Generic Drug User Fee Act Reauthorization (GDUFA II)

Biosimilar User Fee Act Reauthorization (BsUFA II)

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Subcommittee on Health

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Introduction

Mr. Chairman and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS). Thank you for the opportunity to be here today to discuss the first reauthorization of the Generic Drug User Fee Amendments (GDUFA), also referred to as GDUFA II, as well as the first reauthorization of the Biosimilar User Fee Act (BsUFA), also referred to as BsUFA II. Under these user fee programs, industry agrees to pay fees to help fund a portion of FDA's drug review activities while FDA agrees to overall performance goals, such as reviewing a certain percentage of applications within a particular time frame. Under these user fee programs FDA has dramatically reduced the review time for new products, without compromising the Agency's high standards for demonstration of safety, efficacy, and quality of new drug products prior to approval.

Reauthorization of GDUFA

The remarkable success of the GDUFA program demonstrates how FDA, industry and other stakeholders can work together to achieve tremendous results. GDUFA has expanded access to affordable generic medicines. About 25 percent of all generic drugs that FDA has ever approved were approved in the past four years. At the same time, GDUFA helps assure the quality of generic drugs. Patient confidence that generic drugs will work the same as brand products, and can be freely substituted, is the foundation for trillions of dollars in savings that generics produce for the healthcare system.

Historically, the generic drug program has been a great success.

The generic drug industry has grown from modest beginnings into a major force in healthcare. According to the QuintilesIMS Institute, generic drugs now account for 89 percent of prescriptions dispensed in the United States, and saved the U.S. healthcare system $1.46 trillion from 2005 to 2015.

This success brought new challenges.

Over the last several decades, the generic industry, the number of generic drug applications, and the number of foreign facilities making generic drugs grew substantially. As a result, FDA's generic drug program became increasingly under-resourced. Its staffing did not keep pace with the growth of the industry.

Solution: GDUFA

After much negotiation, FDA and the generic drug industry, in consultation with other stakeholders, developed a proposal for a generic drug user fee program and submitted it to Congress. Congress enacted it (GDUFA I) as part of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).

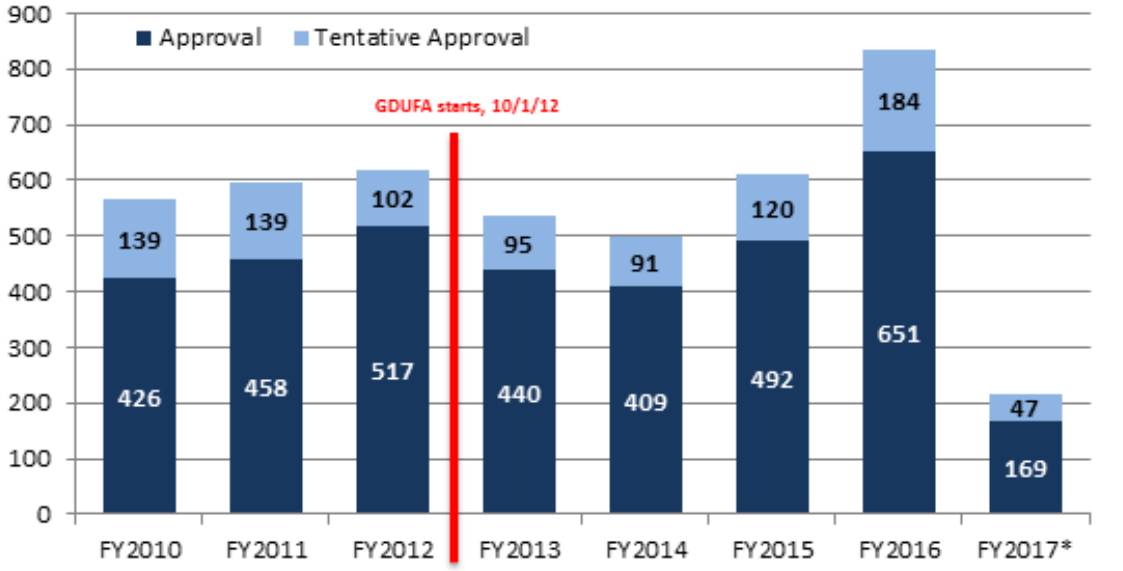
Under GDUFA I, industry agreed to pay approximately $300 million in fees each year of the five year program. In exchange, FDA committed to performance goals, including a commitment to complete reviews in a predictable time frame.

GDUFA Achievements

Met or Exceeded All Submission Review Goals to Date. FDA met or exceeded all GDUFA review goals to date, including goals for original Abbreviated New Drug Applications (ANDAs), ANDA amendments, Prior Approval Supplements (PAS), and controlled correspondence.

Record Increase in Approvals. In FY 2016, FDA approved or tentatively approved 835 ANDAs. This was the most approvals ever in one year. Our previous high was 619.

Figure 1. FY2016 – A Record Year
Approvals and Tentative Approvals



*As of 1/1/17. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Expanded Consumer Access to Quality, Affordable Generic Medicines. As noted previously, approximately 25 percent of all currently approved generic drugs were approved over the past four years.

Prioritization and Approval of "First Generics." FDA expedites the review of potential "first generic" ANDAs because they can open the market to generic competition for the first time. Most "first generic" ANDAs cannot lawfully be filed until a specific date, either four or five years after the innovator drug was approved. On this date, FDA often receives a bolus of ANDAs, from many different applicants. Beginning October 2014, in accordance with GDUFA I, these ANDAs received goal dates. We worked hard to review ANDAs for first generics even faster, expediting their review like an express line at the supermarket. For example, last year we had timely approvals of nine generic versions of Crestor, a cholesterol drug with approximately $5 billion in annual sales. Significant first generic approvals for 2016, and the indications (abbreviated) for which these products were approved, are listed in the text box below.

Significant First Generic Approvals for Calendar Year (CY) 2016	
Brand (Generic Name)	**Indication**
Namenda (Memantine Hydrochloride) Extended Release	Alzheimer's Disease
Nasonex (Mometasone Furoate) Nasal Spray	Allergies
Tamiflu (Oseltamivir Phosphate)	Influenza A and B
Crestor (Rosuvastatin Calcium)	High cholesterol
Ammonul (Sodium Phenylacetate and Sodium Benzoate)	Acute hyperammonemia and associated encephalopathy • Approved for Orphan Indication • Acute hyperammonemia is life-threatening emergency that can rapidly result in brain damage or death
Benicar (Olmesartan Medoxomil)	High blood pressure
Seroquel XR (Quetiapine Fumarate)	Schizophrenia; Bipolar Disorder
Cellcept (Mycophenolate Mofetil Hydrochloride) Injectable	Prevent organ rejection for kidney, heart, or liver transplants
Emend (Fosaprepitant Dimeglumine)	Chemotherapy-associated nausea and vomiting
Sprycel (Dasatinib)	Cancer (Chronic Myeloid Leukemia)
Treanda (Bendamustine Hydrochloride)	Cancer (Chronic Lymphocytic Leukemia)
Sustiva (Efavirenz)	HIV-1 infection
Kaletra (Lopinavir and Ritonavir)	HIV-1 infection
Tikosyn (Dofetalide)	Atrial fibrillation/flutter
Banzel (Rufinamide)	Seizures

Increase in First Cycle Approvals. Prior to GDUFA, ANDAs were approved in one review cycle less than one percent of the time. Now, approximately nine percent of ANDAs are approved in the first review cycle.

Expanded Communications. To facilitate generic drug approval, in CY 2016 the Agency sent product developers approximately 1,800 communications and ANDA applicants approximately 6,600 communications. The Agency also issued 158 product-specific guidances, identifying methodologies for developing drugs and generating evidence needed to support generic approval. These guidances help companies develop ANDAs that will meet FDA's regulatory expectations. Over 1,500 product-specific guidances are currently available as resources for prospective applicants.

Risk-Based Inspection Parity. Before 2012, the law required us to inspect domestic facilities at a two-year interval, but was silent on frequency for foreign facilities, regardless of their relative risk. Since 2012, FDASIA directed us to target inspections globally on the basis of risk. Many ANDAs rely on third-party facilities to manufacture active pharmaceutical ingredients or perform other roles in product development, and many of these facilities are located outside of the United States. Thanks to GDUFA, we have achieved the goal of risk-based inspection parity for foreign and domestic facilities.

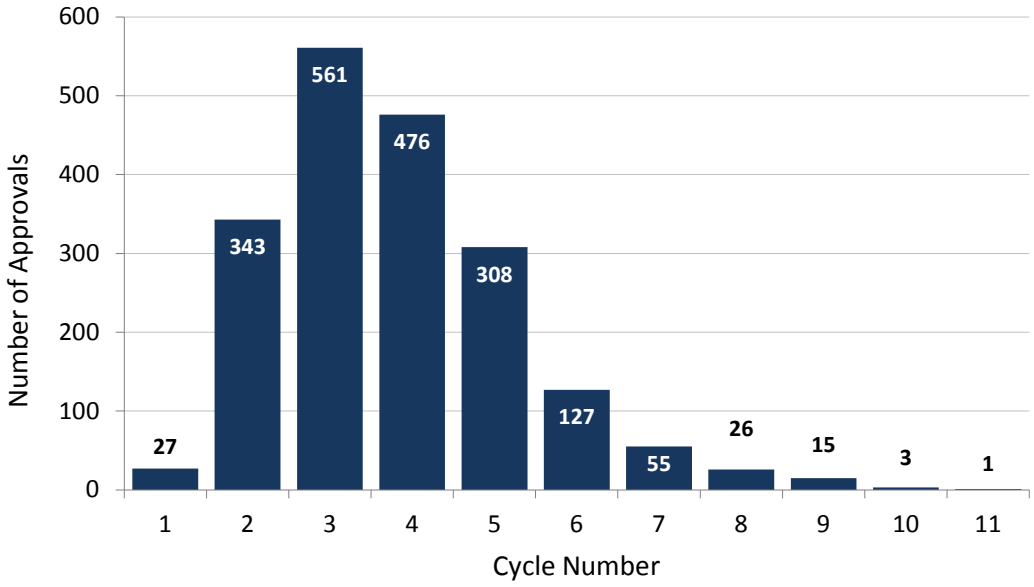
How did FDA achieve these results?

Deep, foundational restructuring. We achieved these results by building a modern generic drug program to comply with our commitments in GDUFA I. This involved major reorganizations. We reorganized the Office of Generic Drugs and elevated it to "Super-Office" status, on par with the Office of New Drugs. We established a new Office of Pharmaceutical Quality to integrate the quality components of ANDA review. FDA's Office of Regulatory Affairs also made significant inspection program enhancements. In addition, we reengineered our business processes, developed an integrated informatics platform to support the review process, and hired and trained over 1,000 new employees.

Current Challenges

We do have some ongoing challenges. The first challenge relates to submission completeness. Historically, it has taken on average about four review cycles to approve an ANDA as a result of deficiencies by generic drug sponsors in submitting complete applications.

Figure 2. Review Cycles for ANDAs
2009 through July 2014



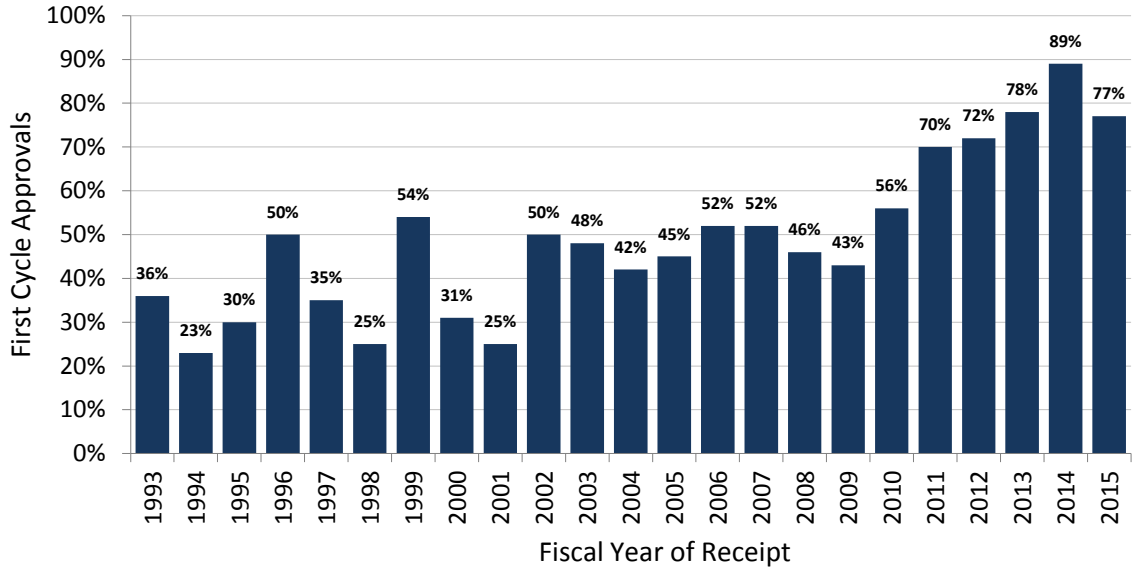
This has resulted in the submission of numerous amendments to applications by the companies to correct deficiencies in the original ANDAs and comprises a huge amount of re-work for FDA and industry alike. Currently, about 1,800 applications are back with industry awaiting resubmission to correct deficiencies in the original application. More work by both FDA and industry will be necessary to have the filings be "right the first time."

Improvement may take some time. In the first few years of the Prescription Drug User Fee Act (PDUFA) program, the first cycle approval rate for new drugs was as low as 23%. Now it is about 80% on average. Achieving this was the result of many years of cooperative work by the Agency and industry in establishing standards and meeting these expectations.

Figure 3. First Cycle Approval Rate Under PDUFA

CDER NME NDAs/BLAs†

First Action Approval Rate



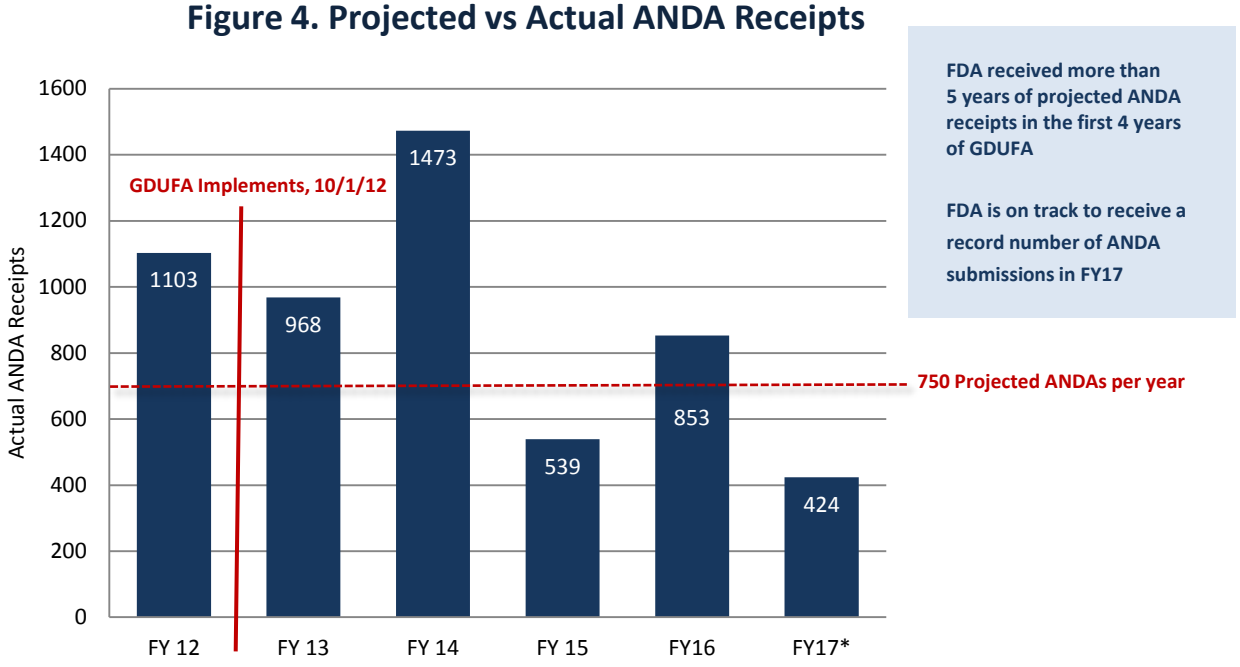
Data as of 12/9/2016

† Multiple applications pertaining to a single new molecular/biologic entity (e.g., single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicative of workload in the PDUFA V Program.

† Original BLAs that do not contain a new active ingredient are excluded. Percentages exclude pending applications from the denominator.

The second challenge relates to the volume of applications. We received many more applications than expected. As the GDUFA I Commitment Letter stated, GDUFA I review goals and planning were based on the assumption that FDA would receive approximately 750 ANDAs per year. We budgeted and planned with this projection in mind. However, in FYs 2012, 2013 and 2014, we received over 1,000, nearly 1,000 and nearly 1,500 applications, respectively. As discussed below, GDUFA II would have a program size commensurate with the Agency's overall ANDA workload.

Figure 4. Projected vs Actual ANDA Receipts



* As of 12/31/16. Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Third, several factors can delay timely consumer access to less expensive generic medicines. These factors include:

- inappropriate use of statutory requirements regarding single-shared system Risk Evaluation and Mitigation Strategies (REMS) to delay generics entry to the market;
- delaying or denying generic companies' access to reference listed drug products, thereby preventing the companies from conducting studies required for approval; and
- misuse of FDA's citizen petition process as a means to block generic approvals.

Reauthorization

Faster review of priority ANDAs. GDUFA II would establish faster review of priority submissions. Priority review would be available for submissions that FDA considers to be public health priorities pursuant to CDER's Manual of Policies and Procedures (MAPP) 5240.3 Rev.2, *Prioritization of the Review of Original ANDAs, Amendments and Supplements,* as revised (the CDER Prioritization MAPP). In the final year of GDUFA I, all ANDAs receive a review goal of 10 months. In GDUFA II, standard ANDAs would continue to be reviewed within 10 months of submission. But priority ANDAs would be reviewed within eight months of submission. To help ensure the more aggressive eight month timeline can be met, for each priority review, the applicant would have to submit a pre-submission facility correspondence (PFC) listing all of the facilities that will require FDA inspection at least two months prior to the date of ANDA submission.

GDUFA II – Faster Review of Priority ANDAs

- GDUFA I: 10 month review of all ANDAs.
- GDUFA II Proposal: 8 month review of Priority ANDAs.
- Front end: FDA identifies and communicates deficiencies in "real time".
- Back end: Applicants can correct deficiencies.
- Increase odds of approval in current review cycle.
- Reduce number of cycles to approval.
- Increase overall rate of approval.
- Concept drawn from PDUFA.

FDA and the generic drug industry agreed to an eight month priority review goal for two main reasons: First, it is the shortest time feasible given the global nature of generic drug manufacturing. In most cases, before the ANDA can be approved, FDA needs to inspect one or more manufacturing facilities to confirm that the drug will meet quality standards. Many ANDA applicants rely on multiple overseas manufacturing facilities, and conducting inspections of facilities in foreign countries requires additional time for FDA inspectors to obtain State Department approval and country-specific visas, and to meet other travel-related requirements. By providing FDA with information about the manufacturing facilities in advance of the ANDA submission, the PFC would give the Agency critical lead time to determine whether facility inspections will be needed, and when they are, to initiate travel planning.

Second, eight months is enough time for FDA to communicate–and applicants to correct–application deficiencies, so a priority ANDA can be approved in the current review cycle, not a later review cycle. A goal date set at fewer than eight months would wind down work just when it is gaining momentum. Applicants would not have time to make corrections and thus get their ANDAs approved. To resolve outstanding issues, an additional cycle of review would be necessary. Approval would be delayed for at least six to 10 more months, depending on how quickly the applicant could develop an amendment and the GDUFA II review goal for the specific type of amendment submitted.

Pre-ANDA Program Enhancements.

To reduce the number of cycles to approval, particularly for complex products, GDUFA II would establish a pre-ANDA program. It would clarify regulatory expectations for prospective applicants early in product development and help applicants develop more complete submissions, thus promoting a more efficient and effective review process.

Pre-ANDA Program

- Clarify regulatory expectations early in product development.
- Help applicants develop complete submissions.
- Ensure ANDAs are "right the first time".
- Increase efficiency and effectiveness.
- Reduce number of cycles to approval.
- Increase overall rate of approval
- Special focus on complex products, which can be more challenging to develop and review.

The GDUFA II pre-ANDA program would establish three types of meetings for complex products. In a product development meeting, FDA would provide targeted advice concerning an ongoing ANDA development program. Pre-submission meetings would give applicants an opportunity to discuss and explain the content and format of an ANDA before it is submitted. Mid-review-cycle meetings would occur post-submission, after the last key review discipline has communicated deficiencies, and would enable applicants to discuss current concerns and next steps. FDA intends to issue a guidance concerning the pre-ANDA program, setting forth meeting policies and procedures. In addition, the Agency intends to establish metric goals for product development and pre-submission meetings.

For products that are not complex, GDUFA II would direct the Agency to establish metric goals for FDA to issue product-specific guidance. Product-specific guidance identifies the

methodology for developing generic drugs and generating evidence needed to support generic approval. They help companies develop ANDAs that will meet FDA's regulatory expectations. In addition, the pre-ANDA program would enhance controlled correspondence, regulatory science, the Inactive Ingredient Database, and Safety Determination Letters.

ANDA Review Program Enhancements. GDUFA II would further refine and modernize the ANDA review process from start to finish.

ANDA Review Program Enhancements

- Expand frequency and scope of communications.
- Collaboration with applicants in "real time".
- More opportunities to correct deficiencies in current review cycle.
- Reduce number of cycles to approval.
- Increase overall rate of approval.

The GDUFA II ANDA review program would start with submission of an ANDA. When an ANDA is submitted, FDA first determines whether an ANDA is sufficiently complete to permit a substantive review. If it is sufficiently complete, then FDA "receives" it within the meaning of the statute. FDA would aspire to make these receipt determinations within consistent deadlines. The Agency also would increase receipt-related communications in an attempt to fix applications and resolve certain receipt disputes within consistent timelines.

When the ANDA has been received and is under review, pursuant to GDUFA II, FDA would communicate review deficiencies beginning at about the mid-point of the review. Then, communications would continue on a rolling basis. In GDUFA I, many deficiencies were communicated at the very end of the review, in the form of a Complete Response Letter, too late for the applicant to fix them. This produced additional cycles of review, and delayed approval. By contrast, GDUFA II would use "real time" communications to give applicants more opportunities to correct deficiencies in the current review cycle.

To support product launches and business planning that can improve access to generics, Regulatory Project Managers (RPMs) would provide review status updates and certain other

types of notifications. The Agency would also establish new technical procedures to facilitate approval of tentatively approved ANDAs on the earliest lawful approval date.

When deficiencies in an ANDA prevent FDA from approving it, FDA issues a Complete Response Letter (CRL) itemizing deficiencies that must be corrected for the ANDA to be approved. GDUFA II would establish post-CRL teleconferences to allow applicants to seek clarification concerning deficiencies identified in CRLs. This would help applicants meet FDA's expectations when an ANDA is re-submitted for additional review. There would be metric goals for such teleconferences, and for formal dispute resolutions.

Finally, in GDUFA I, different cohorts and tiers of submissions received very different goals. The scheme was challenging for FDA to operationalize and administer. In addition, there was a significant gap between the negotiated commitments and stakeholder expectations. We appreciate that this has been an understandable area of concern for all of us. In GDUFA II, all ANDAs and ANDA amendments would fall within a single, consolidated review goals scheme. This would simplify and streamline GDUFA operations, and better align commitments with expectations.

Drug Master File (DMF) Review Program Enhancements. DMFs are submissions that provide FDA with confidential information about facilities, processes, or articles used to manufacture, process, package, or store drugs. They support approval of ANDAs and are often submitted by API manufacturers that sell to ANDA sponsors. The commitment letter that accompanies GDUFA II contains five significant DMF review program enhancements.

Facility Assessment Enhancements. As previously mentioned, FDASIA eliminated longstanding minimum inspection frequency requirements and, instead, directed FDA to inspect drug facilities globally on the basis of risk. The transition to this new paradigm has been commercially disruptive for industry, which over time had developed expectations and business processes based on the old model. To mitigate export-related challenges identified by U.S.-based active pharmaceutical ingredient (API) manufacturers, GDUFA II would require FDA to issue guidance and conduct outreach to foreign regulators on the risk-based selection model and take steps to support exports. To mitigate ANDA sponsor concerns, FDA would enhance the speed and

transparency of communications concerning facility assessment, and generally update and seek feedback from industry. In addition, to enhance transparency concerning GDUFA facilities and sites, FDA would update its existing, publicly-available facility compliance status database.

Accountability and Reporting Enhancements. In GDUFA II, enhanced infrastructure and analytics would increase transparency and accountability and strengthen program management and resource use. FDA would develop internal capacity to enable improved productivity and performance through regular assessment of progress towards GDUFA II goals and transparent, efficient administration, allocation and reporting of user fee resources. In addition, an independent third party would evaluate the program.

FDA would expand GDUFA program reporting on a monthly, quarterly and annual basis. Robust performance reporting would enable Congress, industry and other stakeholders to gauge the generic drug program's performance.

Program Size Commensurate with Overall ANDA Workload. ANDAs are the primary workload driver of the generic drug program. In GDUFA I, the number of submissions received substantially exceeded projections. In order to maintain productivity and implement proposed GDUFA II improvements, FDA and the generic drug industry agreed that user fees should total $493.6 million annually, adjusted for inflation.

Modification of User Fee Structure. For program stability, user fee collections must be predictable. Application volume can fluctuate from year to year. But there is a relatively stable universe of generic drug facilities and ANDA sponsors. To maintain a predictable fee base and better align responsibility with program costs and fee-paying ability, FDA and industry propose to shift the burden more towards annual program fees. Firms that sponsor one or more approved ANDAs would pay an annual fee. In addition, Finished Dosage Form (FDF) and API facilities would continue to pay annual fees as they did in GDUFA I.

In GDUFA I, ANDA sponsors making changes to an already approved ANDA through a Prior Approval Supplement (PAS) were required to pay a PAS application fee. The volume of PASs is unpredictable. Collecting the fees was resource intensive. The new ANDA program fee is meant

to be an investment in the program, and includes the cost of reviewing PAS submissions. For these reasons, FDA and industry propose to eliminate the PAS fee.

Small Business Considerations. GDUFA II takes small business considerations into account. First, no facility or ANDA sponsor would be charged an annual fee until an ANDA in which it is listed is approved. This eliminates a situation that occurred in GDUFA I, where a company could be charged an annual fee, sometimes for several years in a row, even though no ANDA linked to the facility had been approved yet. Second, the annual program fee would have three tiers—small, medium and large—based on number of approved ANDAs owned by the firm and its affiliates. Third, Contract Manufacturing Organizations (CMOs are hired by ANDA sponsors to manufacture their generic drugs) would pay one-third the annual facility fee paid by ANDA holders.

In summary, FDA and the regulated industry, in consultation with other stakeholders, spent nearly a year developing the proposed GDUFA II agreement. It contains numerous, major reforms to address the main challenge facing the generic drug review program—namely, multiple review cycles. It is very inefficient for FDA and applicants alike to cycle through an ANDA over and over again. 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. While we have made significant progress in our generic drug review, GDUFA II will support the agency in improving consumers' timely access to generic medicines.

Reauthorization of BsUFA

FDA is supportive of and fully engaged with the development and approval of biosimilar and interchangeable products. Many of our most important drugs are biological products. Biological products are used to treat patients who have serious and life-threatening medical conditions including rheumatoid arthritis, diabetes, and cancer. It is important for the public health of the U.S. population to have access to safe, effective, and affordable biological products. Biosimilars can provide more treatment options for patients, and possibly lower treatment costs, enabling greater access for more patients.

To earn and sustain both physicians' and patients' confidence in biosimilar and interchangeable products, FDA is applying a scientifically rigorous review process and approval standard. Healthcare providers and patients have consistently emphasized that FDA's approval of biosimilars should provide assurance that biosimilars will have the same clinical performance as the originator, or reference product. FDA is committed to providing this assurance, and recognizes its importance to the uptake and acceptance of these products, and the future success of the biosimilars program.

Biologics Price Competition and Innovation Act (BPCI Act) and Biosimilar User Fee Act (BsUFA): Important Additions to FDA Statutory Authority

BPCI Act

As you know, the Biologics Price Competition and Innovation (BPCI) Act established a new abbreviated approval pathway for biological products shown to be "biosimilar to" or "interchangeable with" an FDA-licensed biological product. With this abbreviated approval pathway, an applicant can get a biosimilar approved by demonstrating, among other things, that it is highly similar to a reference biological product already licensed by FDA. Biological products are made from living organisms and usually consist of large, complex molecules that cannot be easily copied, in contrast to "small molecule" drugs that generally are produced through chemical processes and can be replicated as "generic" drugs. Unlike generic drugs, biosimilars must be highly similar to, not the same as, the reference product to which they are compared. While biosimilars may have certain allowable differences from the reference product, the

applicant must demonstrate that there are no clinically meaningful differences between the biosimilar and its reference product in terms of safety, purity and potency.

The abbreviated approval pathway permits a biosimilar application to rely, in part, on FDA's previous determination that the reference product is safe and effective, saving the applicant time and resources and thereby encouraging price competition and lowering healthcare costs. The ongoing and future impact of this relatively new law is significant. FDA's biosimilars program has sparked the development of a new segment of the biotechnology industry in the United States. The growth of this new market segment should expand opportunities for technical innovation, job growth, and patient access to treatment.

BsUFA I

The Biosimilar User Fee Act (BsUFA) was enacted as part of the FDA Safety and Innovation Act (FDASIA) (Public Law No. 112-144, enacted on July 9, 2012). The first Biosimilar User Fee Agreement (BsUFA I) between the Agency and industry allowed FDA to begin development of the infrastructure needed to support this new program and devote additional resources to support the abbreviated development process leading to the approval of safe and effective biosimilar products for patients.

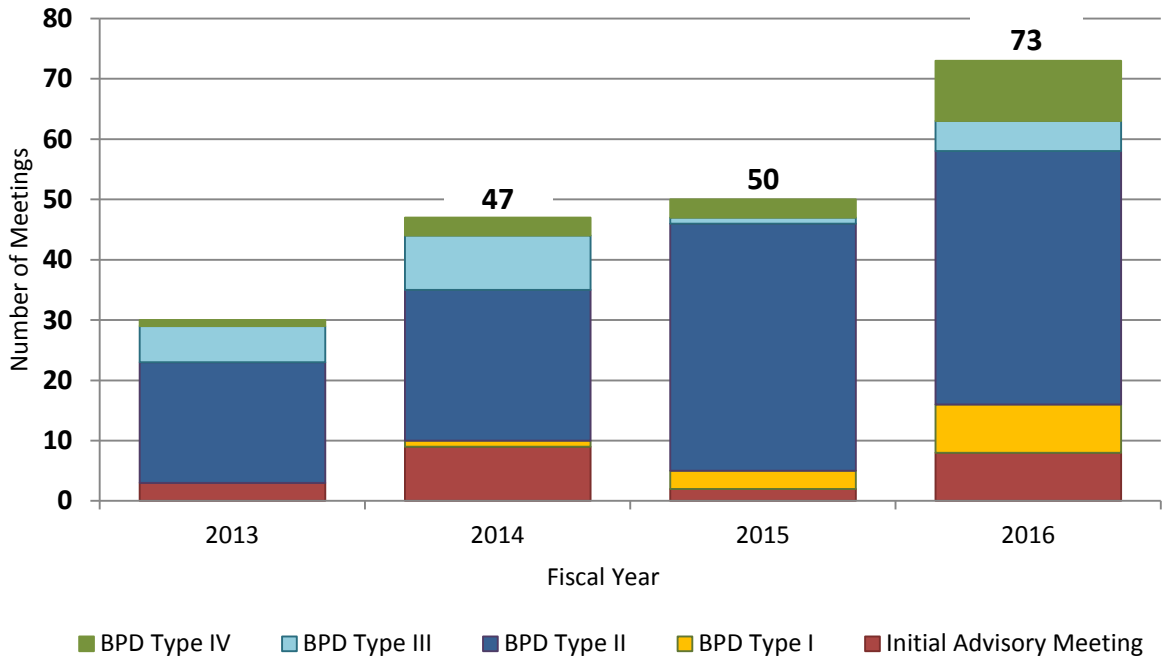
One of the first steps in the development and review process for a biosimilar is for an applicant to join FDA's Biosimilar Product Development (BPD) Program. The BPD Program was created as a part of BsUFA I to provide a mechanism and structure for applicants to engage with FDA during the development of a biosimilar. As of February 2017, 64 programs were enrolled in the BPD Program and CDER has received meeting requests to discuss the development of biosimilars for 23 different reference products.

In engaging with sponsors regarding biosimilar development, CDER holds development-phase meetings and provides written advice for ongoing development programs. These meetings include a Biosimilar Initial Advisory meeting where there is an initial discussion on whether licensure would be feasible for a particular product; and BPD meeting Types 1-4 where applicants can receive advice at different stages of product development. The meeting that is in highest demand and often requires significant review effort on behalf of FDA is the BPD Type 2

meeting where FDA conducts a substantive review of summary data and an applicant receives advice on specific issues. For additional details on the BsUFA BPD meeting types, please see Appendix A.

As shown in Figure 5 on the next page, the total number of meetings scheduled has increased each year since the beginning of BsUFA I. Additionally, in order to provide ongoing support for BPD programs, FDA has provided written advice to sponsors in instances where meeting requests were denied or cancelled due to incomplete or premature requests.

Figure 5. Number of BsUFA Program Meetings Scheduled
FY 2013 - FY 2016



The BPD meetings have provided valuable advice to biosimilar sponsors in the development of their products and associated biosimilar marketing applications. Since program inception and as of February 2017, nine companies have publicly announced submission of 13 applications for proposed biosimilar products to FDA.

FDA approved the first biosimilar in the United States, Zarxio (filgrastim-sndz), a biosimilar to Neupogen, on March 6, 2015. In 2016, FDA approved three additional biosimilars: Inflectra (infliximab-dyyb), a biosimilar to Remicade; Erelzi (etanercept-szzs), a biosimilar to Enbrel; and Amjevita (adalimumab-atto), a biosimilar to Humira.

Challenges

While we have made significant progress in creating and implementing this fairly new program, there is more work to do and, as with any new initiative, there are challenges that we need to address. These challenges in BSUFA I provide context for the discussions we had with industry during the BSUFA II negotiations. The ability to hire the right staff is critical to ensure the timely review of new biosimilars. While it's true that FDA has been somewhat limited in its capacity to recruit and retain the critical scientific, technical, and professional talent needed to address the complex and often novel scientific and legal issues involved in biosimilar review, we are committed to making meaningful and measureable progress.

The lack of additional staffing to handle the increased workload for biosimilar review also has impacted review performance. For example, in FY 2015, FDA was able to schedule only 50 percent of Initial Advisory meetings within the 90 day meeting goal, only 67 percent of Type 1 meetings within the 30 day meeting goal, only 49 percent of Type 2 meetings within the 75 day meeting goal, and zero Type 4 meetings within the 60 day meeting goal. FDA's performance during FY 2016 was an improvement from FY 2015; however, FDA still faced challenges and was unable to meet some of the applicable performance goals. Despite the BsUFA I performance challenges, industry indicated that in BsUFA II, they would like to see more meetings and faster turnaround of Agency advice.

BsUFA II

FDASIA directed FDA to develop recommendations for BsUFA II for fiscal years 2018 through 2022. To develop these recommendations, FDA consulted with industry and public stakeholders, including scientific and academic experts, health care professionals, and patient and consumer advocates, as directed by Congress. In addition to meetings with industry

organizations, FDA held two public meetings on December 18, 2015 and October 20, 2016 to obtain input from public stakeholders.

As discussed below, BsUFA II incorporates lessons learned from implementation of BsUFA I and provides a roadmap to successfully overcome some of the unexpected challenges encountered with BsUFA I.

Proposed Fees. At the time BsUFA I was authorized, the size and costs of the program were uncertain. As such, it was agreed that user fees for BsUFA I should be based off the fees established under the PDUFA program. As part of the recommendations for BsUFA II, FDA and industry agreed to establish an independent fee structure based on BsUFA program costs to generate a total of $45 million in revenue for FY 2018. FDA and industry representatives also propose that FDA can adjust this amount to reflect updated workload and cost estimates for FY 2018 when FDA publishes the Federal Register (FR) notice establishing fee revenue and fees for FY 2018. The adjustment cannot increase the target revenue more than $9 million, and FDA must describe the methodology used to calculate the adjustment in the FR.

FDA's recommendations for the BsUFA II user fee structure include additional changes to enhance the predictability of BsUFA funding levels and sponsor invoices, minimize inefficiency by simplifying the administration of the program, and improve FDA's ability to manage program resources and engage in effective long-term planning. These changes include the removal of the supplement fee and establishment fee, while retaining the initial, annual, and reactivation biosimilar biological product development (BPD) fees. Under the recommendations, the product fee is renamed the BsUFA Program fee and includes a new provision that sponsors shall not be assessed more than five BsUFA Program fees for a fiscal year per application. These changes are consistent with changes proposed for the fee structure under PDUFA VI.

Under BsUFA II, FDA also would establish a capacity planning adjustment as well as an operating reserve adjustment. The capacity planning adjustment, once operational (expected in FY 2021), would establish a mechanism to adjust the annual fee revenue target based on analytically-demonstrated sustained changes in BsUFA workload. The operating reserve adjustment would provide the ability to further adjust up or down the annual fee revenue to

ensure the program is adequately resourced to sustain operations, while also preventing the accrual of unnecessarily large carryover balances. Under BsUFA II, the $20 million (adjusted for inflation) spending trigger would be considered to be met in any fiscal year if the costs funded by budget authority are not more than 15 percent below the inflation adjusted amount for that year. This flexibility, similar to the spending trigger provisions in PDUFA and GDUFA, will enhance FDA's level of certainty that it can allocate and spend the required amount of non-user fee funds for a given fiscal year and thereby spend user fee funds in that fiscal year.

Proposed Performance Goals. The BsUFA II commitment letter establishes an application review model similar to "the Program" established under PDUFA V for new molecular entity new drug applications and original biological licensing applications. This new model is intended to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles necessary for approval. The parameters of the Program will include the following: 1) pre-submission meeting, 2) original application submission, 3) Day 74 Letter, 4) review performance goals (10 month user fee clock starts at 60-day filing date), 5) mid-cycle communication, 6) late-cycle and advisory committee meetings, 7) inspections, and 8) assessment of the Program.

The additional two-month review clock time (10 month plus 60 days, noted above) is intended to provide FDA more time to complete additional late cycle activities added as part of the new review model (e.g., late-cycle meeting) and address other late cycle review work, such as application deficiencies, Advisory Committee advice, and inspection issues to improve the efficiency of the first review cycle.

Under the BsUFA II commitment letter, Biosimilar Initial Advisory meetings will occur within 75 calendar days, instead of 90 days agreed to in BsUFA I, from receipt of the meeting request and meeting package. This type of meeting will be limited to a general discussion on whether a proposed product could be developed as a biosimilar and to provide high-level overarching advice on the expected content of the development program. To provide necessary time for FDA discussions and to develop comprehensive responses, BPD Type 2 Meetings will occur within 90 calendar days, instead of 75 days as in BsUFA I, from receipt of the meeting request and meeting package. There will be phased-in performance goals for meeting these deadlines of 80 percent in fiscal years 2018 and 2019 and 90 percent in fiscal years 2020 through 2022.

In addition, the Agency will send preliminary responses to the sponsor's questions contained in the background package no later than five calendar days before the face-to-face, videoconference or teleconference meeting date for BPD Type 2 and Type 3 meetings.

Proposed Guidance Development. While the BPCI Act states that there is no requirement for FDA to issue guidance before reviewing or taking an action on a biosimilar application, industry has indicated to FDA that guidances are an important product development tool. As part of its work to implement the BPCI Act, FDA has finalized six guidances and issued four draft guidances. The six guidances that are final are:

1. *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (finalized on April 28, 2015)
2. *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product* (finalized on April 28, 2015)
3. *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009* (finalized on April 28, 2015)
4. *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* (finalized on November 17, 2015)
5. *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (finalized on December 28, 2016)
6. *Nonproprietary Naming of Biological Products* (finalized on January 12, 2017)

Under the BsUFA II commitment letter, FDA has committed to publishing a revised draft guidance on *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants* no later than September 30, 2018, and updating the draft guidance on *Best Practices for Communication Between IND Sponsors and FDA During Drug Development* by December 31, 2018.

Additionally, under the BsUFA II commitment letter FDA has committed to publishing draft or final guidance describing the following:

- *Considerations in Demonstrating Interchangeability with a Reference Product* (draft on or before Dec. 31, 2017, and revised or final guidance 24 months after close of the public comment period),
- *Statistical Approaches to Evaluate Analytical Similarity* (draft on or before Dec. 31, 2017, and revised or final guidance 18 months after close of the public comment period),
- *Processes and Further Considerations Related to Post-Approval Manufacturing Changes for Biosimilar Biological Products* (draft on or before March 31, 2019, and revised or final guidance 18 months after the close of the public comment period),
- *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (draft guidance published in May 2014, revised or final guidance will be published on or before May 31, 2019)
- *Nonproprietary Naming of Biological Products* (draft guidance published in August 2015, revised or final guidance will be published on or before May 31, 2019)
- *Labeling for Biosimilar Biological Products* (draft guidance published March 2016, and revised or final guidance on or before May 31, 2019)

FDA has already published or finalized three of these guidances ahead of schedule: the draft *Considerations in Demonstrating Interchangeability with a Reference Product* and final guidance on *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product and Nonproprietary Naming of Biological Products.*

As with all review programs within FDA, the ability to hire and retain qualified staff is critical to ensure the availability of new safe and effective drugs and biologics. Congress included much needed new hiring authorities in the recently enacted 21st Century Cures Act. FDA looks forward to applying these new authorities to further improve our biosimilars program. Several FDA goals in the BsUFA II commitment letter support this process: FDA will strengthen staff capacity; modernize the hiring system and infrastructure; augment human resources capacity

through the use of dedicated expert contractors; establish a dedicated function for the recruitment and retention of scientific staffing; set clear goals for hiring; and conduct a comprehensive and continuous assessment of hiring and retention practices. These enhancements will allow us to meet our performance goals which in turn will help us save the applicant time and resources and ultimately encourage price competition and lower healthcare costs.

The Path Forward

BsUFA I provided critically needed funding for FDA to implement the beginning of a successful biosimilars program. BsUFA II will allow FDA to continue building this program and make improvements where needed. This relatively new pathway for biosimilar and interchangeable products has the potential to offer a significant contribution to the public health of many Americans by increasing access to more affordable biologics. At FDA, we are working hard to ensure this positive impact can be realized. We are optimistic and energized about the future of biosimilars.

CONCLUSION

Human drug user fees have revolutionized the drug review process in the United States since they were adopted 20 years ago for prescription drug products, allowing FDA to speed the application review process without compromising the Agency's high standards. User fees offer a strong example of what can be achieved when FDA, industry and other stakeholders work together on the same goal. User fees provide a critical way for leveraging appropriated dollars, ensuring that FDA has the resources needed to conduct reviews in a timely fashion. The reauthorization of GDUFA and BsUFA will allow FDA to build upon the demonstrated success of these programs.

Appendix A. BsUFA Meeting Types

The BsUFA program established five meeting types specific to biosimilar development programs:

- A Biosimilar Initial Advisory meeting is an initial assessment limited to a general discussion regarding whether licensure under section 351(k) of the Public Health Service (PHS) Act may be feasible for a particular product.
- A BPD Type 1 meeting is a meeting that is necessary for an otherwise stalled BPD program to proceed. Examples of a BPD Type 1 meeting include discussion of: a clinical hold, a special protocol assessment, an important safety issue, dispute resolution, and/or a Complete Response.
- A BPD Type 2 meeting is a meeting to discuss a specific issue (e.g., proposed study design or endpoints) or questions where FDA will provide targeted advice regarding an ongoing BPD program. This meeting type includes substantive review of summary data, but does not include review of full study reports.
- A BPD Type 3 meeting is an in-depth data review and advice meeting regarding an ongoing BPD program. This meeting type includes substantive review of full study reports, FDA advice regarding the similarity between the proposed biosimilar biological product and the reference product, and FDA advice regarding the need for additional studies, including design and analysis. This meeting has no counterpart in the Prescription Drug User Fee Act (PDUFA) program and is unique to BsUFA to support an evaluation of residual uncertainty regarding the demonstration of biosimilarity and to support the concept of stepwise evidence development.
- A BPD Type 4 meeting is a meeting to discuss the format and content of a biosimilar biological product application or supplement to be submitted under section 351(k) of the PHS Act.