Prescription Drug User Fee Act Reauthorization (PDUFA VI)

Medical Device User Fee Act Reauthorization (MDUFA IV)

Generic Drug User Fee Act Reauthorization (GDUFA II)

Biosimilar User Fee Act Reauthorization (BsUFA II)

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Committee on Health, Education, Labor and Pensions

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INTRODUCTION

Mr. Chairman and Members of the Committee: We are the Directors of the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), and Center for Devices and Radiological Health (CDRH) at the U.S. 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 reauthorization of the Prescription Drug User Fee Act (PDUFA VI), the reauthorization of the Medical Device User Fee Act (MDUFA IV), the first reauthorization of the Generic Drug User Fee Amendments (GDUFA II), and the first reauthorization of the Biosimilar User Fee Act (BsUFA II). The User Fee programs help FDA to fulfill its mission of protecting the public health, while improving the predictability of review processes and accelerating innovation in the industry. Since the inception of these 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 drugs or devices prior to approval.

The reauthorization proposals for PDUFA, MDUFA, GDUFA, and BSUFA that are described below were submitted to Congress in January, under the previous Administration and reflect a different approach to the Federal Budget. The Blueprint Budget supports many of the goals of the reauthorization proposals but proposes a different way of financing these goals. The Administration looks forward to working with Congress, with industry input, to develop reauthorization proposals that speed the development and approval of vital medical products that are safe and effective.

PDUFA

The timely review of the safety and effectiveness of new drug applications (NDAs) and biologics license applications (BLAs) is central to FDA's mission to protect and promote the public health – and PDUFA is essential to these efforts.

Before PDUFA's enactment in 1992, Americans' access to innovative, new medicines lagged behind other countries. FDA's premarket review process was understaffed, unpredictable, and

slow. The Agency lacked sufficient staff to perform timely reviews or develop procedures and standards to assure a more rigorous, consistent, and predictable process.

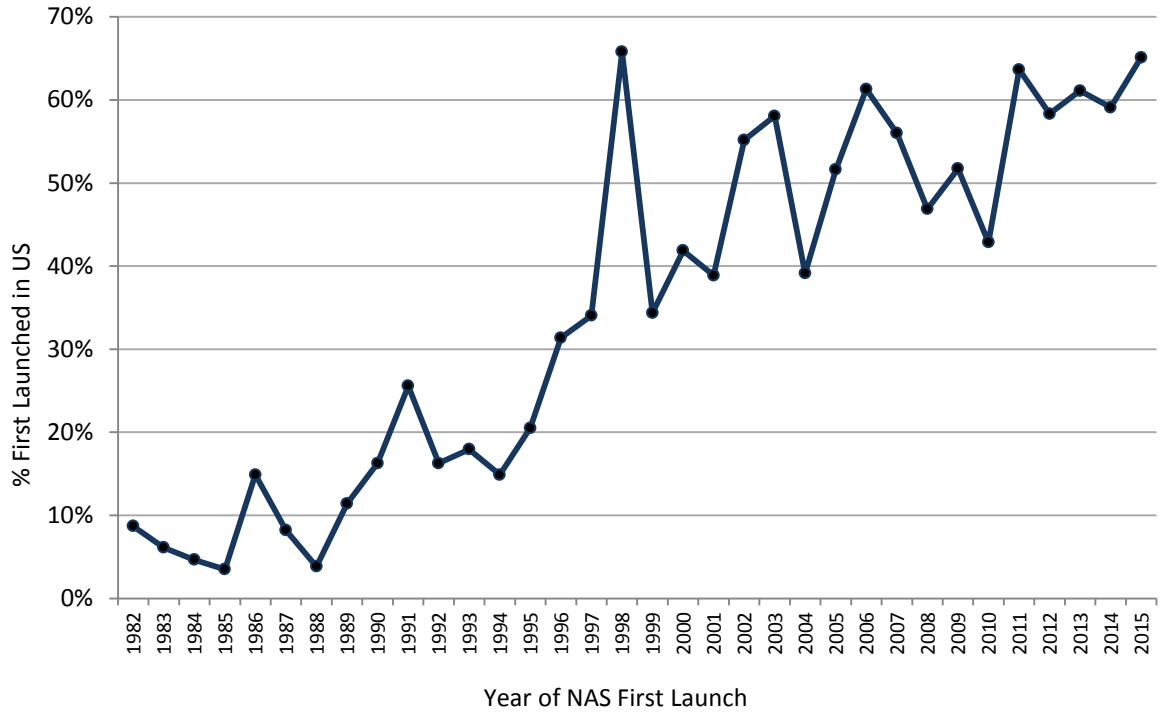
To tackle these challenges, Congress passed PDUFA, which authorized FDA to collect industry user fees to hire additional staff and upgrade its information technology systems. In return, it committed the Agency to speed the application review process for new drugs without compromising its high standards for new drug safety, efficacy, and quality.

Speeding Americans' Access to Safe and Effective New Therapies

PDUFA has revolutionized the United States' drug approval process. It reversed the lag in drug approvals that prompted its creation, providing Americans with more rapid access to safe and effective new drugs and biologics.

As shown in Figure 1, today, almost two-thirds of new active substances approved in the world market are launched first in the United States. To put this figure in perspective, that is more than triple the rate approved first in the United States in the first year of PDUFA.

Figure 1. US Share of New Active Substances (NAS) Launched on the World Market



Source: *Scrip Magazine* (1982 - 2006), *Pharmaprojects/Citeline* **Pharma R&D Annual Review** (2007 - 2016)

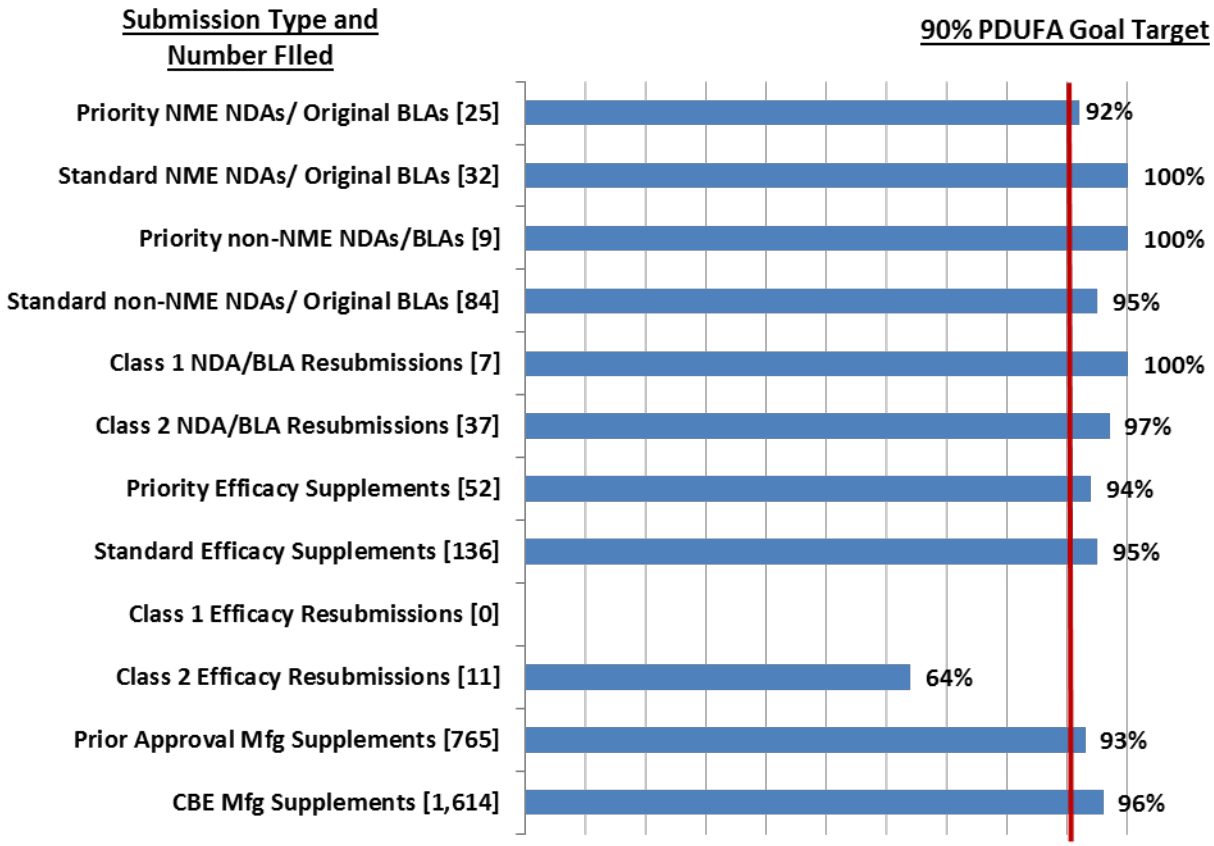
The five-year reauthorization cycles for PDUFA have supported continuous program innovation, evaluation, and improvement. The enhancements to the process of human drug review originally focused on the FDA pre-market review of NDAs and BLAs. Through successive PDUFA reauthorizations, program enhancements have evolved and expanded to include extensive communication and consultation between drug sponsors and FDA throughout drug development. This has enabled better incorporation of advances in regulatory science applied to drug development and regulatory oversight. The continued modernization of drug review under PDUFA has also strengthened and enabled innovation in approaches to post-market safety. Most recently, the program has been enhanced by increasing patient focus and modernizing supporting informatics.

These enhancements have contributed to the United States becoming a global leader in drug innovation and Americans are typically the first to benefit from safe and effective new

medicines. PDUFA, with its reauthorization cycles, has resulted in a scientifically and financially strong program with transparent stakeholder engagement as a routine way of doing business.

Throughout this program evolution, FDA has continued to review large volumes of sponsor submissions and deliver predictably high levels of performance against PDUFA goal commitments for timely regulatory review and development phase consultation, as shown in Figure 2, below.

Figure 2. FDA Review Performance - FY 2015: Percent of Submissions Acted on by Goal Date[1]



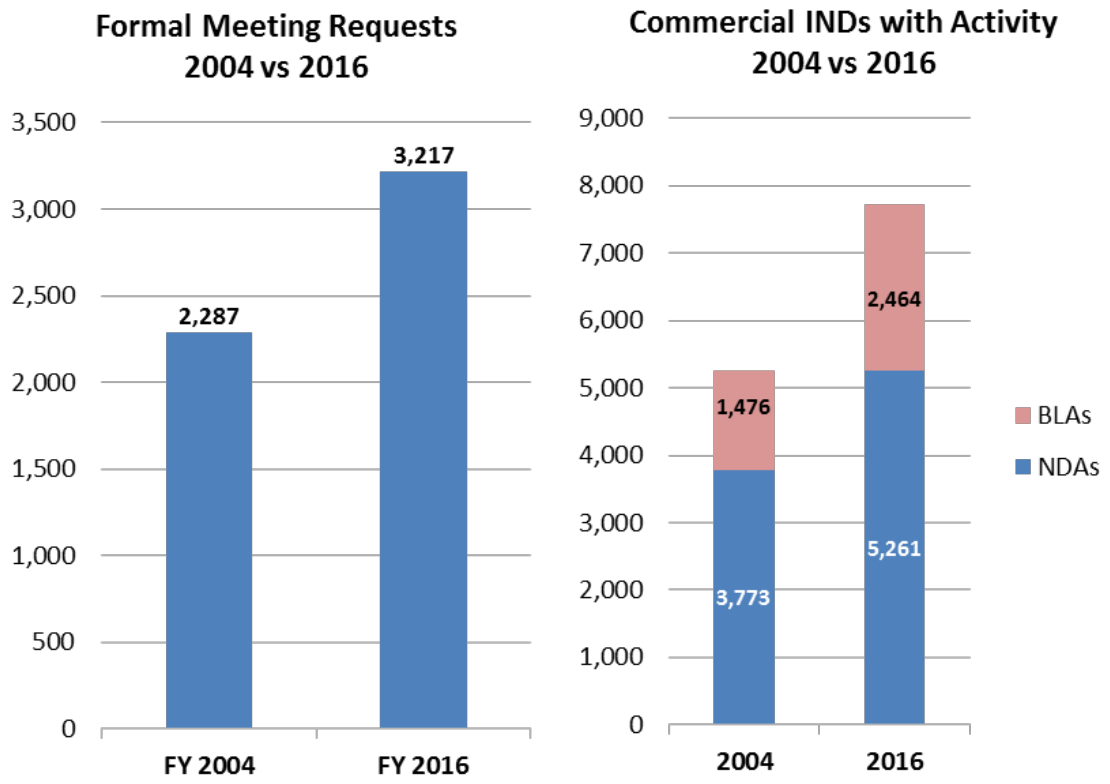
Data as of 9/30/2016

Increasing the Timeliness and Efficiency of Premarket Review

A key element of the success of the PDUFA program is ongoing development-phase consultation provided to drug sponsors by FDA, helping to minimize unnecessary or suboptimal development steps, and getting important new drugs to patients more rapidly and efficiently. FDA's capacity to provide sponsors, including small first-time innovators, with timely advice enabled by PDUFA funding, has contributed to the strong drug development pipeline in the United States today. This is reflected in the increased numbers of drug development programs underway in companies, and the corresponding growth in company requests for development phase meetings with FDA, as shown in Figure 3.

[1] NME = New Molecular Entity; NDA = New Drug Application; BLA = Biologic Licensing Application; CBE = Changes-Being-Effected

Figure 3. FDA Commercial Investigational New Drug (INDs) with Activity and Formal Meeting Requests 2004 vs. 2016

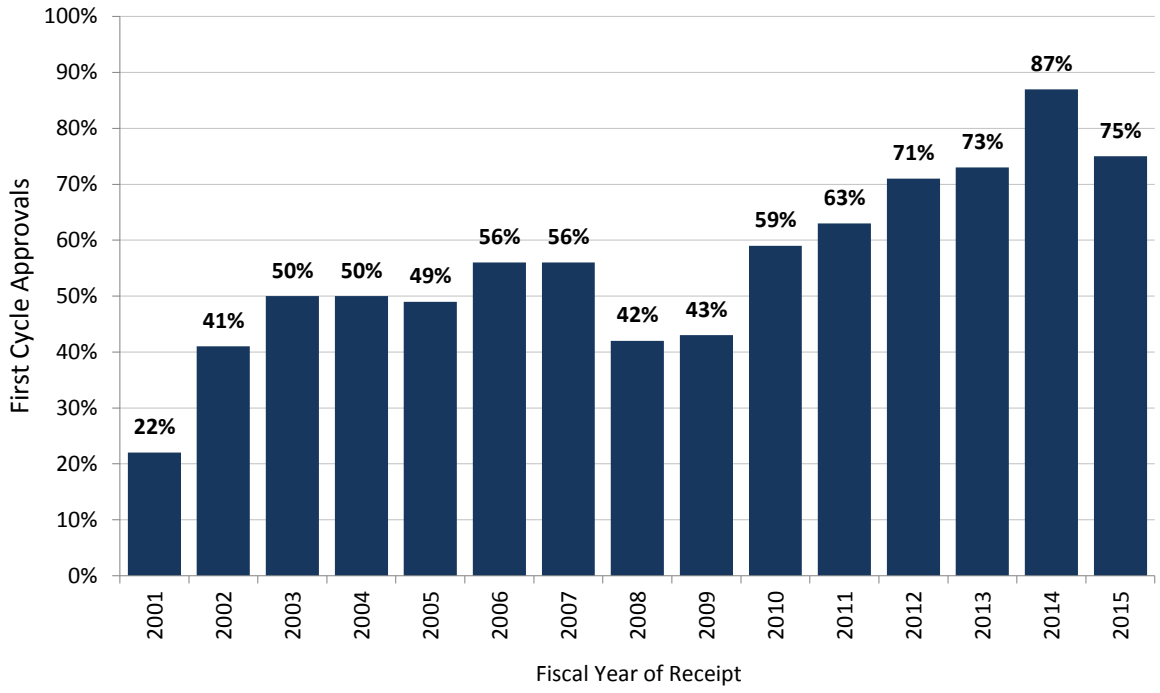


- IND Data represents a 12 month Academic period of July 1st-June 30th
- Activity is defined as any incoming submissions received within the reporting period on/after the date of the new IND application.
- Meeting Data as of 9/30/2016.
- Data includes activity for both FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

The volume of formal meetings requested by drug sponsors has steadily grown over the course of PDUFA. Early and frequent communication between sponsors and FDA serves to improve the efficiency of drug development. Indeed, it is one of the cornerstones of the Breakthrough Therapy program. FDA-sponsor meetings help sponsors navigate key milestones during drug development, support the assembly and submission of sponsors' marketing applications, and enable sponsors to clarify requirements for complete application submissions and potentially avoid the need for an additional review cycle.

The improvement in the quality of drug development programs and the submitted applications, supported by these PDUFA-enabled consultations between FDA and drug sponsors, is but one explanation for the observed trend toward higher first cycle approvals of applications for novel drugs (referred to as new molecular entity (NME) NDAs and BLAs), as shown in Figure 4.

Figure 4. FDA NME NDA/BLA First Action Approval Rate



- Multiple applications pertaining to single new molecular/biologic entity (e.g. single ingredient and combinations) are only counted once. Therefore, the numbers represented here for filings are not indicate 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.
- Data includes activity for both FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

Development-phase consultations can be particularly helpful in support of the most innovative drug programs. Of the NME NDAs and BLAs that FDA approved in calendar year (CY) 2016, over one-third were indicated for rare diseases. In addition, over one-third (36 percent) of the drugs approved by the Center for Drug Evaluation and Research were first in their drug class and over eighty percent (86 percent) were approved first in the United States.

While a standard review is typically completed in ten months, FDA expedites review for priority drugs to be completed within six months. Priority drugs are generally targeted at severe illnesses with few or no available therapeutic options. They typically receive greater assistance from FDA reviewers throughout the development process, including providing advice in the design and implementation of the clinical trials necessary to demonstrate product safety and effectiveness.

In 2016, over 60 percent of NME NDAs and new BLAs approved by FDA benefited from one or more of FDA's expedited programs.

Expanded Access to Investigational Products

While the best means of providing access to useful medical treatments for all Americans is to approve drugs demonstrated to be safe and effective as quickly as possible, FDA also recognizes circumstances in which there may be value to patients and physicians in having access to products prior to marketing approval. In some cases where an individual has a serious or life-threatening disease and lacks a satisfactory therapy, that individual may believe that a promising but not yet fully evaluated treatment is his or her best choice.

FDA allows for access to investigational products through clinical trials and the Agency's Expanded Access program. Clinical trials collect the necessary clinical information needed for FDA review and, if appropriate, approval, of investigational drugs, thereby making the drug widely available to patients. However, there are times when an individual cannot enroll in a clinical trial. In these cases, the patient may be able to gain access to an investigational therapy through the Expanded Access program.

In order for an individual patient to qualify for the Expanded Access program, several criteria must be met, including that the patient must have a serious or life-threatening disease or condition and no comparable or satisfactory alternative therapy. The patient's physician then approaches the pharmaceutical company to ask for its agreement that it will provide the drug being sought. The company has the right to approve or disapprove the physician's request. If the company agrees to the physician's request, the physician can then apply to FDA for

authorization to proceed. Should they do so, they are highly likely to be allowed to proceed with the expanded access use. FDA has authorized more than 99 percent of the requests received in Fiscal Years 2010-2015. Emergency requests are usually granted immediately over the phone and non-emergencies are processed in a median of four days.

Access to investigational products requires the active cooperation of the treating physician, industry and FDA in order to be successful. In particular, the company developing the investigational product must be willing to provide it – FDA cannot force a company to manufacture a product or to make a product available. Companies might have their own reasons to turn down requests for their investigational products, including their desire to maintain their clinical development program or simply because they have not produced enough of the product.

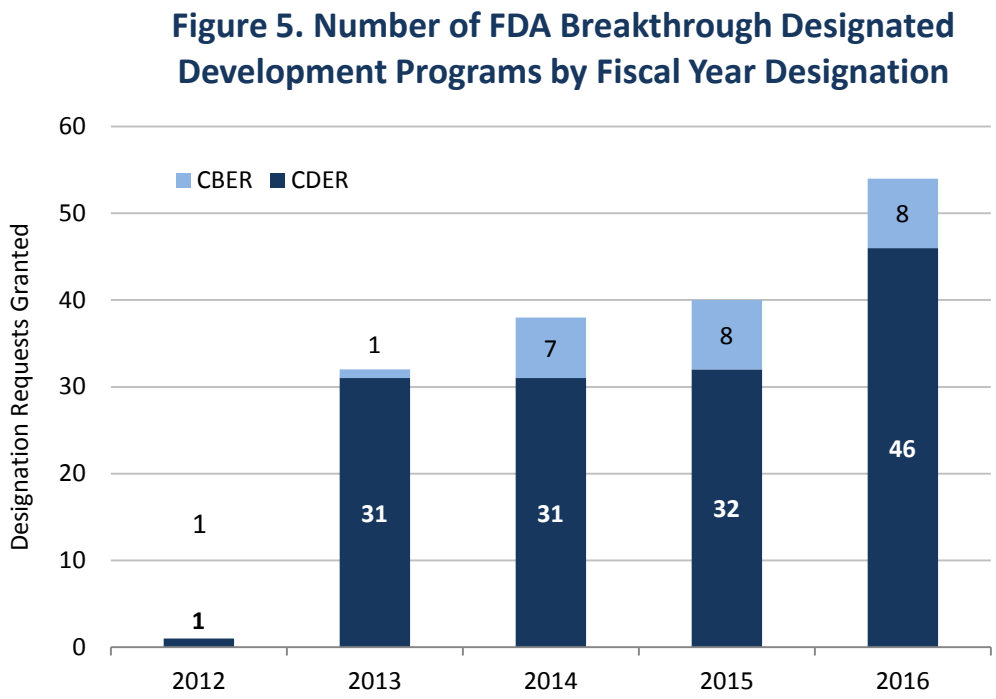
For over 20 years, FDA has been committed to ensuring that this program works well for patients and has recently made significant improvements to its functioning and efficiency.

Breakthrough Therapy Designation

The Breakthrough Therapy (BT) program, authorized by the FDA Safety and Innovation Act (FDASIA), has further enhanced the engagement of FDA and sponsors during drug development. This program, which is for new drugs to treat serious and life-threatening diseases with unmet medical need, calls for intensive FDA-sponsor consultation during development, when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints.

Given the known benefits of development-phase consultation with FDA, the BT designation has been much sought after by sponsors. As of November 30, 2016, FDA had received 492 requests for BT designation and had granted 165 requests. Figure 5 shows the trend of increasing numbers of development programs.

Figure 5. Number of FDA Breakthrough Designated Development Programs by Fiscal Year of Designation



Although oncology, hematology and antiviral products account for the largest share of BT designation requests in CDER, it should be noted that BT requests and the granted designations and ongoing programs span the entire spectrum of disease areas as shown in Figure 6a, reflecting granted designations as of November 30, 2016. In CBER, most of the BT designation requests and granted designations are for gene therapies, vaccines and immunotherapies as shown in Figure 6b.

Figure 6a. CDER Breakthrough Therapy Requests Granted by Product Type

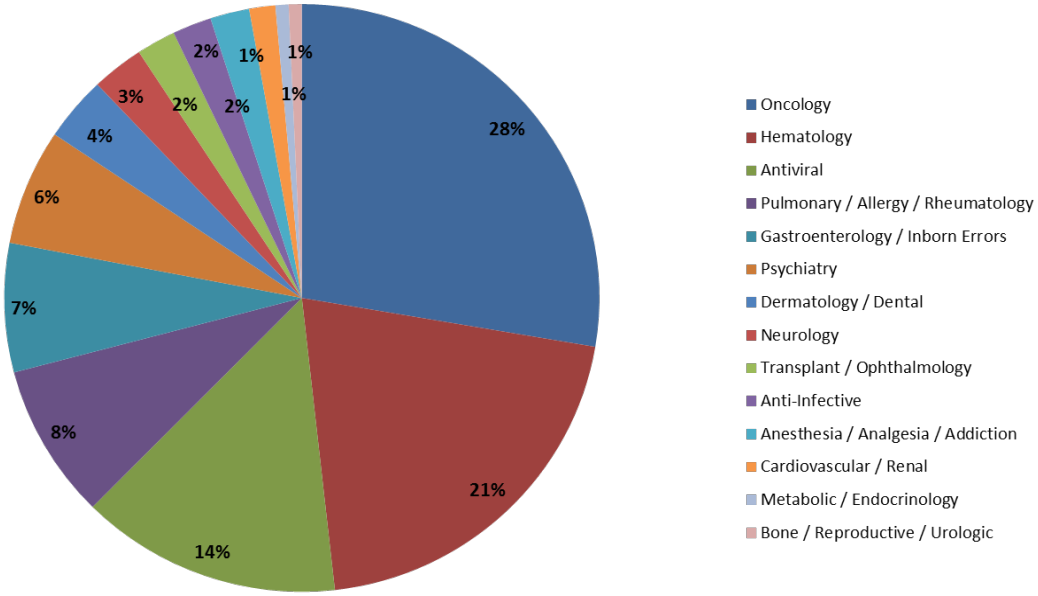
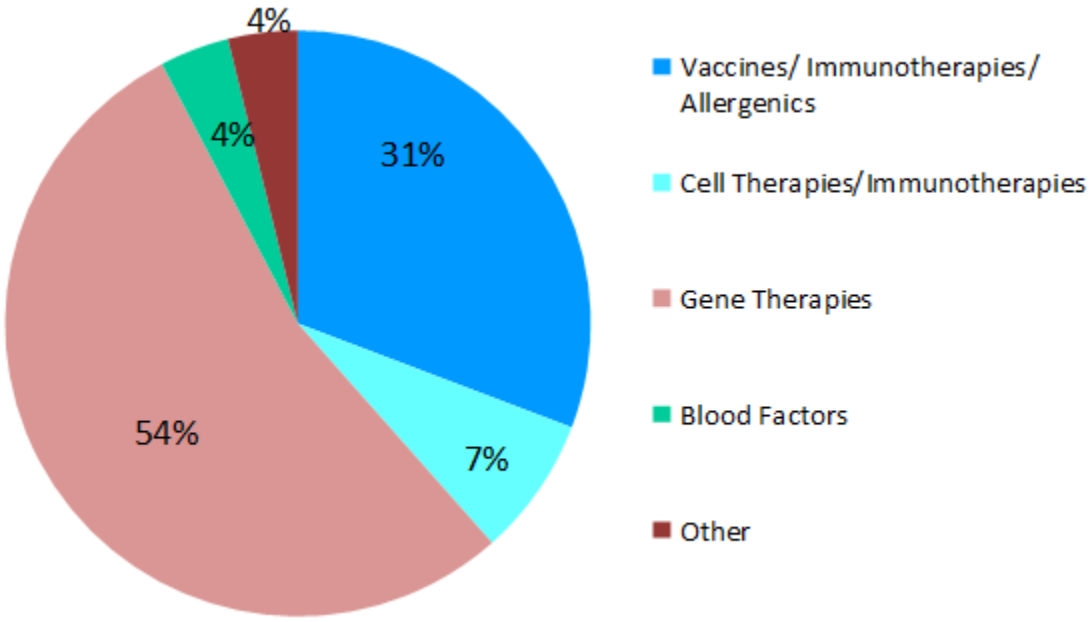


Figure 6b. CBER Breakthrough Therapy Requests Granted by Product Type



Data as of 12/1/16. Figures include total # of granted breakthrough designations for drug/indications under active IND development but have not yet received marketing approval or rescission decision.

PDUFA V

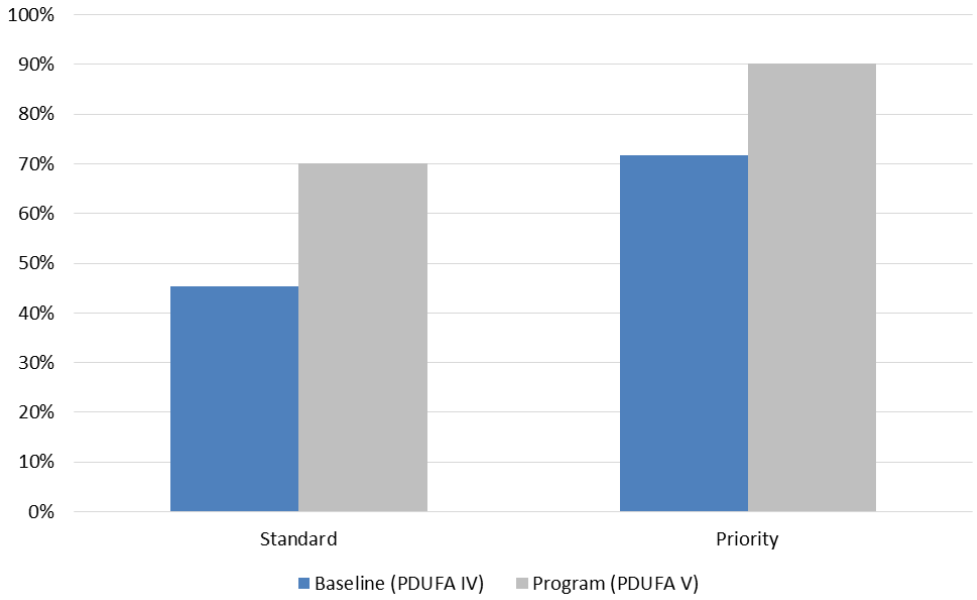
We are currently in the final year of the PDUFA V program. Over the years since the start of

PDUFA I in 1992, the complexity of scientific and clinical issues in the study of new drugs has grown, including use of genetic targeting, biomarkers, novel trial designs, plans and programs to ensure effective post-market risk management. These approaches and issues were less common or nonexistent at the start of PDUFA. In addition, predictability and increased communication with FDA during drug development and application review emerged as a top priority for drug sponsors.

PDUFA V sought to achieve a better balance between the desire for increased communication with sponsors and the need to ensure adequate review time for the most complex and innovative products reviewed by FDA. This resulted in a cornerstone of the PDUFA V agreement, a new program for NME NDAs and BLA reviews that is designed to promote greater transparency and improve communication between the FDA review team and the applicant. We anticipated that the increased communications before application submissions and at key points within the first review cycle would ensure that FDA had access to all of the information that might inform and enable a first-cycle approval for those applications that could be approved, avoiding unnecessary additional cycles of review. This would enable faster access to new drugs for the patients who need them and would help reduce avoidable costs for drug sponsors.

A key measure of program success is the percentage of applications approved in a single, first review cycle. Figure 7 illustrates the success of the PDUFA V NME Program in achieving its first cycle review goals for both standard and priority reviews. The figure presents the share of first-cycle approvals for priority and standard NDAs and BLAs filed. First cycle approvals for NME NDAs and new BLAs have been significantly higher under the new PDUFA V review program.

Figure 7. Findings of the Final Assessment of the PDUFA V NME Review Program



Data includes activity for both FDA's Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research.

Other PDUFA V enhancements include improved communications during drug development, strengthening the rare disease program, exploring new methods for regulatory science, and implementation of structured benefit-risk assessment. PDUFA V also provided for additional drug safety enhancements focused on standardizing the design of Risk Evaluation and Management Systems (REMS) and using the Sentinel Initiative, FDA's active surveillance systems for post-market safety (see PDUFA IV), to evaluate drug safety issues. This has prepared the way for expanded reliance on the data from Sentinel.

Patient-Focused Drug Development

As part of the PDUFA V benefit-risk assessment initiative, FDA and industry recognized that patients are uniquely positioned to inform aspects of FDA's benefit-risk assessment, particularly the understanding of the disease and its severity and the adequacy of existing treatment options. Therefore, FDA committed to hold at least 20 public meetings over the five year period, with each meeting focused on obtaining direct patient input in a specific disease area. This initiative, referred to as "patient-focused drug development," has since been described as potentially

transformational in advancing the role of the patient in drug development and decision-making. Although initially committing to conduct 20 meetings, FDA is on track to conduct 24 meetings each in different disease areas. The goal of the meeting is to hear from patients and their caregivers about the impact of their disease on their lives, and for FDA to hear more about what treatment benefits would be most meaningful to patients, and what treatment burdens are most important to consider. Following each meeting FDA develops a *Voice of the Patient* report to capture what was heard in the meetings (and comments from patients received in the docket); these documents serve as a valuable reference for FDA reviewers in subsequent drug reviews and related decision making.

Patient-focused drug development has provided key learnings for FDA that are being carried forward and integrated into our methods and approaches to development and decision making. We recognize that patients with chronic serious disease are experts on what it is like to live with their condition, and we have learned that they want to be as active as possible in the work to develop and evaluate new treatments. In the past, patients' "chief complaints" were often not factored explicitly into drug development plans (as endpoints and measures of drug benefit planned in trials), and this is an area of needed attention going forward. Although the PDUFA V patient-focused drug development initiative was intended as a pilot to elicit broader patient input, a key question for the agency was how to best build upon this pilot to advance the science and processes for effective incorporation of the patient's voice in drug development and decision making.

In preparing for PDUFA VI reauthorization discussions, FDA has worked to build on the successes and learnings of PDUFA V and pursue new areas of opportunity for innovation in the enhancement of regulatory decision tools and new potential sources of evidence to inform drug development and review.

PDUFA VI Reauthorization Process

Congress directed the Agency to reach out to all stakeholders to solicit thoughts and insights on PDUFA reauthorization and changes to PDUFA performance goals. FDA held an initial public meeting on July 15, 2015, which included presentations by FDA and representatives of different

stakeholder groups, including patient advocates, consumer groups, regulated industry, health professionals, and academic researchers. A transcript and Webcast recording are available on FDA's website at *https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm*.

Based on comments to a public docket, and the Agency's own internal analyses of program challenge areas, FDA developed a set of potential proposed enhancements for PDUFA VI and began negotiations with industry. Parallel discussions with public stakeholders were held monthly from September 2015—February 2016 to update participants on ongoing negotiations and solicit thoughts. Meeting minutes were posted on FDA's website and are available at *https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm*.

A final public meeting was held on August 15, 2016, to discuss the PDUFA VI agreement and engage with interested parties on proposed recommendations. A summary of the agreement and a draft of the Commitment Letter were provided a month in advance of this discussion. Final PDUFA VI recommendations were transmitted to Congress in December 2016.

PDUFA VI Overview

Building on the success of previous agreements, PDUFA VI continues to support early and meaningful communication between FDA and drug sponsors to deliver safe and effective medications to Americans more quickly, and, expands on such communications by providing resources for the popular, highly successful, and resource-intensive Breakthrough Therapy program and streamlining review of products combining a drug or biologic with a device. It enhances drug development tools including biomarker qualification and provides resources to increase our understanding of how "real-world evidence" can be generated and used appropriately in regulatory decision making. The agreement also enables us to leverage the use of real-world health data by enhancing the capabilities of FDA's Sentinel System.

Many of these core provisions are explained in greater detail below.

Capturing the Patient Voice in Drug Development

Central to PDUFA VI, and its largest single investment component, are plans to elevate patient voices in developing new drugs to treat their diseases. The agreement shares the Committee's goals reflected in the 21st Century Cures Act ("Cures") – and the highest priority of our stakeholders – to leverage essential patient input and insights to fight disease.

We are building on the success of PDUFA V which established the Patient-Focused Drug Development (PFDD) program to obtain valuable patient perspectives. Areas of focus were carefully chosen based on a public process soliciting patient and stakeholder input. Under PDUFA VI, we look forward to engaging in a transparent, multi-stakeholder approach that will lead to development of the methods and approaches to ensure patients not only become active participants but informants to industry drug development and agency review. The performance commitments and matching resources to sufficiently staff this critical new work are intended to bridge from patient-focused drug development meetings to fit-for-purpose tools to collect meaningful patient input, including capturing information on the natural progression of disease.

To help identify sound and rigorous methods to capture science-based, disease-specific patient input, FDA has committed to enhance its staff capacity, hold a series of four public workshops, and develop four key guidance documents on needed methods and approaches. The Agency will also publish on its website a repository of publicly available tools as a resource for stakeholders and ongoing efforts.

We are gratified by the enthusiastic response within the patient community to PFDD, and look forward to working with the broader community to advance the science of patient input – and deliver new and better treatment options.

Building a Solid Foundation for Breakthrough Therapies

The Breakthrough Therapy program, authorized by FDASIA, has become one of the most popular components of the human drug review program with requests and designations far exceeding expectations.

The increase in promising new drugs to treat serious and life-threatening diseases with unmet medical need is, of course, a very good thing for both patients and public health. But the growth of the BT program has strained limited available review staff resources. A hallmark of the BT program is intensive Agency interaction with sponsors during the development process on complex products with transformative potential. This "all hands on deck" approach provides a sponsor of a designated breakthrough product with guidance from the Agency on efficient drug development beginning as early as the Phase I period, an organizational commitment to involve senior managers, and eligibility for rolling review. Many of the BT designations granted so far have been for rare disease indications.

The PDUFA VI agreement provides dedicated funding to ensure the sustained success of the BT program. Additional resources will enable FDA to increase review staff and to supplement resources for clinical pharmacology, statistics, and product quality. This renewed commitment will enable the Agency to continue to work closely with sponsors to ensure expedited development and review of breakthrough therapies for serious or life-threatening diseases.

Advancing Biomarker Development

FDA and industry share the goals of Cures to accelerate development of reliable biomarkers to advance important new therapies. Biomarkers are currently used throughout the drug development process, including as surrogate endpoints to support earlier evidence for regulatory decision-making when evidence from a clinical endpoint could take much longer or require many more patients to be studied.

FDA commonly uses surrogate endpoints in accelerated approvals where confirmatory evidence is required to verify the expected clinical benefit after marketing begins. Surrogate endpoints have been the basis for 60 percent of rare-disease approvals. Once a surrogate endpoint is well established to predict clinical benefit, surrogate endpoints can be used to support traditional approvals as well. For example, FDA regularly relies on a surrogate endpoint for approval of new therapies for diabetes (the HbA1C test, a measurement of hemoglobin with attached sugar in the blood that reflects the extent and persistence of elevated blood sugar) greatly expanding patient treatment options.

The PDUFA VI proposed enhancements include some of the same activities specified in Cures. PDUFA VI addressed the opportunity for application of biomarkers in two different areas, one involving proprietary use of a biomarker as a surrogate endpoint in a specific drug development program, and the other involving the more public process of biomarker qualification as a drug development tool.

FDA recognizes that early consultation can be important to an efficient development program when a sponsor intends to use a biomarker as a new surrogate endpoint that has never been used as the primary basis for product approval in the proposed context of use. The PDUFA VI commitments therefore provide for early consultation with the sponsor to enable the FDA review team to consult with senior management to evaluate the sponsor's proposal before providing advice to the sponsor on a critical aspect of their development program. This will enable FDA to discuss the feasibility of the surrogate as a primary endpoint, any knowledge gaps, and how these gaps should be addressed before the surrogate endpoint could be used as the primary basis for approval.

PDUFA VI also provides enhancements for the more public drug development tool qualification pathway for biomarkers. The biomarker qualification program was established to support FDA's work with external partners to develop biomarkers that aid in the drug development process. To facilitate the enhancement of the drug development tools qualification pathway for biomarkers in PDUFA VI, FDA proposes to convene a public meeting to discuss taxonomy and a framework with standards for biomarkers used in drug development, to develop guidance on biomarker taxonomy, contexts of uses, and general evidentiary standards for biomarker qualification, and to maintain a public website to communicate a list of biomarker qualification submissions in the qualification process.

Meaningful progress in developing additional biomarkers for public qualification requires collaboration among a wide range of stakeholders. FDA will continue to work with the National Institutes of Health, the Biomarkers Consortium, the Critical Path Institute and others to advance biomarker development.

Streamlining Combination Product Review

More streamlined oversight of combination products is another FDA and industry priority reflected in PDUFA VI. Under the proposed enhancements FDA will pursue improvements in inter-center and intra-center combination product review coordination and transparency for PDUFA products that are combination products regulated by CDER and CBER (PDUFA combination products). FDA proposes to enhance staff capacity and capability across the relevant medical product centers and the Office of Combination Products to more efficiently, effectively, and consistently review combination products. FDA also proposes to streamline the process for combination product review and to improve the Agency's ability to track combination product review workload, including a third party assessment of current practices for combination drug product review.

Our goal, consistent with Cures, is to enhance the overall efficiency, consistency, and predictability of combination product review without imposing new administrative burdens.

Under PDUFA VI enhancements FDA will also establish new performance goals and submission procedures for the review of human factors protocols for PDUFA combination products. These goals will be to provide the sponsor with written comments on these protocols within 60 days of receipt. The goals to provide written comments within 60 days will begin at the 50 percent level in FY 2019, and increase to 90 percent by FY 2021.

Advancing the Use of Complex Innovative Trial Designs and Model Informed Drug Development

FDA routinely works closely with industry to facilitate innovative approaches to drug development that maintain our high standards for drug safety and efficacy. PDUFA VI promises to encourage future efforts by advancing Model-Informed Drug Development (MIDD) and the use of complex innovative and adaptive clinical trial designs.

The development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources can be used to inform regulatory decision making, for example, in determining patient selection in clinical trials, individualized dosing for specific populations, or the need for post-marketing studies. To facilitate the development and application of these approaches during PDUFA VI, FDA proposes to convene a series of

workshops to identify best practices for MIDD, to conduct a pilot program, to develop guidance on MIDD, and to update policies and procedures, as appropriate, to incorporate guidelines for the evaluation of MIDD approaches.

To facilitate the advancement and use of complex adaptive, Bayesian, and other novel clinical trial designs during PDUFA VI, FDA proposes to convene a public workshop on complex innovative trial designs, publish guidance on complex innovative trial designs, to conduct a pilot program, and to update policies and procedures as appropriate to incorporate guidelines on evaluating complex innovative trial designs.

Utilizing Real-World Observational Data

It has been said that medical care and biomedical research are in the midst of a data revolution, and networked systems, electronic health records, electronic insurance claims databases, social media, patient registries, and other new sources may comprise an immense new set of sources for data about health and healthcare. In addition, these “real-world” sources can provide data about patients in the setting of their environments—whether at home or at work—and in the social context of their lives. There is little doubt that the new sources of data now becoming increasingly available to researchers, clinicians, and patients hold enormous potential for improving the quality, safety, and efficiency of medical care. More work is needed to understand both the promise and pitfalls of far-reaching technological changes, including the multiple dimensions of quality and fitness for purpose for appropriate use of such data in regulatory decision making.

FDA recognizes the potential value of utilizing "real-world" evidence in evaluating not only the safety of medications but also their effectiveness. To better understand how real-world evidence can be generated and used appropriately in product evaluation, FDA proposes to conduct one or more public workshops, as well as other appropriate activities (e.g. pilot studies or methodology development projects). Considering the available input, FDA will then publish draft guidance on how real-world evidence can contribute to the assessment of safety and effectiveness in regulatory submissions.

Under PDUFA VI, FDA also proposes to pursue a more well-established use of real-world evidence to support post market drug safety surveillance utilizing Sentinel. FDA's Sentinel Initiative is a long-term program designed to build and implement a national electronic system for monitoring the safety of FDA-approved medical products. FDA recently transitioned from the Mini-Sentinel pilot to the Sentinel System, but full utilization of the Sentinel System remains a work in progress. Continued development and integration of the Sentinel System is needed to realize the system's full value to the postmarketing safety review process.

To help realize the full value of the Sentinel System during PDUFA VI, FDA proposes to continue to expand the systems' data sources and core capabilities, to systematically integrate Sentinel into postmarketing review activities, to enhance communication practices with sponsors and the public regarding general methodologies for Sentinel queries, and to conduct an analysis of the impact of Sentinel expansion and integration for regulatory purposes.

Hiring and Retaining Highly Qualified Experts

To speed and improve development of safe and effective new therapies for patients requires that FDA hire and retain sufficient numbers and types of technical and scientific experts to efficiently conduct reviews of human drug applications. In order to strengthen this core function during PDUFA VI, FDA proposes to commit to completing implementation of: a modernized position management system; corporate recruiting practices; augmenting capacity with contractor support; establishing a dedicated scientific recruiting function; setting metric goals for human drug review staff hiring; and conducting a comprehensive independent assessment of hiring and retention system performance. We want to thank you again for providing vital new hiring authority in Cures. Cures will greatly improve FDA’s ability to hire and retain scientific experts in more complex and specialized areas and meet our growing responsibilities.

The hiring commitments proposed in PDUFA VI will complement Cures by supplementing the expertise and resources the Agency needs to perform its vital prescription drug mission.

Enhancing Management of User Fee Resources

FDA is committed to enhancing management of PDUFA resources and ensuring PDUFA user fee resources are administered, allocated, and reported in an efficient and transparent manner. In

PDUFA VI, the Agency proposes to establish a resource capacity planning function to improve its ability to analyze current resource needs and project future resource needs, modernize its time reporting approach, conduct an evaluation of PDUFA program resource management, and publish a five-year PDUFA financial plan with annual updates.

In addition, under PDUFA VI, FDA proposes to enhance the program fee structure and related mechanisms, to achieve increased predictability, stability, and efficiency. The current overall PDUFA fee structure and the fee setting process were established in 1992. Both FDA and industry recognize that updating some elements of the fee structure and the fee setting process will enhance administrative efficiency and the predictability and stability of fee amounts and revenues and improve FDA's ability to engage in long-term financial planning. FDA proposes to shift a greater proportion of the target revenue allocation to more predictable fee-paying types (20 percent to applications; 80 percent to Program fees), and make other modifications to improve efficiency and stability including discontinuation of the establishment and supplement fees, modifying the annual fee billing date to minimize the need for multiple billing cycles, and other technical changes.

We are incredibly proud of the progress FDA has made to speed medical products to patients through the PDUFA program, and look forward to working with Congress and industry to significantly further progress.

MDUFA

Enacted by Congress in 2002, MDUFA is a user fee program through which medical device companies pay fees to FDA when they submit a request for marketing authorization or register their establishments with FDA. The program includes commitments between the U.S. medical device industry and FDA to improve the predictability, transparency, and consistency of regulatory processes, which are intended to reduce the time for FDA to make a decision about whether to authorize marketing of a device.

MDUFA has been reauthorized every five years since Congress created the program. As the program has evolved, FDA and industry have successfully negotiated agreements to improve patient access to medical devices and streamline regulatory processes.

During the 2012 MDUFA III testimony, many of you may recall that the program was in a much different place[2]:

- In FY 2009, it took an average of 427 days to reach a decision on a premarket approval application (PMA), the submission type required for the highest-risk devices.
- In FY 2010, it took an average of 150 days to reach a decision on a premarket notification submission (also known as a 510(k)), the submission type required for low to moderate-risk devices.

Thanks to the investment provided by industry, and direction provided by Congress, we have made substantial progress toward reducing decision times. As of 2015:

- It took an average of just 276 days to reach a decision on a PMA, a 35 percent decrease in six years; and
- It took an average of just 133 days to reach a decision on a 510(k), an 11 percent decrease in five years.

Further, we went beyond our MDUFA III commitments to reduce the median time to approve an Investigational Device Exemption (IDE) study to just 30 days in FY 2015, down from 442 days in FY 2011—a 93 percent decrease in four years. This improvement has allowed companies to begin their clinical trials earlier so they can begin collecting data to support a decision on their submission requesting marketing authorization. In addition, we reduced the average time to reach a decision on a De Novo classification request, the submission type typically used by novel low or moderate-risk devices, to 259 days in FY 2014, down from 770 days in FY 2009—a 66 percent decrease in five years.

[2] See Appendix A: "U.S. Food and Drug Administration, Center for Devices and Radiological Health: Progress in Achieving Our Vision of Patients First."

Changes we have made at CDRH to our culture, policies, and processes—in addition to user fee funding and changes to federal law—have resulted in an improved medical device pipeline and innovative technologies being introduced in the U.S. earlier than in the past. For example, since 2009, the number of innovative devices we have approved has almost quadrupled. In 2016, we approved 91 innovative devices—the highest of any year since the user fee program began in 2003. In 2015, we approved the second highest number of innovative devices.

An example of an innovative technology that FDA approved first in the world is the "artificial pancreas," something many members of this Committee supported. Working interactively with the device manufacturer from the earliest stages of development to assist in making this technology available as quickly as possible, FDA approved the first device in the world that is intended to automatically monitor glucose levels around the clock and automatically provide appropriate insulin doses.

While we have made progress in many areas, we also recognize that more work remains and there are additional opportunities for improvements. We look forward to working with industry and Congress to ensure there are sufficient user fees resources as we strive to make these improvements. MDUFA IV agreement includes a new quality management program that will enhance consistency and predictability in premarket review processes.

MDUFA IV agreement would also allow FDA to move forward in some critical and strategic areas such as strengthening our partnerships with patients[3]. Strengthening patient input will allow us to promote more patient-centric clinical trials, advance benefit-risk assessments that are informed by patient perspectives, and foster earlier access to new devices.

Another critical area supported by the MDUFA IV agreement is the development of the National Evaluation System for health Technology, or NEST[4]. The NEST is system owned and operated by multiple stakeholders that will use real-world data collected as part of routine clinical care. A robust NEST will enable manufacturers to harness real-world evidence that could enable them to drive down the time and cost of bringing a new device to market, expand the indications for

[3] See Appendix B: "Center for Devices and Radiological Health (CDRH): 2016-2017 Strategic Priorities – 2016 Accomplishments."
[4] See Appendix B: "Center for Devices and Radiological Health (CDRH): 2016-2017 Strategic Priorities – 2016 Accomplishments."

already approved devices, and meet postmarket reporting requirements. The NEST will also enable faster identification of safety issues, reducing harm to patients and liability for companies.

The MDUFA IV agreement, which was supported by a broad array of stakeholders during the public review of the draft agreement, will expedite the availability of innovative new products, and its enhancements will continue to increase the efficiency of FDA's programs. Improvements in total time to decision, transparency, consistency, and predictability will benefit industry, healthcare providers, and, most importantly, patients.

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).

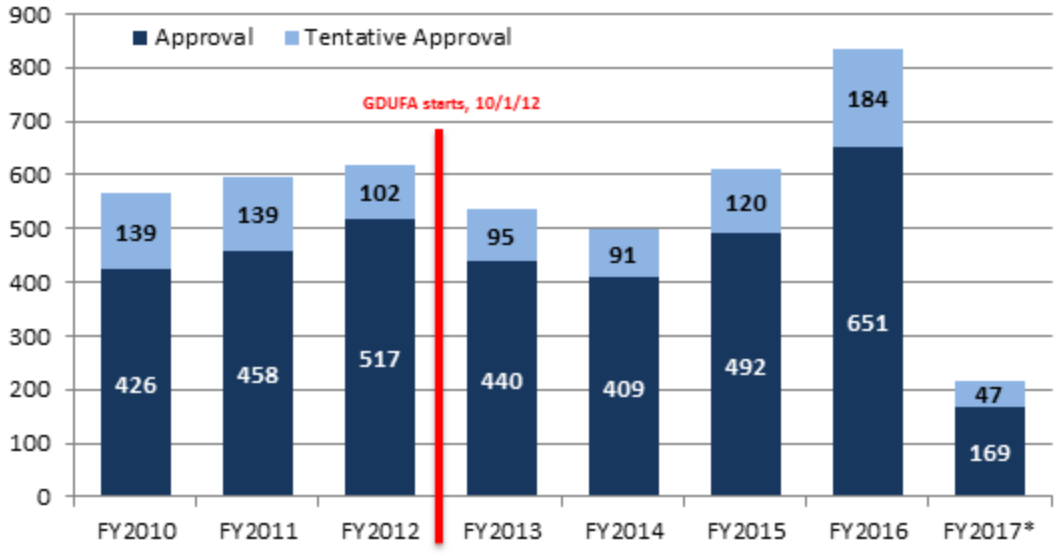
Under GDUFA I, industry agreed to pay approximately $300 million in fees each year of the five year program. In exchange, FDA committed to performance goals, including a commitment to complete reviews in a predictable time frame.

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 8. 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.

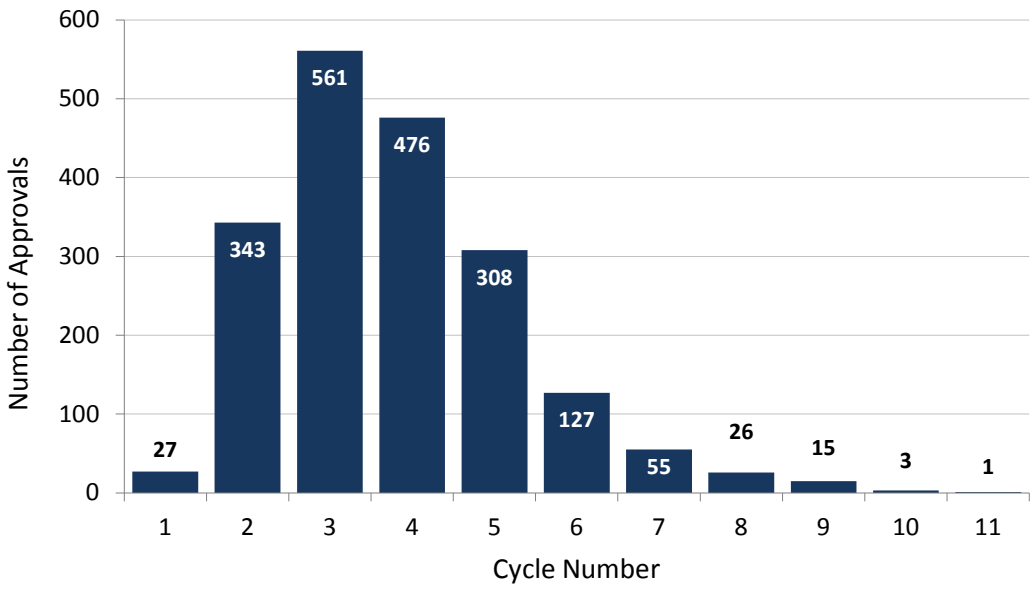
How did FDA achieve these results?

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 9. Review Cycles for ANDAs
2009 through July 2014



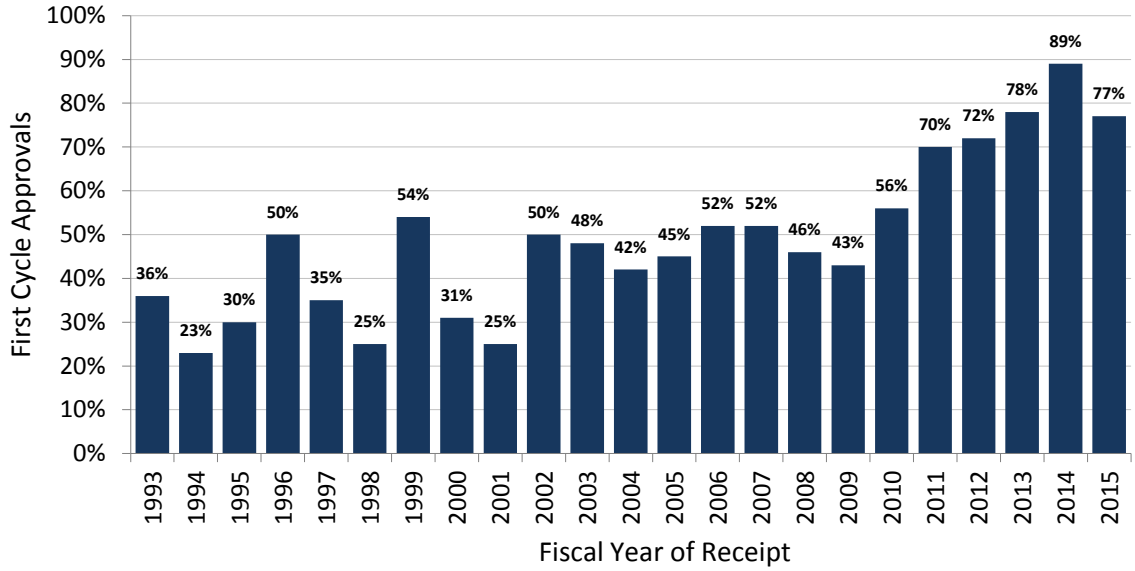
This has resulted in the submission of numerous amendments to applications by the companies to correct deficiencies in the original ANDAs, and comprises a huge amount of re-work for FDA and industry alike. Currently, about 1,800 applications are back with industry awaiting resubmission to correct deficiencies 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 percent. Now it is about 80 percent 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 10. First Cycle Approval Rate Under PDUFA

CDER NME NDAs/BLAs†

First Action Approval Rate



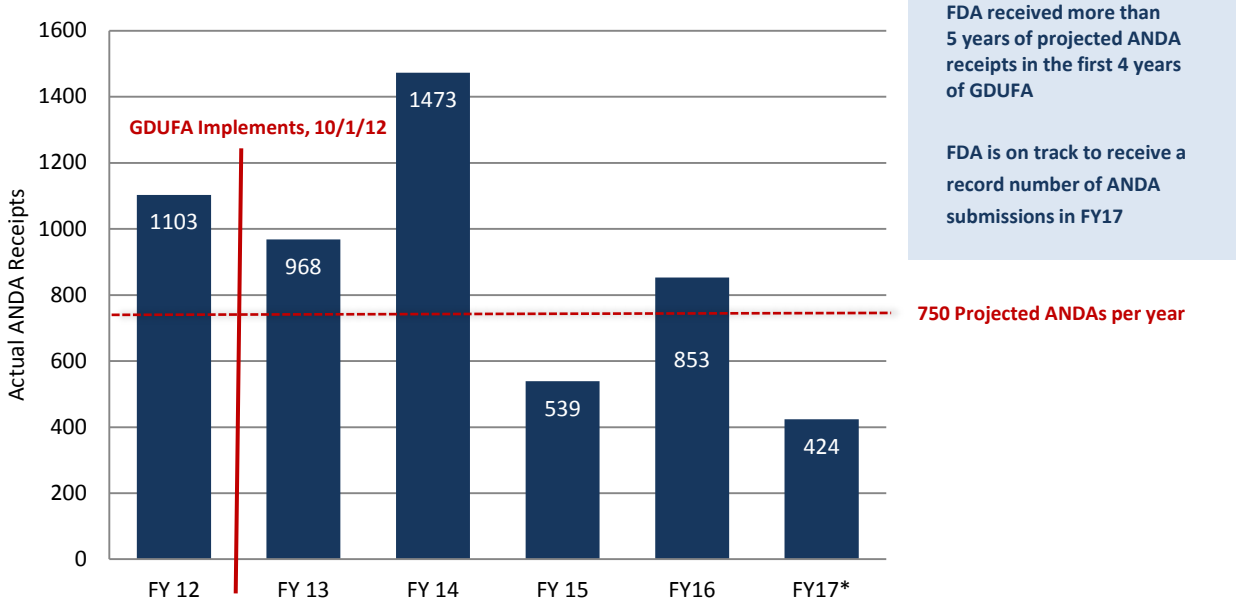
Data as of 12/9/2016

† 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 11. 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.

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.

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.

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.

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

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

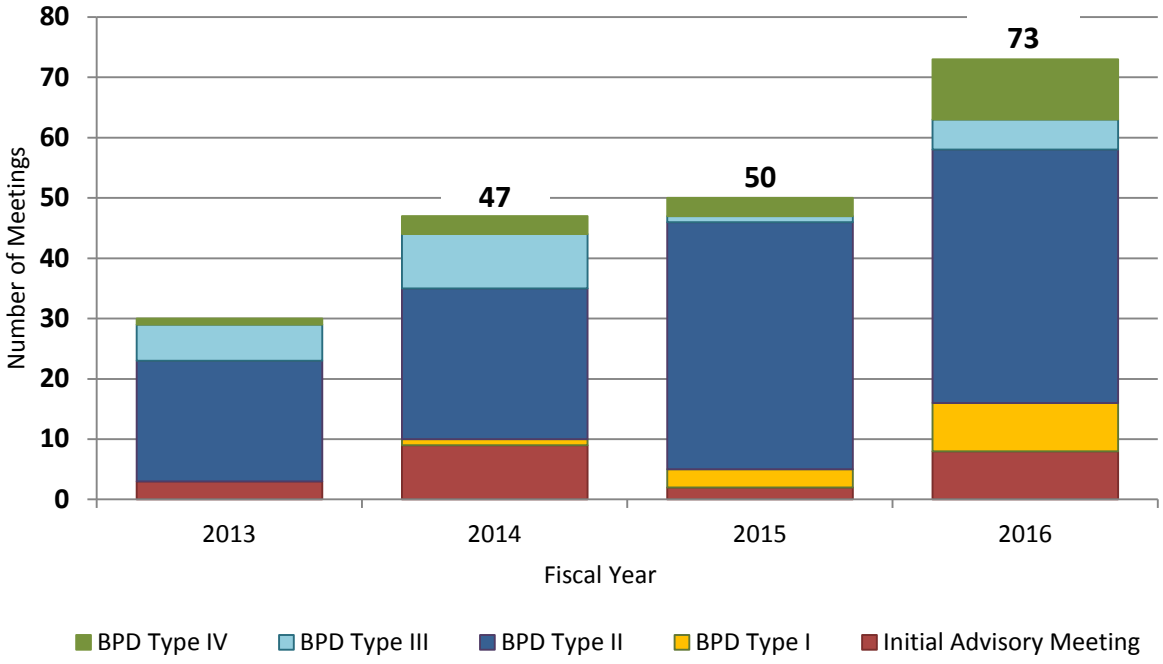
support the abbreviated development process leading to the approval of safe and effective biosimilar products for patients.

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 C.

As shown in Figure 12 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 12. 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 Cures bill. 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.

The Path Forward

BsUFA I provided critically needed funding for FDA to implement the beginning of a successful biosimilars program. We look forward to working with Congress and industry as we continue to strengthen 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.

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 to ensure that FDA has the resources needed to conduct reviews in a timely fashion.

CONCLUSION

The FDA user fee agreements have revolutionized the drug and device review process in the United States since they were adopted, 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 towards the same goal. User fees provide a critical way to ensure that FDA has the resources needed to conduct reviews in a timely fashion. While we have made demonstrable progress in partnering to bring medical products to market in as timely a manner as possible, we know that more work remains to be done to further enhance and optimize our processes. The reauthorization of PDUFA,

MDUFA, GDUFA, and BsUFA will allow FDA to build upon the demonstrated success of these programs, and in so doing, further benefit patients and affirm our nation's standing as a global leader in biomedical innovation.

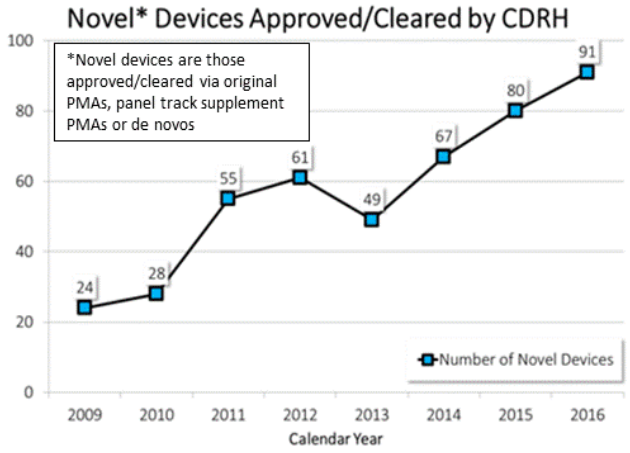
Appendix A

U.S. Food and Drug Administration
Center for Devices and Radiological Health:
Progress in Achieving Our Vision of Patients First

In the early part of this decade, industry argued that FDA regulation hindered innovation and contributed to the growing number of device companies seeking marketing authorization for their devices abroad before introducing them in the United States, and the increasing gap between when a device is approved in another country and when it is approved in the US. This reality, its adverse impact on patients, plus CDRH's own awareness of our declining performance over almost a decade, led CDRH to implement new programmatic changes. These changes, along with increased user fee funding and changes in Federal law have helped us strengthen our performance and better address the rapidly-evolving field of medical device innovation. To guide us in our mission to improve the health and quality of life of patients, in 2012 we adopted a new vision[5] to reflect this change in mindset, that: **Patients in the US have access to high-quality, safe and effective medical devices of public health importance first in the world.**

Doing Business Better

Since late 2009, CDRH has continuously improved the way we do business through a series of culture, policy and process changes. This can be seen through our commitment to providing excellent customer service, new patient-centered paradigms, and our strong performance across a range of objective measures, including the time it takes to review several types of medical device submissions. These improvements are reflected **by the nearly four-fold increase in the annual number of novel medical device approvals.**

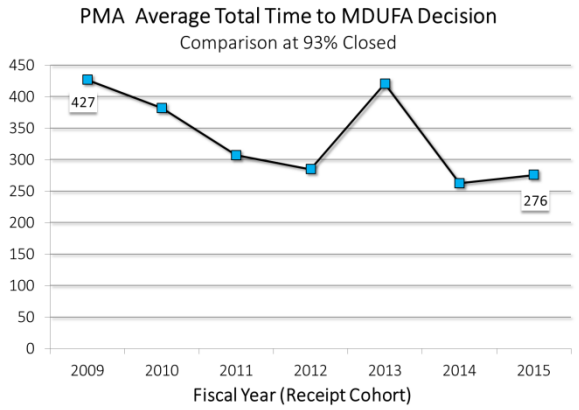


Fast Facts CDRH oversees approximately **175,000 medical devices** on the US market, more than **18,000 medical device manufacturers,** and more than **25,000 medical device facilities worldwide.** Each year we receive some **22,000 premarket submissions** (includes supplements and amendments) and more than **1.4 million reports on medical device adverse events and malfunctions**.

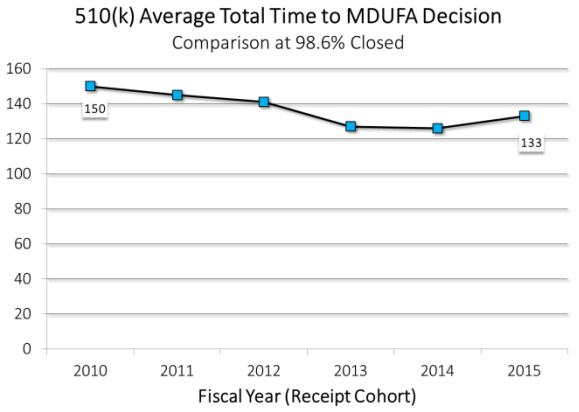
[5] CDRH Mission, Vision and Shared Values

Time Time, with its cost implications, plays a critical role in an innovator's decision as to whether and when to bring a new technology to the US. What good is a new technology if patients do not have timely access to it? How helpful is a new technology that doesn't benefit patients or poses unacceptable risks? By reducing the time of every regulatory stage of the total product life cycle, including the review of medical device submissions, while still assuring robust but appropriate (least burdensome) evidence generation and high-quality decision making, we help patients get access to safe and effective medical technologies and foster innovation. After steadily worsening performance from 2002 to 2010 on a variety of measures, including premarket review times, CDRH has reduced the decision time on all key premarket submission types.

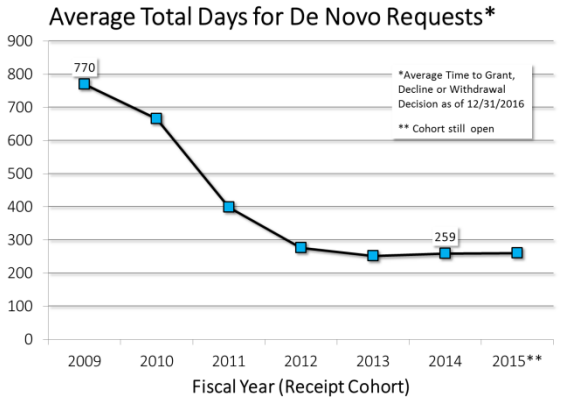
PMA While premarket approval applications (PMAs) only account for approximately one percent of all premarket medical device submissions, they represent medical devices with the highest risk to patients (Class III devices) and, therefore, require more data and a more rigorous review by CDRH. In 2009, it took an average of 427 total days to reach a decision on a PMA. **By 2015, we had reduced the total decision time by 35 percent.**



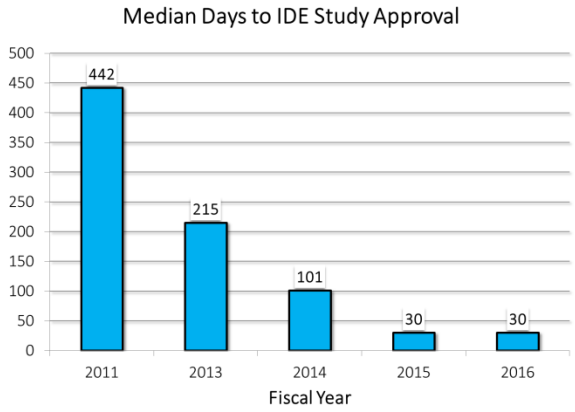
510(k) Named after its section number in federal law, this category represents the bulk of premarket submissions for medical devices. Manufacturers submit 510(k)s to CDRH for devices with low to moderate risk to patients (Class II), and our review standard is based on substantial equivalence (whether a device is at least as safe and effective as a device already on the market). In 2010, it took an average of 150 total days to reach a decision on a 510(k). **By 2015, we had reduced the total decision time by 11 percent.**



De Novo *De novo* classification is a pathway that enables manufacturers of certain low to moderate risk novel devices for which there are no similar marketed devices to come to market, instead of having to submit a PMA. In 2009, it took an average of 770 total days to reach a *de novo* decision. **By 2014, we had reduced the total decision time by 66 percent.**



IDE Manufacturers submit Investigational Device Exemptions (IDEs) for certain devices they want to study via a clinical trial. CDRH reviews an IDE submission before a manufacturer can begin to collect clinical data that may be necessary for future approval. **CDRH slashed median review times for IDE full approvals by more than a year** between 2011 and 2015.



Doing Business Different

Since 2009, CDRH has been evaluating all of our programs to address concerns from patients, industry, health care providers, our own staff, and other customers about issues including review times, backlogs, and our expertise in increasingly complex technology. We have sought to address these concerns by **changing our culture** to put **patients first** and recognizing that **advancing innovation and assuring patient safety are not mutually exclusive**, revising or eliminating old policies, and developing new policies and approaches with an eye on meeting measurable objectives. Increased medical device user fees have supported these efforts so that we are better positioned to respond to the needs of patients.

•Clinical Trials In addition to dramatically improved performance[6] in reviewing IDEs, CDRH has encouraged the use of **innovative methodologies and study designs in clinical trials.** We recognize that manufacturers need CDRH input early and often so that the ultimate **device review process moves as quickly and smoothly as possible.** In 2013, CDRH issued final guidance for manufacturers on early feasibility studies to encourage conducting these studies in the US. Innovators tend to market their technologies sooner in countries where they elect to conduct their early clinical studies. Since 2013, **the number of early feasibility studies approved has more than doubled—from 17 in FY 2013 to 40 in FY 2016.**

CDRH encourages the use of innovative clinical trial designs and statistical methods such as adaptive clinical trials[7] and Bayesian statistics[8] because, where appropriate to use, they can reduce the time and cost of a clinical study. In recent years, many devices have come to market based on the results of clinical trials using adaptive trial designs. **For the period from 2007 to May of 2013, CDRH received 201 submissions that were adaptive.**

CDRH continues to develop computational models that can, in some instances, supplement or replace data from clinical investigations, such as the Virtual Family (VF)[9]—a set of highly detailed, anatomically correct, computational whole-body models, designed to mimic humans of both sexes at various stages of growth. **Since 2007, more than 160 submissions have included Virtual Family research.**

[6] CDRH Clinical Trial Enterprise Targets and Performance
[7] Guidance Document: Adaptive Designs for Medical Device Clinical Studies Issued July 27, 2016
[8] Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials
[9] Virtual Family

•Flexible, Risk-Based Regulatory Approaches

CDRH continues to adapt our oversight policies to emerging new technologies. In a manner consistent with our statutory mission, we now approach a medical technology by first asking whether active CDRH oversight will be value-added. If not, we take a less active regulatory approach. If it would, we focus on assuring timely patient access to technologies that will benefit patients by considering the device's innovation cycles and evidence generation needs.

For example, widespread adoption and use of digital health technologies is creating new and innovative ways to improve health and health care delivery. In **one of the biggest de-regulatory actions for CDRH in decades**, to foster greater innovation in the digital health space while promoting public health, we have exercised our enforcement discretion to cease subjecting certain lower-risk medical devices (such as apps for patient care management and medication reminders) to medical device requirements.

Additionally, balancing data needs between what's collected before the device comes on the market (premarket) and what's collected after it is on the market (postmarket) reflects our approach to best assure timely patient access to safe and effective devices.

In 2015, CDRH completed a retrospective review[10] of the benefit-risk profile of all types of high-risk devices to determine if we could reduce premarket data collection requirements for at least some devices. As a result, for 30 percent of high-risk medical devices, **CDRH determined, based on the current body of evidence and experience, we could consider some devices candidates for down-classification, eliminate some data requirements or shift some premarket data requirements to the postmarket setting**. In 2016, CDRH reached out to stakeholders for input on the results of the retrospective reviews, in order to determine next steps.

•Patient-Centered Benefit-Risk

For the past 5 years, CDRH has encouraged the use of **a more flexible, patient-centric, and transparent benefit-risk framework** to evaluate medical devices, starting with a 2012 guidance on the factors to consider when making benefit-risk determinations in support of device premarket approval decisions, which includes patient perspectives on potential benefits and risks. We are focusing more on what matters to patients.

In 2016 and 2017, CDRH expanded this approach by revising the 2012 guidance to include additional patient-centric factors[11], and issuing two additional benefit-risk guidance documents: one which outlines the principal factors CDRH considers when making benefit-risk determinations during the premarket review process for IDEs[12], and one which outlines factors to consider when determining whether and what postmarket actions[13] we may take to address a problem, such as a recall, based on the benefits and risks of that action to patients.

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[10] CDRH Strategic Priorities and Updates

[11] Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and DeNova Classification (Aug. 24, 2016)

[12] Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Investigational Device Exemptions

[13] Guidance Document: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Product Availability, Compliance, and Enforcement Decisions

•Patients as Partners CDRH had traditionally determined whether the benefits of a device outweighed its risks based on the trade-offs we thought were acceptable. However, patients who live with a disease or condition often have their own perspectives on what benefits and risks related to medical devices they are willing to accept. CDRH collaborates with patient scientists and other experts outside the FDA to help us advance the scientific field of assessing patient preferences and incorporate the patient perspective into our benefit-risk assessments and decision-making.

For example, in 2014, CDRH funded a collaborative study on patient preferences that led to changes in our review paradigm for obesity devices, and used the results to inform our decision to approve the first medical device for treating obesity since 2007. Better understanding of patient preferences can also help **rejuvenate development pipelines**; since then, CDRH has approved or granted marketing applications for five more medical devices that address obesity or weight loss.

In 2016, CDRH issued a final guidance that outlined patient preference information (PPI)[14] that CDRH may use in decision making. Since then manufacturers have begun to submit—and we have approved—IDEs with patient preference studies.

CDRH's efforts to incorporate the voice of patients in our decision making also are reflected in medical device clinical studies, which have been increasingly assessing what matters most to patients. Between 2009 and 2014, the number of **premarket submissions that included clinical studies with patient reported outcomes (PROs) increased by more than 500 percent** and half of IDE pivotal clinical studies now include PROs.

In 2015, CDRH established the first FDA advisory committee focused on the interests and needs of patients, and recruited potential new members in 2016. **The Patient Engagement Advisory Committee[15] will hold its first meeting in 2017**.

•National Evaluation System for health Technology (NEST)

Despite rigorous premarket evaluation, we cannot fully understand how well a medical device works until it is used day-to-day by patients, caregivers, and clinicians. Premarket clinical trials provide critically important information but we don't understand the long-term benefit-risk profile until it is used in routine clinical practice. Currently our nation is limited in its ability to make widespread use of real-world evidence (RWE) to best inform all members of the medical device ecosystem.

CDRH intends for NEST to increase the quality and use of real-world data (RWD) collected as part of routine clinical care, which should also help reduce the time and cost of evidence generation. Ongoing implementation of the Unique Device Identification (UDI) system also will enable NEST to perform enhanced analyses of devices on the market, providing a clear and standard way to identify devices in electronic medical records.

CDRH is already relying on RWE to approve new devices, expand the indications for already marketed devices, and reduce the time and cost for device makers to meet their postmarket study requirements. In

[14] Guidance Document: Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling

[15] The Patient Engagement Advisory Committee

2016, CDRH documented access to more than 28 million electronic patient records (from national and international clinical registries, claims data, and electronic health records) that included device identification and awarded $3 million to the Medical Device Innovation Consortium to establish the NEST Coordinating Center.

•Streamlining the Pathway from FDA Approval to Payer Coverage

Timely access to innovative medical technologies has been identified as a significant issue in the delivery of high quality health care. Manufacturers of innovative medical products have said that after undergoing the FDA approval process the availability of their products to consumers is often slow because, in order to obtain coverage and payment from third-party payers, the manufacturers must go through a second review process by such payers. Therefore, CDRH established the Payer Communication Task Force (PCTF) to facilitate communication between device manufacturers and payers to shorten the time between FDA approval or clearance and coverage decisions. By communicating earlier, manufacturers may design their pivotal clinical trials to produce both the data required for regulatory approval or clearance, and positive coverage determinations.

To support these efforts, CDRH and the Centers for Medicare & Medicaid Services (CMS) began to pilot an approach in 2011 called Parallel Review that would give eligible device makers the voluntary option for CMS to start their national coverage determination process while the device is under review by CDRH. This process serves the public interest by reducing the time between FDA marketing approval or clearance decisions and CMS national coverage determinations. In 2016, CDRH and CMS established Parallel Review as a permanent program. Last year, CDRH also established an additional opportunity for device manufacturers to invite CMS, private payers, or health technology assessment groups (HTAs) to join FDA pre-submission meetings to provide early feedback on clinical trial design.

EVIDENCE OF IMPACT

Our investments are starting to pay off. For example, in 2016, CDRH approved 91 novel medical devices—the highest number since the advent of the user fee program in 2003. This followed the second highest number from 2015, and continued a 7-year trend that has resulted in a marked increase in the annual number of novel device approvals since 2009. These novel technologies, which can help improve the quality of life of patients, especially those that require day-to-day maintenance and ongoing attention, are yielding promising results. In addition, several of these devices are reaching US patients much earlier than they would have in previous years.

• "Artificial Pancreas"

Approximately five percent of diabetics have Type 1 diabetes, also known as juvenile-onset diabetes. People with type 1 diabetes have to constantly monitor their glucose levels throughout the day and have insulin therapy through injection with a syringe, an insulin pen, or an insulin pump, to avoid becoming hyperglycemic (high glucose levels). Working interactively with the sponsor from the earliest stages of development to assist in making this technology available as quickly as possible while assuring it is safe and effective, **CDRH, in 2016, approved the first automated insulin delivery**

(AID) device in the world that is intended to automatically monitor glucose (sugar) and provide appropriate basal insulin doses—what some have called a first-generation "artificial pancreas[16]."

•Transcatheter Aortic Valve Replacement (TAVR) Therapy

About 80,000 surgical aortic valve replacements (SAVR) are performed in the US annually. One-third of these patients are at intermediate surgical risk for death or complications. An aortic valve replacement that can be inserted through the blood vessels or, in some cases, through the tip of the heart by a catheter, rather than through open surgery, could avoid the risks of surgery and provide an alternative effective treatment to patients who are in the "intermediate surgical risk" category.

In 2011, CDRH approved the first TAVR device in the US for patients who are not surgical candidates for SAVR, more than four years after the device entered the European Union (EU) market. When, in 2016, CDRH approved the expanded indication[17] for use for a TAVR device in patients at intermediate surgical risk for death or complications, the positive impact of CDRH initiatives was evident. The gap between EU and US approval for the expanded indication for use was reduced from over four years to only 18 days. US Medicare coverage is also a factor in patients' access to devices. For TAVR devices, access to real-world evidence—what NEST hopes to expand—proved to be a valuable asset. The US Medicare program immediately covered TAVR devices due to the ongoing collection of real-world evidence on these devices in a national registry—there was no delay between US approval and access to this technology. **As a result, more than 25,000 additional patients each year are now eligible for this life-saving procedure.**

•Diagnostics for National Emergencies

Accurate detection and diagnostics are critical to addressing national public health threats. For example, in 2016, CDRH authorized the use of fourteen diagnostic tests for Zika[18] virus under our Emergency Use Authorization (EUA) authority—twelve tests to diagnose active infection and two tests to assess whether individuals who may have recently been exposed to Zika were actually infected. This rapid action provided timely patient access to Zika tests before the summer of 2016, when officials detected the virus in the U.S. **Since 2009, CDRH has granted 50 EUAs, reauthorized 19 EUAs, and granted 30 amendments for tests to help meet the country's needs during a national public health emergency, such as outbreaks from Zika, Ebola, and H1N1.**

[16] The Artificial Pancreas Device System

[17] Press Release: FDA approves expanded indication for two transcatheter heart valves for patients at intermediate risk for death or complications associated with open-heart surgery – Aug. 2016

[18] Zika Virus Response Updates from FDA

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH (CDRH)

2016-2017 STRATEGIC PRIORITIES – 2016 ACCOMPLISHMENTS

Establish a National Evaluation System for Medical Devices

To successfully harness real-world evidence ("evidence from clinical experience") in an efficient manner, the U.S. must develop the necessary infrastructure – a National Evaluation System for health Technology (NEST).

Goal: Increase Access to Real-World Evidence to Support Regulatory Decision Making	
2016 Target	Results
25 Million By December 31, 2016, gain access to 25 million electronic patient records (from national and international clinical registries, claims data, and EHRs) with device identification.	**28.6 Million** Gained access to more than 28 million electronic patient records (from national and international clinical registries, claims data, and EHRs) with device identification using a variety of mechanisms, such as cooperative agreements and access through regulatory process.

Goal: Increase the Use of Real-World Evidence to Support Regulatory Decision Making	
2016 Target	Results
40% By December 31, 2016, increase by 40 percent the number of premarket and postmarket regulatory decisions that leverage real-world evidence. (compared to FY2015 baseline)	**85%** The number of premarket and postmarket regulatory decisions that used real-world evidence increased by 85 percent in 2016. (compared to FY2015 baseline)

Supporting Actions

In 2016, CDRH took a number of actions to achieve the goals and targets established for this priority.:

Establish the National Evaluation System for health Technology (NEST)

In Progress: A multi-stakeholder Planning Board and the Medical Device Registry Task Force issued a series of reports that outlined an organizational structure and infrastructure for the NEST Coordinating Center (February 2015[19], April 2016[20], September 2016[21], and August 2015[22]). In 2016, FDA awarded $3 million to the Medical Device Innovation Consortium (MDIC) to establish the Coordinating Center, and $1 million to other organizations to continue projects that generate real-world evidence on device performance.

Develop a framework for the incorporation of real-world evidence into regulatory decision making.

In Progress: Issued draft guidance[23] to describe how real-world evidence may be used to support pre- and postmarket regulatory decisions. Final guidance is planned for 2017.

[19] *Recommendations for a National Medical Device Evaluation System*
[20] *The National Evaluation System for health Technology: Priorities for Effective Early Implementation; Planning Board Report*
[21] *The National Evaluation System for health Technology: Priorities for Effective Early Implementation; Planning Board Report*
[22] *Recommendations for a National Medical Device Evaluation System*
[23] *Guidance Document: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices*

Partner with Patients

We believe that if CDRH is to successfully achieve a mission and vision in the service of patients, we must interact with patients as partners and work together to advance the development and evaluation of innovative devices, and monitor the performance of marketed devices.

Goal: Promote a Culture of Meaningful Patient Engagement by Facilitating CDRH Interaction with Patients	
2016 Target	Results
10 Organizations By December 31, 2016, establish one or more new mechanisms for CDRH employees to obtain patient input on key pre- and postmarket issues facing CDRH and foster participation of 10 patient groups.	**34 Organizations** CDRH staff participated in 21 patient interaction opportunities, involving 34 patient organizations.
50% By December 31, 2016, 50 percent of CDRH employees will interact with patients as part of their job duties.	**68%** More than 68 percent of CDRH interacted with patients in 2016. When asked, 99 percent of staff who interacted with patients described their interaction as meaningful and 89 percent as relevant to their jobs.

Goal: Increase Use and Transparency of Patient Input as Evidence in Our Decision Making	
2016 Target	Results
50% By September 30, 2016, 50 percent of PMA, *de novo* and HDE decisions will include a public summary of available and relevant patient perspective data considered.	**65%** In FY 2016, 65 percent of PMA, *de novo*, and HDE decisions included a public summary of available patient perspective data.
↑ By September 30, 2017*, increase the number of patient perspective studies (e.g., evaluating patient reported outcomes (PRO) or patient preference information (PPI)) used in support of premarket and postmarket regulatory decisions. (compared to FY 2015 baseline) **2017 Target*	**65%↑ PRO and 4↑ PPI** Increased by 65 percent the number of approved IDEs (pivotal studies only) with patient reported outcomes (PRO). Increased to four (from none) the number of patient perspective studies conducted by sponsors in support of pre- and postmarket regulatory decisions.

Supporting Actions

In 2016, CDRH took a number of actions to achieve the goals and targets established for this priority:

Patient Engagement Advisory Committee Convene the Patient Engagement Advisory Committee to discuss high priority topics regarding patient input in the total product lifecycle.

In Progress: CDRH chartered and began to recruit members for FDA's new Patient Engagement Advisory Committee (PEAC). PEAC members will be selected and announced in 2017.

Education and Training Develop education and training for CDRH staff and industry on the development and use of the science of measuring and communicating patient input throughout the total product lifecycle.

In Progress: CDRH trained more than 80 staff members on patient reported outcomes (PRO) and patient preference information (PPI), to advance staff understanding and CDRH review capacity in these areas.

Promote a Culture of Quality and Organizational Excellence

A manufacturer's ability to design and make high-quality, safe and effective devices and CDRH's ability to provide the necessary oversight to assure devices on the market are high-quality, safe and effective will increase as manufacturers and CDRH embrace a culture of quality and excellence throughout our respective organizations.

Goal: Strengthen FDA's Culture of Quality within the Center for Devices and Radiological Health	
2016 Target	Results
10% ↑ By September 30, 2016, increase by 10 percent the number of CDRH staff with quality and process improvement credentials to improve organizational excellence. (compared to FY 2015 baseline)	**300%** ↑ In FY 2016, CDRH tripled the number of staff with quality credentials by providing on-site quality training and certification examinations.

Goal: Strengthen Product and Manufacturing Quality within the Medical Device Ecosystem	
2016 Target	Results
By September 30, 2016, develop metrics, successful industry practices, standards, and tools that manufacturers can use to evaluate product and manufacturing quality beyond compliance with regulatory requirements.	Partnered with MDIC to develop metrics and best practices to assess quality system performance, and analytical tools to assess device quality by hospital value analysis committees.
By December 31, 2016, pilot voluntary use of product and manufacturing quality metrics and evaluation tools.	Partnered with MDIC and Capability Maturity Model Integration (CMMI) Institute on a proof-of-concept and pilot with three device manufacturers, to evaluate use of the CMMI appraisal process as a foundation for a future third party program.

Supporting Actions

In 2016, CDRH took a number of actions to achieve the goals and targets established for this priority:

Quality Management Framework Resources permitting, continue to implement the CDRH Quality Management Framework.

In Progress: CDRH completed development of its document control system (DCS). DCS will ensure that current and approved quality program and key processes documentation—standard operating procedures, work instructions, forms, templates and process maps—is available to staff.

Education and Training Develop education and training for CDRH staff to facilitate adoption of practices characteristic of a culture of quality and organizational excellence.

In Progress: CDRH became an American Society for Quality (ASQ) enterprise member—enabling every employee at FDA to take advantage of ASQ's vast collection of learning resources. CDRH also offered on-site quality training to 150 staff. More than 90 percent of those who participated in the training earned ASQ quality certifications (Certified Quality Auditor and Certified Quality Improvement Associate).

Case for Quality As part of the Case for Quality, collaborate with members of the medical device ecosystem to identify, develop, and pilot metrics, successful practices, standards, and evaluation tools that will be specific to the medical device industry and focus on assuring product and manufacturing quality.

In Progress: In partnership with MDIC, CDRH collected input from stakeholders through six Case for Quality Forums; developed metrics and best practices designed to assess quality system performance using pre-production, production and post-production data; and led development of a product quality dashboard to assist hospital value analysis committees in identifying high quality devices.

Voluntary Program Identify external partnerships and mechanisms to support a sustainable, voluntary third party program that will utilize quality metrics, practices, standards, and evaluation tools to assess and promote medical device product and manufacturing quality within industry beyond compliance with regulatory requirements.

In Progress: Continuing partnership with MDIC, CMMI Institute and other stakeholders, to expand application of maturity appraisal process; with the goal of developing the framework for a voluntary program in 2017.

Appendix C. 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.