FDA Guidance on Biosimilar Interchangeability Elicits Diverse Views

Current and Potential Marketers Complain About Too-High Hurdles

Stephen Barlas

Differences of opinion among pharmaceutical industry sectors have once again emerged, along typical lines, as the Food and Drug Administration (FDA) struggles to take the next step in its efforts to expand regulatory approval for biosimilars. The agency's draft guidance on "interchangeability," a key regulatory designation that will allow pharmacists to substitute a biosimilar without the approval of the prescribing physician, has produced a not-unexpected division of attitudes on key issues, such as requirements for "switching studies" sponsors will have to perform; the use of extrapolation from real-world evidence (RWE)—a hot buzzword these days—in obtaining add-on indications; whether interchangeability should be sought on an indication-by-indication basis; and other issues.[1]

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The lines blur depending on the issue at hand, but generally, the biosimilar marketers, health plans, and drugstores are on one side urging for lower hurdles, and the patent holders and physicians are on the other side. That lineup gets confused because patent holders, such as Amgen, are also selling biosimilars.

The Supreme Court underlined the value of the FDA providing a clear, achievable definition on June 12 when it decided 9–0 in a case brought by Amgen against Sandoz. The court sided with Sandoz, the first company to win biosimilar approval for its Zarxio (filgrastim-sndz), that biosimilar marketers do not have to wait six months to market a new biosimilar after it is approved by the FDA.[2] That decision creates a bigger profit motive for biosimilar sellers, one that would potentially be expanded even more if the biosimilar received a simultaneous interchangeability definition.

That means that the currently approved biosimilar Renflexis (infliximab-abda, Merck) does not have to wait until October to launch, explains Steven Lucio, Associate Vice President of Pharmacy Services for Vizient:

> The FDA has already approved Pfizer's Inflectra [infliximab-dyyb], whose competitor biological is Remicade [infliximab] from Janssen. Renflexis can launch as soon as Samsung/Merck can bring it to the market. This additional competition should help erode prices in that class further as we will now have three competitors in the market. However, the assessment of value will still be complex as you are attempting to assess the moving targets for both cost and reimbursement. In addition, the reimbursement approach from CMS [Centers for Medicare and Medicaid Services] is not necessarily the strategy that private payers will take.

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The Supreme Court decision ups the ante immediately for P&T committees already wrestling with the Inflectra-versus-Remicade comparison as they decide formulary rules for switching patients to biosimilars in the absence of interchangeability designations. The FDA has approved five biosimilars: Zarxio, Inflectra, Erelzi (etanercept-szzs, Sandoz), Amjevita (adalimumab-atto, Amgen), and Renflexis. The reference drugs, in order, are Neupogen (filgrastim, Amgen), Remicade, Enbrel (etanercept, Amgen), Humira (adalimumab, AbbVie), and Remicade. Only Sandoz's Zarxio and Celltrion's Inflectra are actually being sold. In May 2017, an FDA advisory committee voted 14–1 in favor of the agency approving Pfizer subsidiary Hospira's version of epoetin alfa, an anemia biosimilar that would compete with Epogen (epoetin alfa, Amgen) and Procrit (epoetin alfa, Janssen).[3] Another three or four biosimilar approvals are expected in 2017.

Disease groups allied under the umbrella of the Patients for Biologics Safety and Access (PBSA) are pressing the FDA to issue final guidance, which they say is "urgent," given the recent steps taken by major insurers and pharmacy benefits managers in the absence of final interchangeability guidance. The patient groups are concerned that formulary changes and other coverage changes by insurers could force patients who are stable on their treatments to switch to noninterchangeable biosimilars. PBSA is composed of groups such as the Arthritis Foundation, Lupus Foundation of America, National Alliance on Mental Illness, and National Organization for Rare Disorders, to name a few.

The final requirements for interchangeability designations will determine in good part the speed at which biosimilars are developed. A number of applications beyond the five already green-lighted have been submitted, and big and small pharma companies alike have substantial biosimilar dollars both committed and on the sidelines waiting to see whether the interchangeability guidelines are reasonable or instead present serious obstacles. These "go" or "no-go" decisions could have a big impact for consumers in terms of moderating the cost of expensive biologics, although just how much of a price advantage is still unclear.

Of the five biosimilars approved in the U.S., only two are being sold, Zarxio and Inflectra. Their prices versus their reference drugs are not dramatically lower, and neither has received an interchangeability designation. For example, in June, the Medicare program set payment limits for both Remicade and Inflectra starting July 1, 2017, both based on average sales price (ASP). The Inflectra ASP is $753.40 per vial; Remicade's will be $808.87 per vial. Those prices can be discounted to indi-

vidual payors with final prices considerably reduced. It is quite possible that Remicade will be cheaper in some instances.

Dan Mendelson, President of Avalere Health, a Washington, D.C., consulting company, says Medicare's 6.5% price discount for Inflectra doesn't surprise him at all. New biosimilars, particularly the first to market, face resistance from physicians who are accustomed to using branded products. As acceptance for a biosimilar grows, so does volume. That helps reduce manufacturing costs, which are substantial for biosimilars, and prices decline. The addition of numerous biosimilars into a category will also produce downward price pressure for all products in that category.

Mendelson also notes that an interchangeability designation is not necessarily required to inject price competition into this market. In fact, he thinks that differences between biosimilar products might emerge and be highlighted, much as branded drugs compete within a class. There may be differences in raw materials and manufacturing processes, among other inputs, between branded and biosimilar products in the same category. Experts hypothesize that in some cases it is possible that the noninterchangeable biosimilar might be more effective.

The Biosimilars Council reports that the U.S. spent $115 billion on biologics in 2014, and by 2020 that amount would increase to more than $250 billion. Also by 2020, it is estimated that biological products representing more than $80 billion in annual global sales will lose their patent exclusivity.[4] A 2014 Rand Corporation study found that introducing competing biosimilars could save between $13 billion and $66 billion from 2014 to 2024. It further states that "the magnitude of the price decrease depends in large part on the final FDA regulations."[5]

So the FDA's efforts to pin down the requirements for an interchangeability designation have high stakes. Some physician groups argue the draft, published in January,[1] is not onerous enough. So does the Biotechnology Innovation Organization (BIO), which represents biologic manufacturers. John Murphy, III, Deputy General Counsel of BIO, says the FDA needs to require an "additional showing" of safety and effectiveness of a biosimilar offered up for an interchangeability designation. That is because the Biologics Price Competition and Innovation Act (BPCIA) passed by Congress in 2010 requires "the same clinical result in any given patient" when he or she is switched from a brand-name biologic to an interchangeable biosimilar.

Sandoz, Inc., manufacturer of Zarxio, the first biosimilar approved by the FDA, takes the opposite view. It worries that the final guidance will demand additional data from applicants in the area of proof of safety and quality that is beyond what the applicant already provided when the FDA approved a biologic as biosimilar. Many health system companies, too, say the draft is either unclear or sets its hurdles too high, or both. Shoshana Krilow, Vice President of Public Policy and Government Relations for Vizient, says, "Vizient is concerned that FDA is setting an inappropriately higher standard for interchangeable biologics without scientific justification." Vizient contracts with academic medical centers, pediatric facilities, community hospitals, integrated health delivery networks, and nonacute health care providers.

The apparent fuzziness of some of the terms in the draft complicates matters further. For example, the agency's use of the expression "fingerprint-like similarity" to describe the endpoint of an interchangeable biosimilar has created some confusion. The FDA had provided a definition of "fingerprint-like similarity" in an earlier guidance document. But there is no clarifying language suggesting that "fingerprint-like" is a different standard for approval either for a biosimilar or the same biosimilar submitted for an interchangeable designation.

BIO's Murphy wants the FDA to clarify the meaning of the term "fingerprint-like" and to provide examples of specific tools, analytical processes, and other ways to demonstrate "fingerprint-like" similarity between the proposed interchangeable product and the reference product. The January draft guidance states: "fingerprint-like characterization may reduce residual uncertainty regarding interchangeability and inform the data and information needed to support a demonstration of interchangeability, which may lead to a more selective and targeted approach to clinical studies necessary to demonstrate interchangeability."[1]

Others have pointed to other terms the FDA uses, including a "totality of the data" and "residual uncertainty," as lacking specificity. The latter term comes into play in terms of a company having to pinpoint any differences in the structure of an interchangeable biosimilar and its reference drug. Joanne Palmisano, MD, Vice President of Regulatory Affairs for Boehringer Ingelheim (BI) Pharmaceuticals, Inc., states:

> Although BI appreciates that the agency believes that obtaining an interchangeability designation is possible, we remain concerned that the complexity of requirements that will satisfy a 'totality of the data' proposed for demonstrating interchangeability, and resolve what the FDA designates as 'residual uncertainty,' are still arbitrarily defined and burdensome.

Switching Study Requirements

Switching studies would help uncover any residual uncertainty between the actions of two drugs, and, in the case of interchangeability, that uncertainty needs to be as minimal as possible because of safety concerns related to immunogenicity. The immunogenicity concern arises because manufacturers make changes to their processes over time, sometimes to introduce new equipment, sometimes to change raw materials, perhaps sometimes for more significant reasons, such as the introduction of new cell banks or introduction or replacement of new manufacturing steps. Those potential changes give rise to a biologic from different batches being on the market at the same time and a patient being "switched" from one to another. This same issue arises when a person taking the reference biologic is switched to a biosimilar.

Eliminating that concern is where the switching studies come in. The draft guidance proposes that to demonstrate interchangeability, a sponsor would need to conduct one or multiple switching studies for products that are intended to be administered to an individual more than once. An applicant would have to use a U.S.-licensed reference product for the switching studies.[1] The FDA currently allows manufacturers to utilize non-U.S.-licensed reference products for biosimilar approval as long as there is a bridging study to the U.S.-licensed product. "We are concerned that the guidelines laid out for the

switching studies may be unnecessarily onerous and significantly delay the time taken to demonstrate interchangeability," says Donald Dempsey, Vice President of Policy and Regulatory Affairs for CVS Health. In particular, CVS disputes the need to use U.S. reference products, which would increase costs and slow down any movement to interchangeability applications by companies that, for example, have started switching studies using European Union (E.U.)-available reference products, which are cheaper.

Physicians generally want a higher bar for switching studies and automatic switching by pharmacists. The Biologics Prescribers Collaborative (BPC), composed of physician trade groups, such as the American Association of Clinical Endocrinologists, American College of Rheumatology, and American Gastroenterological Association, wants the FDA to require three switching studies. Moreover, it supports requiring switching studies to be done only with U.S. reference products. The BPC argues there are differences in antigen binding and other technical aspects in E.U. biologics compared with U.S. biologics. These variations could impact patients differently, resulting in clinical studies that do not reflect the patient experience appropriately.

Complicating the debate over switching is the lack of clarity over what that term means. Lisa Bell, Executive Vice President of Global Regulatory Affairs for Coherus BioSciences, Inc., argues that there continues to be ongoing confusion in the marketplace over what the terms "switching" and "substitution" mean. "Providing definitions of these terms would be useful in providing greater clarity for developers and other stakeholders," she adds. Coherus says it expects FDA approval this year for CHS-1701, its biosimilar to Amgen's Neulasta (pegfilgrastim).

Switching studies will have to seek certain kinds of data. The same studies will probably not be required for each interchangeable application. And those with a "fingerprint-like" characterization, whatever that comes to mean, might get by with more targeted studies, which is to say more limited studies. What should these switching studies look at? Amgen argues the biosimilar company should have to conduct clinical studies that utilize pharmacokinetic (PK) and pharmacodynamic (PD) parameters, as well as sensitive measures of immunogenicity.

PK and PD assessments can be expected in many circumstances to provide sensitive endpoints useful in evaluating immunogenicity differences between a proposed interchangeable product and the reference product due to switching or alternating. But BIO's Murphy argues structural differences between an interchangeable product and the reference product can drive immunogenicity responses that may or may not detectably affect PK. "BIO believes that FDA should clarify the contours of a comprehensive assessment of immunogenicity, including the need to consider alternative approaches when scientifically justified," Murphy states.

Some of this testing will have to be done after a drug is approved and will be the responsibility of pharmacists in institutional practices, according to Susannah Koontz, PharmD, President of the Hematology/Oncology Pharmacy Association (HOPA). She agrees with the draft guidance that the tendency for a complex protein-based drug to stimulate the development of antibodies should be monitored and reported for all drugs after they are approved for market use. HOPA recommends that the FDA define the risk of immunogenicity and the strategy used to measure the risk compared to the reference molecule at the time of approval of each drug to facilitate practitioners monitoring the drug in practice.

What Will Be Needed for Additional Indications?

But will a biosimilar sponsor have to perform expensive switching studies for an add-on indication once its interchangeable biosimilar is approved for the original indication? Here is where some parties want RWE to come into play. The assertion is that companies can use post-marketing data from health claims, registries, and other formats to prove that switching is not an issue for an additional interchangeable indication. Amgen says RWE should not be sufficient to earn an interchangeable indication.

But the FDA appears to have opened the door for the use of post-marketing studies, which the Academy of Managed Care Pharmacy (AMCP) has applauded. The AMCP says it has taken a proactive approach to pharmacovigilance by recently launching the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC), an initiative to proactively monitor both biologics and biosimilars using data from distributed research networks for millions of de-identified patients. BBCIC research protocols are currently in progress and initial research findings are anticipated to be presented in the fall of 2017.

The debate over the potential use of RWE leads to the issue of whether a biosimilar sponsor should even have to submit a separate application for each new interchangeable designation. The draft guidance says: "differences between conditions of use … do not necessarily preclude extrapolation."[1] A speaker representing the Biosimilars Council told the FDA's Arthritis Advisory Committee on July 12, 2016:

> FDA has used comparability, or extrapolation of information, for nearly 20 years. In such cases, clinical data are typically provided to confirm safety and efficacy of one indication and, taking into account the totality of information gained from the comparability exercise. Based on the acceptable outcome of the comparability and clinical evaluations, the data may then be extrapolated to the other indications.[6]

But not everyone agrees that extrapolation should be available. In fact, Harry Gewanter, MD, Chairman of the Alliance for Safe Biologic Medicines, wants to go in the opposite direction. He thinks sponsors seeking licensure for a proposed interchangeable product should have to provide evidence to support interchangeability for all of the licensed conditions of use. So, if a biosimilar wants to prove interchangeability with biologic X, which has been approved for indications A, B, and C, the interchangeability application would have to support interchangeability for A, B, and C, even if the company was only planning to market for indication A. The clinical reality, Dr. Gewanter argues, is that if a biologic is approved as interchangeable for one indication, it will be assumed that it is interchangeable for all conditions of use, regardless of whether the agency has considered sufficient supporting evidence. "This approach is not appropriate for biologic medicines and has the potential to lead to inappropriate substitution that can put patient safety at risk," he says.

The Naming Debate Continues

The interchangeability draft also reprises differences of opinion over the "naming" of interchangeables, a discussion that appeared to be resolved last year when the FDA published its final guidance on naming of biosimilars. The FDA decided that a company would "name" its biosimilar (and biologics already on the market) by using its nonproprietary name separated with a hyphen from a random four-letter suffix. That format had satisfied almost no one; brand-name and generics manufacturers plus pharmacy groups got almost none of the changes they asked for. The American Society of Health-System Pharmacists was particularly unhappy with the decision, arguing that the addition of a suffix will force drug companies to rename the thousands of biologics now on the market, causing particular financial distress to hospitals, which would have to spend thousands of hours on information technology redesign and reprogramming.

The interchangeability guidance essentially follows the naming convention the FDA advanced in August 2015 for six products: filgrastim-sndz, filgrastim, tbo-filgrastim, pegfilgrastim, epoetin alfa, and infliximab. The FDA originally designated Sandoz's Zarxio, when it was first approved, as filgrastim-sndz. Amgen's Neupogen (filgrastim) is its reference biological. Sandoz will now have to come up with a new suffix because the "sndz" is not random, it approximates "Sandoz." Sandoz has apparently not changed Zarxio's proprietary name yet to conform to the final FDA guidance. Sandoz had vehemently opposed the use of nondescript suffixes. A Sandoz spokeswoman did not answer emails requesting comment.

It is possible the FDA will change its naming convention for interchangeable biosimilars based on whatever comments it receives on the draft guidance, and patient groups certainly hope that will be the case. "AARP has long believed that biologics and biosimilars should have the same international nonproprietary name," says David Certner, Legislative Counsel and Legislative Policy Director for AARP. "AARP continues to believe that requiring all biologic products to have unique nonproprietary names will jeopardize patient safety and inhibit the development of the biosimilar market intended by the BPCIA, thereby reducing much-needed price competition and patient access."

It is not clear how many of the companies with the five approved biosimilars have applied for an interchangeability designation, if any. The first FDA designation will help clarify requirements. Given all the national attention to high drug prices, it seems reasonable to assume the requirements won't be impossibly onerous. But the accepted notion that interchangeable biosimilars will undercut innovator prices the way conventional generics undercut brand-name competitors is just that, a notion. However, even 10% to 15% price discounts are significant for some patients given the price of some of the innovator biologics.

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