New User Fee Agreements Aim at Ensuring Relief From High Drug Prices
But Trump’s Budget Proposal Threatens to Upend Completed Negotiations

Stephen Barlas

President Trump’s controversial budget plan for the next fiscal year threatens to throw a monkey wrench into the tentative agreement reached by the Food and Drug Administration (FDA), industry, and drug companies to ratchet up competition for expensive drugs. Nearly finalized agreements over the next generation of the Generic Drug User Fee Act (GDUFA)1 and the Biosimilar User Fee Act (BsUFA)2 are meant to encourage generics and biosimilars marketers to generate new products that would provide inexpensive competition for brand-name drugs and bring down the prices of sole-source generics. But Trump wants to greatly increase the generic and biosimilar user fees drug manufacturers have already agreed to pay in carefully crafted agreements developed over the past few years. According to the Alliance for a Stronger FDA, Trump’s budget outline anticipates a doubling of FDA user fees to $2 billion. Although that general outline doesn’t fill in numbers for any Department of Health and Human Services (HHS) agency (that will happen in May), a group that includes the FDA, the HHS itself would see its budget cut by 16.2%.

“In the context of the President proposing $54 billion in nondefense program cuts, we can think of no other purpose for an extremely large and totally unplanned increase in user fees than to derive a roughly similar amount in savings from budget authority … $900 million would represent a third of the agency’s BA appropriation,” the Alliance for a Stronger FDA says.

There are three drug user fees, including the Prescription Drug User Fee Act (PDUFA), a medical device user fee, and an animal drug user fee. It is not clear from the sketchy Trump budget document which of those fees the administration wants to increase. The three drug user fees totaled $1.4 billion in fiscal year (FY) 2016. Congress has not decided on an FY 2017 budget, though that year began on October 1, 2016.

Up until President Trump produced his FY 2018 budget outline, industry, FDA, and Congressional negotiations over GDUFA II and BsUFA II (both were first authorized and funded starting in FY 2013 for five years) were the “quiet” health care story, compared with the fireworks surrounding efforts to repeal and replace Obamacare. Both programs must be reauthorized by September 30, 2017.

Neither GDUFA I nor BsUFA I has been particularly successful, mostly because the user fees paid by drug companies have been insufficient to pay for the staff needed to handle what has been, at least for generics, an unexpected workload. The FDA has picked up the pace on generics approvals in the last few years. But even Janet Woodcock, MD, Director of the FDA’s Center for Drug Evaluation and Research (CDER), acknowledges the agency could be doing better in certain areas, especially cutting down on the number of review cycles that applications must navigate to get approval. This is a particular problem for first-to-market generics, considered the leading candidates to bring down the prices of brand-name and sole-source medicines.

The goal is to replicate the recent rush of generics into the market for epinephrine auto-injectors after Mylan not only jacked up the price of its brand-name EpiPen but also introduced a high-priced generic version. For example, in January, CVS Health said it would offer its own generic alternative to EpiPen under a deal with Impax, which markets a rival brand called Adrenaclick. The authorized generic will be produced by Impax and sold at CVS for $109.99 per two-pack. Mylan’s generic is sold for $339.00.

Generics account for 89% of the prescriptions written in the U.S. but only 27% of the total spent on drugs. Even with that market penetration, the opportunities for generics and biosimilars are still considerable. There are currently 182 brand-name drugs that are off-patent with no generic competition. There are 546 drug categories in which the brand name has stopped selling product and there is only one generic competitor—a sole-source situation. Of course, part of the reason for lack of competition in brand-name-only or sole-source markets is that the potential markets are small, so the incentive to develop an entrant is small. In addition, brand-name companies are loath to provide samples to generics and biosimilars companies. However, where markets are large, there can be enthusiastic competition. For example, last year the FDA had timely approvals of nine generic versions of Crestor (rosuvastatin calcium, AstraZeneca), a cholesterol drug with approximately $5 billion in annual sales.

Encouraging the development of generics for less-juicy markets is the objective of the GDUFA II and BsUFA II programs. These lay out target dates for the FDA to act on drug applications and require companies to pay fees to the agency, which supplements the FDA’s annual congressional appropriation meant to allow the agency to hire additional technical staff. The key objective of the second-generation agreements is to give the FDA a kick in the pants so it approves generics and biosimilars during first-cycle review periods, which can range from eight to 10 months. That is not presently happening in most instances. The typical generic drug goes through four review cycles, and some withstand between eight and 11. The potential of facing

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such an extended timetable is a substantial disincentive for many companies. There are currently 1,800 applications that the FDA has reviewed at least once and then sent back to the submitter for additional information. Teva, for instance, has 330 product applications pending at the FDA.

Where Things Stand Now

The provisions included in GDUFA II and BsUFA II were agreed upon by the Obama administration’s FDA, and there is no guarantee that the Trump FDA will go along, although it is probably likely, given the time and effort that went into restructuring both programs. Scott Gottlieb, nominated by President Trump to serve as commissioner of the FDA, will probably have some input. He worked at the FDA during the George W. Bush presidency as Deputy Commissioner for Medical and Scientific Affairs from 2005 to 2007. He has written extensively about the agency, arguing its excessive rules have stifled competition, especially in its handling of generic approvals for complex medicines. However, the Senate is unlikely to confirm him until sometime this spring, and Congress may have already put a bipartisan imprimatur on the GDUFA and BsUFA reauthorization bills by the time he formally becomes commissioner.

That is not to say there won’t be any controversy over the bills as they move forward. There will be amendments offered to both reauthorizations. One likely attachment is the Lower Drug Costs Through Competition Act (H.R. 4784), co-sponsored by Representatives Kurt Schrader (D-Oregon) and Gus M. Bilirakis (R-Florida).4 It has bipartisan support and may well be appended to the GDUFA reauthorization. H.R. 4784 was the subject of hearings held in the House Energy and Commerce Health Subcommittee on March 2.

GDUFA I was funded at a level of $299 million annually, adjusted each year for inflation and workload based on the assumption that the FDA would receive 750 abbreviated new drug applications (ANDAs) per year. Over the first four years, the FDA actually received approximately 1,000 ANDAs a year and is projected to spend about $430 million in the current fiscal year for the agency. To maintain current productivity and implement a number of negotiated improvements including faster review cycles, the FDA and industry are proposing user fees totaling $493.6 million annually, adjusted each year for inflation and workload, for GDUFA II during FYs 2018–2022.

BsUFA I has been a very minimal program because relatively few biosimilar applications have been submitted. The FDA approved the first biosimilar in the United States, Zarxio (filgrastim-sndz, Sandoz, Inc.), a biosimilar to Amgen’s Neupogen, on March 6, 2015. In 2016, the FDA approved three additional biosimilars: Inflectra (infliximab-dyyb, Celltrion), a biosimilar to Janssen’s Remicade; Erelzi (etanercept-szsz, Sandoz, Inc.), a biosimilar to Amgen’s Enbrel; and Amjevita (adalimumab-atto, Amgen), a biosimilar to AbbVie’s Humira. The FDA estimates that the fees negotiated for BsUFA II will average approximately $45 million per year.

Current User Fee Problems

Neither GDUFA nor BsUFA have been crowning successes, and the second iterations are aimed at upgrading both programs. “For a variety of reasons, generic competition is lacking for certain products despite the absence of patent protection,” says Representative Michael Burgess (R-Texas), Chairman of the House Energy and Commerce Health Subcommittee. When GDUFA I was passed in 2012, the FDA was underwater with an 1,800 generic-drug backlog in its approval pipeline. Those 1,800 applications have either been approved or the sponsor has withdrawn the application. Of that cohort, the FDA approved 56 new first-in-category products. Subsequently, according to Dr. Woodcock of CDER, the agency has approved 405 “first generics” in the past three years. Those are from ANDAs submitted after 2013. In addition to the four biosimilars that have been approved, there are 64 biosimilar applications submitted under BsUFA I for 23 biological categories.

It is not just that the number of generics and biosimilars approved has been disappointing, but the time it has taken the FDA to approve those drugs has satisfied no one, the FDA included. FDA representatives are quick to point out the 1,000 staff openings at the agency, the result of funding shortfalls, as one reason for the delays. That shortfall is the result of inadequate congressional annual appropriations for the agency over the last five years or so. Despite the industry user fees, the median time for review of generics has increased since the start of GDUFA I in 2012 to 48 months in 2015, according to Burgess, and only 9% of ANDAs are approved in their first review cycle, typically 10 months. “This doesn’t seem [to be] in the right direction,” he comments. That contrasts markedly with the record in the PDUFA in which first-cycle approvals are more than 80%. But Dr. Woodcock explains that when PDUFA came into existence in 1992, the first-cycle approval number was just 23%.

Dr. Woodcock argues that GDUFA I has been a success. “We have met all our program goals,” she states. In FY 2016, the FDA approved or tentatively approved 835 ANDAs. This was the most approvals ever in one year. (The previous high was 619.) But she acknowledges that the agency has not met all of its meeting-with-sponsors goals under BsUFA I. Congressional legislation allowing the approval of biosimilars in the U.S. was approved by Congress in 2009. So it is a new industry, and biosimilars are much more complex then generics. They are trickier to manufacture, and they must undergo clinical trials, while generics do not. So approval of biosimilars requires much more effort by application submitters and diligence by the FDA, particularly in terms of the inspection of manufacturing facilities.

Staffing shortfalls impact the biosimilar program particularly because applicants need much more handholding given the complexity of the manufacturing process. That handholding is done in a variety of different meetings in which the FDA supplies intensive help on shaping and completing applications. But the FDA has faltered badly in meeting the goals it set in BsUFA I. For example, in FY 2015, the FDA was able to schedule only 50% of initial advisory meetings within the 90-day meeting goal, only 67% of type-1 meetings within the 30-day goal, only 49% of type-2 meetings within the 75-day goal, and zero type-4 meetings within the 60-day goal. The FDA’s performance during FY 2016 was an improvement from FY 2015; however, the agency still faced challenges and was unable to meet some of the applicable performance goals, according to Dr. Woodcock.
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Improving the Generics Review Process

Dr. Woodcock admits that her agency faces ongoing challenges, not all of them of its own making. The first challenge relates to submission completeness. Historically, it has taken an average of about four review cycles to approve an ANDA as a result of deficiencies by generic-drug sponsors in submitting complete applications. This has resulted in the submission of numerous amendments to applications by the companies to correct deficiencies in the original ANDAs and comprises a huge amount of rework for the FDA and industry alike. Approximately 1,800 applications were returned to industry, and the FDA awaits those resubmissions correcting deficiencies in the original application.

According to FDA statistics for years 2009–2014, only 27 ANDAs were approved in the first review cycle. Twenty-six needed eight cycles. The largest group of ANDAs approved was 561, and that was in three review cycles. “It is very inefficient for FDA and applicants alike to cycle through an ANDA over and over again,” Dr. Woodcock explains. “GDUFA II’s pre-ANDA program, ANDA review program enhancements, and priority review program will increase the odds of first-cycle approval, reduce the number of cycles to approval, and expand consumer access to quality, less expensive generic medicines.” The FDA’s “commitment letter” outlining its many pledges is nearly 30 pages long and top-heavy with jargon.

GDUFA II would establish faster review of priority submissions at eight months. Categories of drugs that would be eligible for priority review include submissions that are:

- Related to drug shortages;
- Subject to special review programs, such as the President’s Emergency Plan for Acquired Immunodeficiency Syndrome Relief;
- Related to public health emergencies;
- Related to certain government purchasing programs; or
- Subject to statutory mandates or other legal requirements.

To help ensure that the more aggressive eight-month timeline can be met, for each priority review, the applicant would have to submit a presubmission facility correspondence that lists all of the facilities that will require FDA inspection at least two months prior to the date of ANDA submission. Standard ANDAs would continue to be reviewed within 10 months of submission, which was the case in GDUFA I.

There will also be separate accommodations for complex products, which number somewhere between 150 and 170, according to David Gaugh, RPh, Senior Vice President of Sciences and Regulatory Affairs at the Association for Accessible Medicines (AAM) (formerly the Generic Pharmaceutical Association). This category includes complex active ingredients, complex formulations, complex routes of delivery, and complex drug–device combinations. For these products, a new pre-ANDA program would be established consisting of three types of meetings. “I think this will take a large step toward getting first-cycle review approval for complex products,” Gaugh states.

For products that are not complex, GDUFA II would direct the agency to establish metric goals for the FDA to issue product-specific guidance. Product-specific guidance identifies the methodology for developing generic drugs and generating the evidence needed to support generic approval. It helps companies develop ANDAs that will meet the FDA’s regulatory expectations.

Improving the Biosimilar Review Process

One of the first steps in the development and review process for a biosimilar is for an applicant to join the FDA’s Biosimilar Product Development (BPD) program. The BPD program was created as a part of BsUFA I to provide a mechanism and structure for applicants to engage with the FDA during the development of a biosimilar. As of February 2017, 64 applicants were enrolled in the BPD program, and CDER has received meeting requests to discuss the development of biosimilars for 23 different reference products. Various meeting types mentioned above undergird the program. Since program inception and as of February 2017, nine companies have publicly announced the submission to the FDA of 13 applications for proposed biosimilar products. Four have been approved.

Shortage of technical staff is the biggest reason the FDA failed to reach meeting goals in BsUFA I. Company fees will increase in BsUFA II to help alleviate that problem and are scheduled to be $45 million in FY 2018. The BsUFA II agreement reached by the FDA and industry aims to establish an application review model similar to that established under PDUFA V (FYs 2013–2017) for new-molecular-entity new drug applications and original biologics license applications. The parameters of the program under BsUFA II will include: 1) presubmission meeting, 2) original application submission, 3) day 74 letter, 4) review performance goals (10-month user-fee clock starts at the 60-day filing date), 5) mid-cycle communication, 6) late-cycle and advisory committee meetings, 7) inspections, and 8) assessment of the program. Kay Holcombe, Senior Vice President of Science Policy at the Biotechnology Innovation Organization, explains, “The program provides applicants with new opportunities during the course of the review to receive updates from FDA about how the review is proceeding.” The goal would be that 90% of first applications are reviewed within 10 months.

Possible Congressional Amendments

There are a couple of leading candidates for amendments to GDUFA II and BsUFA II. One is H.R. 4784, which would require the FDA to review applications for generic versions of “acute or chronic life-saving medications” for which there is little or no competition within 180 days, according to Schrader. That would include drugs that are designated in a shortage status. It would also offer companies that submit such applications a voucher promising speedier review of another generic product. But that six-month period is not much faster than the eight-month period for priority applications the FDA has committed to under GDUFA II. The bill also authorizes a study on whether the FDA’s Risk Evaluation and Mitigation Strategy (REMS) program—which mandates restricted distribution for some drugs considered potentially dangerous—makes it hard for generics to obtain samples to re-engineer them.

Dr. Woodcock acknowledges that, in many cases, generics companies are denied access to patented drugs by name-brand
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manufacturers that are concerned the drugs will be misused during testing, creating liability for the brand-name manufacturer. When asked, the FDA sends a letter to the branded company vouching for the generics company based on data submitted to the agency by the generics company, mainly its proposed testing protocols. “But we cannot compel a branded company to give its drugs away,” Dr. Woodcock notes.

There may be an effort to amend H.R. 4784 by replacing the REMS study with language that would force the branded company to turn over samples in some instances. “We don’t need another study on REMS,” Gaugh argues. He says somewhere between 80 and 95 drugs are now subject to REMS and another 40 to 45 have restricted distribution not connected to REMS. But Schrader and Bilirakis have refused to include solutions advanced by the AAM in their bill, according to Gaugh. Bruce A. Leicher, Senior Vice President and General Counsel at Momenta Pharmaceuticals, Inc., and Board Chair of the Biosimilars Council (affiliated with the AAM), says that those REMS are an even bigger problem for biosimilar companies because they need to purchase a much larger quantity of drug in order to conduct a clinical trial.

The GDUFA II bill Congress passes will have some sort of REMS provision, and the overall bill is unlikely to be torn up and rewritten because of President Trump’s desire to increase already agreed-upon fees. But there is likely to be at least a little more controversy over the two new user fee programs than there has been to date.

REFERENCES


