Frustration Over Generic Drug Shortages and Prices Prompts Federal and Private Actions

Health Systems Take Matters Into Their Own Hands

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an Liljenquist, a Vice President at Intermountain Healthcare, says he recently fielded a phone call from a top executive at another health care system who complained with evident frustration that his chief pharmacy officer spends 90% of her time trying to track down generics in shortage. Whether other hospital pharmacy personnel are spending that much time navigating shortages of intravenous, injectable, and other generic medicines is unknown. What is known is that generic shortages are draining hospital resources throughout the U.S. and in some cases imperiling inpatient treatment.

That serious situation was the backdrop to the announcement in January that Intermountain, Ascension, SSM Health, and Trinity Health are teaming up with the Department of Veterans Affairs to establish a new nonprofit company that will manufacture generic drugs in shortage, probably via contracting arrangements. Liljenquist has been on the phone with interested parties in an attempt to round up funding. He says he expects the company will have products on the market by sometime in 2019. There's a 10-generics priority list that he declines to share.

Generic drug shortages have plagued hospitals for years, of course, but exorbitant price increases that have garnered headlines in the past few years have ratcheted up attention on the absence of generic competition for many branded drugs. In addition, the inability of Congress and the Trump administration to make headway on reducing the price of patented specialty drugs has heightened interest in greater generics availability, given the fact that generics are generally 80% or more below the price of their patented reference drug.

The FDA's Performance, Pro and Con

The establishment of the hospital-based nonprofit manufacturing effort may be viewed by some as an indictment of the Food and Drug Administration (FDA), which has struggled to reduce the number of generic shortages and price bumps. Scott Gottlieb, MD, Commissioner of the FDA, announced a Drug Competition Action Plan in early January. The plan is aimed at promoting competition and access, especially in the development of generic drugs in pharmaceutical categories that lack competition. The plan has three main components: reducing gaming by branded companies that can delay generic drug entry; resolving scientific and regulatory obstacles that can make it difficult to win approval of generic versions of certain complex drugs; and improving the efficiency and predictability of the FDA's generic review process to reduce the time it takes to get a new generic drug approved and to lessen the number of review cycles generic applications undergo before approval.2

Dr. Gottlieb proudly pointed out that records were broken several times in 2017 for the number of generic medicines approved in a single month, most recently in November, when the agency approved the highest number of generic medicines in FDA history. For the full year, the FDA approved a record number of generic drugs, including first generics, high-priority medications, and drugs meeting vital public health needs. In addition to the increase in the volume of drugs being approved, the average number of review cycles needed to approve each eligible application is decreasing. The FDA took action on more applications in the last six months of 2017 than any other six-month period in FDA history.2

David R. Gaugh, RPh, Senior Vice President for Sciences and Regulatory Affairs at the Association for Accessible Medicines, the generic industry trade group, says Dr. Gottlieb's action plan is "a positive step that also ties into GDUFA II." GDUFA II, the second iteration of the Generic Drug User Fee Amendment, was passed by Congress in 2017 and raises fees the generics manufacturers pay the FDA to support approval of their drugs. In exchange, the FDA commits to take action on a certain percentage of new applications by a certain time. Gaugh points out that the FDA approved a record number of generics in 2016 and then beat that record in 2017. The agency receives about 1,000 new generic applications a year and has its hands full, especially given staff shortages in the Center for Drug Evaluation and Research.

The FDA has room for improvement, however. The Government Accountability Office (GAO) has issued a report critical of the FDA's efforts to expedite approval of an important subcategory of generics—"nonbiological complex drugs (NCDs)."3

Dr. Gottlieb's new boss, Alex Azur, not only has authority over the FDA as Secretary of Health and Human Services (HHS), but also runs the Centers for Medicare and Medicaid Services (CMS), which has recently taken some incipient actions to make more generics available—a move opposed by some brand-drug manufacturers. That move came as part of a proposal in the CMS-proposed changes to Medicare Part D for calendar year 2019.4

The GAO's Report

The GAO report focused on nonbiological complex drugs, a category that includes drugs with physical and chemical

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properties that are more difficult to characterize because of the complexity of the drug’s active ingredient or formulation. Although chemically synthesized, NCDs are similar to biological products in that they are not easily characterized. Determining that a generic NCD is similar to a branded reference drug presents a number of challenges. The GAO looked at 28 NCDs, but the universe is larger than that.³

As of August 2017, the FDA had reviewed and approved generic versions of six NCDs through the abbreviated new drug application (ANDA) pathway. An ANDA application generally does not require clinical trials, costs less, and requires less time for FDA approval than a new drug application (NDA). The GAO report said all five of the representatives of brand-name companies the GAO interviewed “questioned whether recent technological advances have been adequate to overcome the challenges the reviews of generic NCDs present. Two brand sponsor representatives and one external expert group suggested that FDA’s approach of relying on a group of overlapping tests to make approval decisions has not been sufficient to demonstrate equivalency for generic NBCDs,” another acronym for NCDs.³

Generics manufacturers argue that the FDA has not approved enough guidance documents for NCDs, which lay out the kinds of data a generics company must submit with an ANDA. Those guidelines are by necessity very specific for a particular category of NCD. Of the 28 NCDs the GAO examined, generics have been approved for six, but one of those is no longer being manufactured, leaving 23 NCDs with no approved generic. Of those 23, the FDA had issued guidance before a generic sponsor submitted an ANDA in eight cases. For two of those, the FDA issued guidance one year or less before the first ANDA was submitted, “which may have been too late in the process to be helpful for generic sponsors, who generally told us that they begin developing their ANDAs years before submitting them to FDA,” the GAO said. For five of the eight cases, the FDA has issued a product-specific guidance document and no ANDAs have been submitted. For the remaining drugs, the FDA issued guidance more than a year before the first ANDA was submitted.³

In Dr. Gottlieb’s response to the GAO report, he referred, among other things, to four draft guidance documents on NCDs that the FDA issued in October and November 2017. One of those was ANDAs for Certain Highly Purified Synthetic Peptide Drug Products that Refer to Listed Drugs of rDNA Origin. That draft guidance addressed five categories of NCDs, one of which is glucagon. The other four are liraglutide, nesiritide, teriparatide, and teduglutide.⁴

Complications and Generic Guidance Documents

The FDA’s plan for faster approval of NCDs in those five categories has produced a hailstorm of criticism, some of it counterintuitive but nonetheless reflective of the hurdles the FDA faces in approving NCDs. A good example is the uproar about how that draft guidance would affect generic NCDs for glucagon. While the draft guidance could be considered “pro-generic” in that it establishes a process for generic NCDs, such as glucagon, to be approved via an ANDA instead of a more expensive, time-consuming NDA, a number of commenters criticized the draft for complicating the approval of generic competitors to Eli Lilly’s Glucagon, a medicine used to treat severe low blood sugar (hypoglycemia). Lilly sells a glucagon “emergency kit” that includes a vial of glucagon and a syringe. Novo Nordisk sells a different formulation than Lilly’s, and it, too, was approved via an NDA, not an ANDA.

According to Charles Fournier, Vice President of the Type 1 Diabetes Defense Foundation, Lilly has a near monopoly on glucagon emergency kits, which list for $300, cost $30 at the pharmacy, and net Lilly about $5 after rebates work themselves back from Eli Lilly to the pharmacy benefit managers and insurance companies. Lilly advises type-1 diabetes patients to keep six kits on hand. Those kits expire after one year. Fournier says those same kits cost $15 to $30 at pharmacies in Europe, and they may cost Lilly less than $5 to manufacture. (Sales of Novo Nordisk’s competing emergency kit pale, for a variety of reasons, compared to Lilly’s sales of Glucagon kits.) Requests for comments to both Lilly and Novo Nordisk went unanswered.

Because of complex technical issues, the Type 1 Diabetes Defense Foundation, which takes no corporate funding and represents individuals with diabetes, says the draft will complicate the entrance of generic competitors to Lilly’s Glucagon, and the Pharmaceutical Research and Manufacturers of America (PhRMA), the patented-drug industry lobby, agrees, according to Fournier. Briefly, the five peptides are small molecules, making them chemical in structure, but they are manufactured like large-molecule biologics via biosynthesis. It will be impossible for a small innovator company to win approval for a glucagon generic through the ANDA process, Fournier argues. As a result, it will have to access the more complicated, more expensive, longer NDA application process. Fournier and PhRMA think the five peptides should be classified as biologics based on their manufacturing process, not the size of molecule, so they could have access to the newly established biosimilar accelerated approval process.

There is support for Fournier’s contention within the draft. In footnote 12 of its draft guidance, the FDA states: “Based on the types of data permitted to be submitted in an ANDA, FDA does not believe that an ANDA could include sufficient evidence for approval of a proposed peptide of rDNA origin.”⁵

Some of the comments on the other four NCD categories also reflect the challenges the FDA faces in faster approval of generic NCDs. Pfenex, a clinical-stage biotechnology company, thinks the FDA should toughen its requirements for ANDA approval even more. Pfenex is developing a biologic generic called PF708 that would compete with Lilly’s Forteo (teriparatide). Teriparatide is one of the five synthetic peptides addressed by the draft guidance. Forteo is an osteoporosis treatment that works to increase bone formation, as opposed to previous medications that attempt to halt bone breakdown. In its comments to the FDA, Pfenex wrote: “For any synthetic peptide to be eligible for ANDA approval, we propose that stringent criteria on allowable impurities must be applied. Specifically, a synthetic peptide candidate cannot contain new product-process-related impurities relative to the recombinant RLD [reference listed drug].”⁶

Are Biosimilars Generics?

Just as the debate over NCDs revolves around the sometimes confusing dividing line between drugs with chemical
and biological properties, so too is there debate over whether a biosimilar drug should be classified as a generic or biologic. That question has raised its head in the context of the CMS-proposed rule making changes to the Medicare Part D drug program in calendar 2019. The CMS wants to classify biosimilars as “generics” for seniors in Part D who are receiving a low-income subsidy (LIS). Generally, these seniors are called “dual eligible,” meaning they also receive Medicaid. They would get the cost-sharing benefit from their first drug purchase in a year. They account for approximately 30% of Part D members, and they already have very low copays for both generic and brand-name drugs. So categorizing biosimilars as generics won’t constitute much of a cost-savings for them.

The much larger Part D population is composed of non-LIS recipients who would only benefit in the catastrophic portion of Part D, when their out-of-pocket costs exceed $5,000. Non-LIS recipients would get a greater benefit, but it is not clear how many seniors in that category cross the $5,000 threshold each year. It also isn’t known how many of that group would be in the market for a biosimilar. Only two of the nine biosimilars approved by the FDA are on the market at the moment. Moreover, those two cost only 15% or so less than their patented reference biologicals.

Nonetheless, the CMS mucks up this decision—to treat biosimilars as generics for LIS and non-LIS enrollees in Part D—by going on to say that it wants to limit inclusion of biosimilars as generics beyond this one application “to avoid causing any confusion or misunderstanding that CMS treats follow-on biological products as generic drugs in all situations. We do not believe that would be appropriate because the same FDA requirements for generic drug approval (for example, therapeutic equivalence) do not apply to biosimilar biological products, currently the only available follow-on biological products. Accordingly, CMS currently considers biosimilar biological products more like brand-name drugs for purposes of transition or midyear formulary of the benefit applicable to all other Part D drugs.”

Health Systems Aim to Cure Generic Shortages

Based on their establishment of the new nonprofit generics manufacturing company, some health systems have decided not to wait for the FDA or the CMS to fix the generics shortage problem. Liljenquist says the nonprofit will focus initially on inpatient, acute-illness drugs that are in short supply, most of them sterile injectables that were developed in the 1950s, on inpatient, acute-illness drugs that are in short supply, most of them sterile injectables that were developed in the 1950s, 1960s, and 1970s and are “foundational” treatments in hospitals. Several hundred drugs fall into the nonprofit’s target category. “In some ways these older generic drugs have been left behind,” Liljenquist explains. “The markets have fallen into disrepair, and there are either shortages or extortionate prices. Hospitals are scrambling to find these drugs every day.”

No company has been formed yet as the health systems leading the effort line up financial sponsors, who have shown tremendous interest, according to Liljenquist. No budget has been established. “We hope to have generic drugs on the market by as early as next year,” he states. That would likely be accomplished by contracting with manufacturing companies as opposed to the nonprofit building its own manufacturing facilities. The company will either have to submit an ANDA to the FDA for approval before marketing a drug or purchase the license for a drug—perhaps one that a manufacturer plans to discontinue.

The founders of the effort are under no illusions that injecting a competitor into a monopoly market will be a walk in the park. “It may be kind of tricky in some instances bringing capacity online,” Liljenquist says. “We could end up with a price war. We would expect a competitive response.”

It is no surprise that brand manufacturers use all sorts of strategies to defend market share against generics. But as Intermountain and its allies are trying to prove, in certain areas such as generic shortages, there are no brand manufacturers to blame—hospitals have to roll up their sleeves and take matters into their own hands. The FDA can be of some help, but beyond getting final guidance documents out faster (and that goes for biosimilars as well), there isn’t much the agency can do beyond what it is doing already to speed up introduction of new generics.

REFERENCES