugs being discussed.

Granger Good question—and I don't know. I suppose that there should be some data for each situation that is requested for approval for the biosimilar. At least an argument needs to be made that the data that are available from other sources fulfill the needs. I don't know if you need to have a study on each and every indication. If there are some indications that are very similar, probably not, but you should at least have an argument for why it's not needed.

Bussey I think trying to determine interchangeability is a nearly impossible task, and I'm not really sure that we need to worry about interchangeability. We need to worry about similar safety and efficacy. And we only know that if we have adequate clinical data on a new biologic.

Hiatt FDA needs to improve the rigor of its review.

Pollack I think they're being too quick to consider agents equivalent based strictly on their chemistry as opposed to clinical trials to establish the safety and efficacy of these agents.

The balance is that if two drugs work, then I have no problem using the cheaper version. But I don't want to use it if I don't know for sure if a drug's going to work. The fact that it's cheaper, but I don't know that it's safe and effective, is not going to make me comfortable using it.

Kessler Well, what I would hope is that as this umbrella or oversight generic committee is put into practice, that they include physicians who are using these drugs on a daily basis and who understand the biochemistry, the physiology and the potential complications, as well as the benefits that could arise from using these drugs.

Conclusion

The recently passed Patient Protection and Affordable Care Act effectively addressed the intellectual property issues surrounding biologics and their generic versions, biosimilars. But it did a poor job of establishing a clear abbreviated approval pathway for biosimilars in the near future.

That failure could raise serious concerns about the FDA and its recommendations, especially the question of whether its decisions are guided strictly by safety and efficacy, or whether costs will play a role.

What is clear from the experts IPI interviewed is that they are very skeptical about approving biosimilars without at least some clinical evidence that the follow-on biologic is safe. Considering the complexity of making biologics and the fact that the country has already experienced tragedy with a Chinese-made heparin, which led to dozens of deaths, a presumption of safety and efficacy is not enough; doctors want some clinical assurance that the biosimilar will work.

Obtaining that evidence will take a little longer and cost a little more, but it's the least we can do for patients. Anything that could be perceived to be cutting corners will only raise concerns that the FDA is putting costs and expediency above patient safety and efficacy.

About the Editor

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