

Generic Drug Battles Heat Up

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Innovators and generics makers are staking out positions on follow-on proteins and other manufacturing issues.

It seems that everyone wants to hop on the generic drug manufacturing bandwagon. Novartis recently moved to become a lead player in the sector, and other major brand-name firms may follow (see sidebar, “Brands move in on generics”). Biotech companies as well as generics makers are eyeing opportunities to develop follow-on protein products. The Bush administration is promising to approve more generic AIDS therapies for distribution to third-world nations. With Medicare poised to greatly expand government purchases of prescription drugs, pressure is mounting for regulators and legislators to remove obstacles that block low-cost generic products from the market. Generic drug makers are challenging the sale of “authorized generics” by innovators and are opposing legislation that would grant patent extensions to brand-name firms that conduct research on counterterrorism agents. The US Food and Drug Administration is examining ways to process citizen petitions more efficiently along with other steps to streamline its system for approving new generics for market.

Slow but steady

After more than a year of discussion and delay, FDA now seems poised to develop formal guidance on how drug manufacturers should tackle the tricky task of developing and testing “comparable,” “equivalent,” or “follow-on” protein products (FOPPs). The last term reflects general agreement that FOPPs may be similar and comparable but not necessarily therapeutically equivalent to an innovator product and thus require a different testing and approval process from that for conventional generic drugs.

Innovator firms insist that biopharmaceuticals made from living organisms seldom have manufacturing processes and product formulations that are exactly the same; generics firms, therefore,

should be required to conduct animal tests and clinical trials to document comparable safety and efficacy. Generics makers agree in part but claim that improved analytical technology makes it possible to produce very similar products that require much less clinical and preclinical testing to come to market, particularly for less-complex products such as insulin, human growth hormone, and erythropoietin. FDA has accepted abbreviated testing approaches by permitting biotech firms to make significant changes to manufacturing processes without conducting new clinical trials to prove that the changes do not alter product safety, efficacy, or quality.

At a hearing before the Senate Judiciary Committee in June 2004 on key issues related to follow-on biotherapies, then-chairman Orrin Hatch (R-UT) said that legislation authorizing FDA to move forward with FOPPs was “inevitable.” He urged biotech firms to stop stonewalling and engage in a constructive dialogue on legitimate scientific concerns.

Because generic drugs promise to expand patient access to less costly medicines and to make the Medicare prescription drug benefit more affordable in coming decades, FDA officials are under pressure to articulate a clear pathway for manufacturers to test and ensure the quality and equivalence of FOPPs. Biopharmaceuticals are proliferating and becoming more important for patient treatment, especially for serious and rare diseases, a trend likely to accelerate with the anticipated shift toward more personalized medicines. Increased competition among biotech manufacturers promises not only to reduce product prices, but also to limit the risk of shortages, to encourage product refinement and improvement, and to limit human and animal testing.

Current FDA policies make it difficult and costly to develop generic versions of biologics. The laws that govern drugs and biologics are confusing in how they define product “sameness” and “difference,” which are critical parameters for determining drug equivalence and comparability. In light of the current criticism of FDA for being too lax about drug safety, officials are leery of taking any

action that might smack of lowering quality standards. Scientists and manufacturers acknowledge that biologics can produce immune system responses, opening the door to a debate over how much preclinical and clinical testing is needed to detect any problems with immunogenicity, toxicity, and carcinogenicity.

To ensure that all parties have ample opportunity to air their views on these con-

troversial issues, FDA is proceeding at a very deliberate pace in developing new policies for marketing FOPPs. To this end, FDA cosponsored a workshop with the Drug Information Association (DIA) in February to examine the scientific and technological issues related to FOPP development and marketing. This discussion further detailed an initial FDA open meeting on follow-on biologics held this past September.

FDA next will issue a background document recapitulating agency regulation of proteins and the scientific basis for past and current policies, including immunogenicity, characterization, impurities, pharmacology-toxicology studies, clinical safety, and efficacy. The plan is to lay out the scientific underpinnings for draft guidance on policy changes needed to approve FOPPs, which may appear as a set of "interlocking guidances" that address key scientific issues, explained Janet Woodcock, FDA acting deputy commissioner of operations. After issuing the draft guidance, the agency will hold another public forum to discuss the proposal before finalizing any regulatory approach.

Need for clinical data?

The hot-button issue is how much preclinical and clinical data a generics manufacturer should have to collect to doc-

Brands move in on generics

Although generics makers and innovator firms have staked out fairly clear positions in the battle over follow-on protein products (FOPPs), industry consolidation may blur the lines a bit. Some small biotech firms are poised to take on larger competitors by pursuing development of FOPPs. And some leading innovator firms are moving forcefully into the generics business.

Novartis leads the trend with the planned addition of European generics firms Hexal AG and Eon Labs to its Sandoz unit. The deal would make Novartis the world's top generics drug maker, passing Teva and Mylan, while it also remains a leading innovator firms. Although some brand-name companies have been burned from the low-margin, high-volume generic drug business model, Novartis executives expect to gain from positioning the company as a prime source of both generic and branded products for major drug purchasers.

Novartis's move also reflects interest in developing FOPPs. In September 2004, Novartis senior vice-president Mathias Hukkelhoven said at the FDA public meeting on follow-on biologics that Novartis supported efforts by FDA and Congress to establish a robust and responsible policy for producing safe and efficacious new versions of protein products. FOPPs should have to meet high safety and efficacy standards, he said, but offer an opportunity to minimize duplication of preclinical and clinical testing to promote patient access to affordable medicines and to allow the "most innovative companies" to succeed.

ument that a follow-on product is equivalent to a drug from an innovator firm. Although pharmacokinetic (PK) testing may be sufficient to document bioequivalence and therapeutic equivalence for small molecules, pharmaceutical companies maintain that more data from clinical trials are necessary to ensure the safety and efficacy of protein products. Innovators acknowledge that full product char-

acterization is critical for documenting sameness, but that clinical trials and documented compliance with good manufacturing practices (GMPs) also are needed for a manufacturer to bring a follow-on biologic to market. At the February workshop, Amgen noted that it plans to conduct fairly large clinical trials for its products undergoing manufacturing process changes to ensure that a change in cell line

does not produce adverse reactions or other safety problems.

The European Medicines Agency (EMA) appears to agree with the innovator position. Even though some Eastern European generics firms have produced and marketed equivalent biotech therapies, EMA stated in a November 2004 policy document that because of the complexity of biological products, "the generic approach is scientifically not appropriate."

Generics makers argue that no one-size-fits-all testing approach is appropriate because biopharmaceuticals have a broad range of complexity. Protein products with a long history of patient use and multiple manufacturers should be able to gain market approval on the basis of product characterization plus pharmacodynamic studies that document bioequivalence. Additional clinical studies should be required only when there is still uncertainty about product comparability remains even after analytical and bioequivalence studies, and some kind of abbreviated regulatory pathway should be possible even for more-complex products.

Focus on quality production

A key rationale for modifying clinical testing requirements for FOPPs is that more-sophisticated analytical technology may improve product characterization and assess product similarities and differences more closely. These techniques include mass spectroscopy, circular dichroism spectroscopy, and near-infrared tools that have been refined to be increasingly sensitive. State-of-the-art characterization technology involves physiochemical, immunochemical, and *in vitro* biological studies, which may include protein sequencing, disulfide linkages, and three-dimensional structure. Scientists also are developing enzyme tests that can predict how an individual will interact with an experimental agent.

Investment in these sophisticated approaches to ensure the quality of similar biopharmaceuticals also has the potential to improve biotech manufacturing processes overall. Follow-on manufacturers have strong incentives to adopt and improve methods that can demonstrate product quality and sameness. Thorough investigation of a protein's physiochemical and biochemical properties, and expanded understanding of the role glycans



play in shaping complex molecules also may help characterize proteins and identify product equivalence.

At a public meeting this past September, FDA officials expressed some skepticism that a generics maker could fully address concerns about immunogenicity and potency without doing at least some clinical and preclinical testing. Agency experts acknowledged, though, that generics firms

should not have to repeat every innovator test to bring a follow-on protein to market and should be able to rely on added information that emerges with clinical experience in using a therapy.

Now experts appear to agree that a follow-on protein may not be identical to a comparator drug, but that it may be possible to document sufficient similarity to establish safety and efficacy. Keith Webber,

acting director of the Office of Biotechnology Products in the FDA's Center for Drug Evaluation and Research (CDER), acknowledged that product characterization alone probably is not sufficient to establish clinical safety and efficacy and that the potential immunogenic concerns related to protein pharmaceuticals raise a range of safety issues.

But Webber also noted general support for establishing a hierarchy of testing and data requirements that relates to product complexity. He pointed to overall agreement that some biotech products are more complex than others and because of intrinsic product features (e.g., size and shape), the possible presence of impurities and contaminants, the range of functional uses (antagonist, agonist, enzymatic activity) and differences in patients' health status and concomitant medication use.

The workshop provided FDA with academic support for establishing a framework for developing and marketing FOPPs. Although considerable uncertainty remains about the safety, efficacy, and manufacturing processes of any specific FOPP, Ajaz Hussain, deputy director of CDER's Office of Pharmaceutical Science, warned that overly risk-averse approaches that demand too much information or set standards too high could discourage innovation and block opportunities to improve patient care.

No slow-down for generics

Because of all the complexities associated with follow-on proteins, FDA review and approval of FOPP applications probably will be handled by CDER's new drug review office, as opposed to the Office of Generic Drugs (OGD). That's fine with OGD staffers, who continue to struggle with an increasing number of abbreviated new drug applications (ANDAs). OGD received more than 600 ANDAs in 2004—double the volume of 2001—and there's no slow-down in sight, according to OGD director Gary Buehler. OGD has managed to reduce median ANDA approval times to less than 16 months (from more than 20 months in the mid-1990s) and is testing further innovations to improve the process. But new challenges and tight budgets may make it hard to cut review times much more.

One new OGD assignment is to pro-



vide expedited reviews for new generic AIDS therapies. These generic submissions are coming in response to the President's Emergency Plan for AIDS Relief (PEPFAR); FDA approval of generics made in India and other countries makes them eligible for purchase by PEPFAR for distribution to developing nations. Buehler anticipates processing 40 or 50 applications for AIDS drugs in the coming months. He expects to process ANDAs for single entity and combination AIDS drugs in only four to five months by starting a review before receipt of full stability data; if an application comes in with complete stability testing, the review could be completed in two months. Shifting PEPFAR applications to the top of the queue, however, may slow the processing of some ANDAs not related to AIDs.

To offset delays, Buehler is continuing efforts to streamline the ANDA review system. A main goal is to help manufacturers submit more-complete applications that the agency may evaluate in one or two review cycles. A prime initiative is to reduce

delays caused by inadequate drug master files. FDA is testing a process for identifying and reviewing drug master files before an ANDA comes up for review. OGD also is urging manufacturers to calculate product specifications more carefully to reduce the time OGD staff must spend negotiating tighter limits. And the agency is seeking ways to improve the process for dealing with citizen petitions, which absorb considerable time and resources and may delay final ANDA market approval.

Other generic drug streamlining strategies include:

- Encouraging manufacturers to submit dissolution data early in the process so that OGD may resolve dissolution issues early on.
- Testing a question-based review of manufacturing quality and formulation data. This strategy involves eliminating non-scientific specifications that have no relation to product quality.
- Continuing a pilot cluster review process. When a large group of applications for the same product come in,

OGD wants to assign a special review team to process all the ANDAs together. This approach has proven to be more efficient, even though it raises some eyebrows by violating OGD's "first-in, first-reviewed" policy. FDA is considering issuing an internal memo that would clarify when the cluster review approach is appropriate and procedures for implementing it.

OGD benefited from additional funding in recent years, which has allowed Buehler to establish a third chemistry review division and expand bioequivalence teams. OGD also has worked hard to help manufacturers improve the quality of their applications, with some success: Less than 10% of applications now fall into the refuse-to-file category. But FDA's budget is slated to be very tight next year, with most additional funds targeted to drug safety activities. The prospect is dim that OGD will be able to add more people to handle the office's growing workload, placing even more importance on identifying and implementing more-efficient approaches. **PT**

C O M M U N I C A T I O N S