



Examining FDA's Prescription Drug User Fee Program

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Few in biomedical science can recall a time of greater scientific progress. Hardly a day goes by without reports of a new medical breakthrough, a new partnership to drive discovery forward, or a new milestone toward addressing a previously untreatable disease. This pace of scientific discovery represents an unparalleled opportunity to improve human health. While it offers great hope for the future, progress has not been universal, and significant challenges remain. In the field of oncology, certain types of cancer are no longer the deadly diseases they once were, but instead are much like chronic conditions that can be effectively managed for a lifetime. But other types of cancer have not seen a new treatment for decades, if at all, leaving some to wonder if they will ever reap the benefits of progress.

The drugs and biologics being developed today to treat many diseases are far more effective than their predecessors, but they're also more complex. Even for some of the most notable new advancements benefit only a subset of patients. This additional complexity adds to the process of developing a new medicines, which already reportedly takes upwards of 12 years and costs over \$1 billion.¹ But together we have the opportunity to support breakthrough science, design systems that can surmount new challenges, and pave the way for new discoveries to reach the people who need them most. I, and millions of people across this country, hope that the work of this committee will be a catalyst to accelerate getting the right medicines to the right patients at the right time.

¹ Adams, C. P. and Brantner, V. V. *Health Economics*, 19 (2010), 130–141. doi: 10.1002/hec.1454

A critical component to achieving this goal is a well-resourced, accessible, and scientifically-oriented Food & Drug Administration (FDA). The FDA continues to be an agency that is highly responsive to public health needs and evolves with cutting edge science. It is able to do so, in part, because of the Prescription Drug User Fee Act (PDUFA).

The Prescription Drug User Fee Act

PDUFA was first passed in 1992 to alleviate a backlog of new drug applications. Prior to the initial user-fee authorizations, patients in other parts of the world were gaining access to new medicines more readily than Americans, with only about 10% of new treatments reaching U.S. patients first.² Today, that paradigm has largely been reversed. Funds provided through the PDUFA mechanism have allowed the FDA to clear the backlog of applications and have made the review process more predictable, efficient, and accessible. As a result, patients in this country have gained timely access to new medicines. In fact, in a study that we first published in *Health Affairs*,³ we examined the review times for new oncology drugs by the FDA and its European counterpart, the European Medicines Agency (EMA). Between the years 2003 and 2016, 73 new cancer drugs were approved by both the FDA and EMA. Of those drugs, 97% (71 of 73) were available in the U.S. before Europe. Furthermore, the FDA approved new cancer drugs on average nearly 6 months faster than the EMA (Fig. 1). Other research groups have also demonstrated that FDA regularly approves products faster than other global regulatory agencies and that this is the case for all drug reviews, not just for oncology drugs.⁴

² Hearing of the Committee on Health, Education, Labor, and Pensions, US Senate: FDA User Fee Agreements: Strengthening FDA and the Medical Products Industry for the Benefit of Patients. 112th Congress. March 29, 2012. <https://www.gpo.gov/fdsys/pkg/CHRG-112shrg90814/html/CHRG-112shrg90814.htm> Accessed 3.17.17

³ Roberts S, Allen J, and Sigal E. *Despite Criticism Of The FDA Review Process, New Cancer Drugs Reach Patients Sooner In The United States Than In Europe*. *Health Aff* July 2011 vol. 30 no. 7:1375-1381: <http://content.healthaffairs.org/content/30/7/1375.full.html> Accessed 3.17.17

⁴ Downing NS, Aminawung JA, Shah ND, Braunstein JB, M.D., Krumholz HM, Ross JS. *Regulatory Review of Novel Therapeutics — Comparison of Three Regulatory Agencies*. *N Engl J Med* 2012; 366:2284-2293: <http://www.nejm.org/doi/full/10.1056/NEJMsa1200223#t=article> Accessed 3.17.17

Figure 1. Comparison of FDA and EMA Review of New Oncology Drugs (2003-2016)

Drugs Approved by FDA and EMA		
	n=73	
	FDA	EMA
Median Review Time (in days)	183	356
# Drugs reviewed w/in 6 months	36 (49%)	1 (1%)
# Drugs reviewed w/in 1 year	70 (96%)	45 (62%)

The initial PDUFA authorizations were an indisputable success in speeding FDA review times and injecting greater predictability into the way drugs are approved by the agency. However, their initial impact was limited to the period after a new drug application was submitted to the FDA, leaving the much lengthier development process that precedes FDA review unaddressed. But the period in which the FDA reviews a new drug application accounts for only a fraction of the time that it frequently takes to develop a new medicine. Since then, however, the FDA has become increasingly involved at earlier stages of the development process. As such, the FDA has played an increasingly important and active role in reviewing interim results from earlier stage studies, and has provided feedback on research study designs through a variety of meetings with clinical study sponsors. The FDA has also played an increasingly active and valuable role in providing regulatory perspectives and participating in scientific discussions outside of activities related to a specific product application.

Over time, the FDA's more active role in product development has led to expansions to the agreements between the FDA and the drug manufacturers that supply the user fees. Recent user fee agreements have allowed funds to be applied to activities that are beyond the primary application review functions, such as programs to advance the science that serves as the basis for new product development. In addition to funding core product review and personnel, the sixth authorization of the user fee

agreement will support key projects that ensure the FDA can conduct critical scientific programming, participate in public workshops, and develop guidance for its employees and external stakeholders regarding cutting-edge science and new strategies for drug development and regulation.

Highlights of the PDUFA IV Agreement

PDUFA VI Advances the Role of Patients and Their Experiences

As part of the PDUFA V programs, the FDA began to build a robust Patient Focused Drug Development program. This included quarterly public meetings with patients, caregivers, advocates, and FDA personnel. Each meeting focused on a specific disease and was designed to gain insights directly from people who experience that condition on how it impacts their daily lives. The 21st Century Cures Act takes important steps to operationalize this type of feedback. It begins to set up processes to assist organizations and researchers in collecting patient-experience data, creates channels for providing such data to the FDA, and it will help develop methods for analyzing it.⁵ The PDUFA VI agreement further builds on these programs and sets the course for further incorporation of the patient voice in drug development. Under the agreement, user fees will be used to hold public workshops, develop guidance documents, strengthen internal capacity, and establish new methods for clinical outcomes assessments and patient reported outcome measures.

PDUFA VI Supports the Continued Success of the Breakthrough Therapy Designation

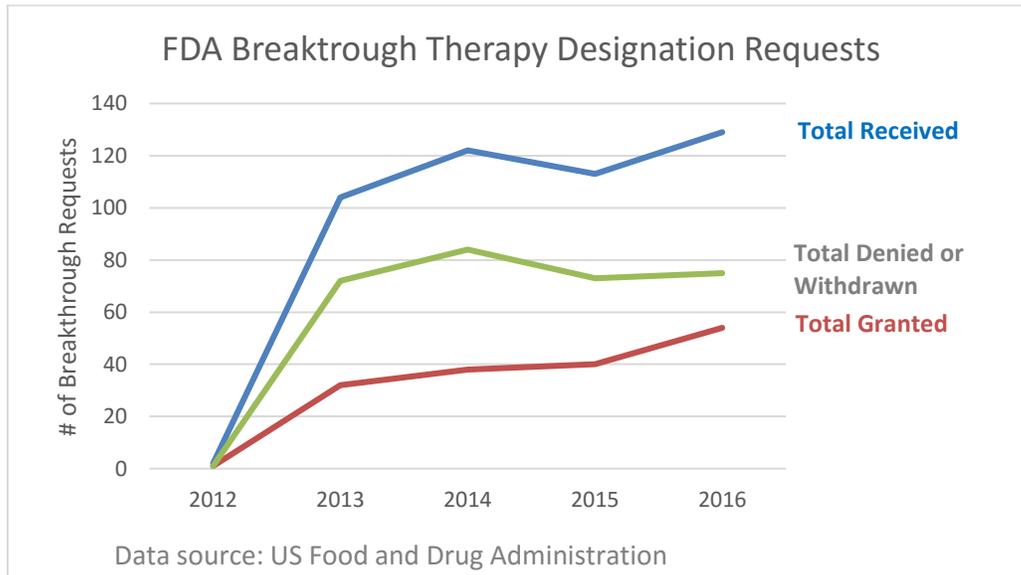
In 2012, the FDA Safety and Innovation Act (FDASIA), which contained the reauthorization of PDUFA V, established the Breakthrough Therapy Designation. This designation may be given to a drug intended to treat a serious illness for which preliminary clinical evidence indicates a substantial improvement over any existing intervention.⁶ This designation was rapidly implemented into drug development programs,

⁵ PL 114-255. The 21st Century Cures Act. Title III Subtitle A Patient Focused Drug Development

⁶ PL 112-144. FDASIA Sec. 902 Breakthrough Therapies.

and to date, 170 Breakthrough Therapy Designations have been granted, leading to 79 indications approved by FDA using this process (Fig 2).

Figure 2. Breakthrough Therapy Designation Use 2012-2016



Year	Total Received	Total Granted	Total Denied	Total Withdrawn
2012	2	1	1	0
2013	104	32	62	10
2014	122	38	70	14
2015	113	40	52	21
2016	129	54	62	13
2017	35	5	8	0
Total	505	170	255	58

Data source: US Food and Drug Administration

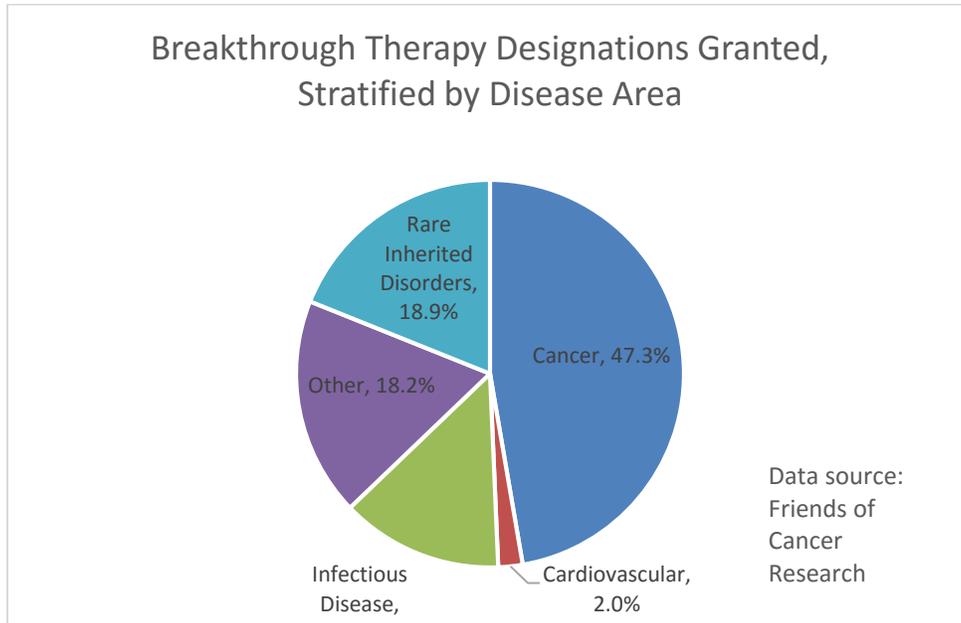
When the Breakthrough Therapy Designation is granted by the FDA, an intense collaboration is initiated between the agency and the sponsor to expedite the development of the drug. This process results in near real-time interactions between the FDA and sponsors, the involvement of senior leadership at the FDA, use of cross disciplinary project teams for optimal coordination of different application components, and consideration of different study designs that can minimize the number of patients

exposed to inferior agents throughout clinical testing. While these process enhancements can add efficiencies to the development process of drugs that demonstrate extraordinary clinical activity, they are also resource intensive. As indicated in Figure 2 by the more than 500 requests for Breakthrough Therapy Designation received since FDASIA established the designation in 2012, it is a widely-used program that continues to demand a heavy workload from the FDA.

In a recent analysis to explore the impact of the designation for new oncology products, we found that breakthrough-designated cancer drugs were reviewed in an average timeframe 3 months shorter than for those without the designation. While review times are important, the key goal of the Breakthrough Therapy Designation is to expedite drug development. It does so by acknowledging that new drugs demonstrating transformative potential early in their clinical testing may be permitted to employ novel approaches to demonstrate the safety and efficacy required for approval. Upon examining the pre-market development time of new cancer drugs, calculated as the number of years from submission of an investigational new drug (IND) application to submission of a new drug application (NDA) or biologics license application (BLA), we found that development time was 2.2 years shorter for approved breakthrough-designated drugs than for those without the designation.⁷ While this may be attributed in part to differences in natural disease trajectory of different cancers, the observed difference in development times provides preliminary evidence for the positive impact of the Breakthrough Therapy Designation and the collaboration it spurs. It is important to note that the Breakthrough Therapy Designation has been applied in a variety of different disease settings (Fig. 3), with under half of publicly disclosed designations going to products that treat forms of cancer.

⁷ Shea M, et al. *Impact of breakthrough therapy designation on cancer drug development*. Nat Rev Drug Dis. Vol. 15 p. 152. March 2016.

Figure 3. Breakthrough Designations by Disease



The PDUFA VI agreement will provide critical resources to allow the successful Breakthrough Therapy Designation to continue to facilitate rapid access to highly promising new medicines for patients suffering from serious diseases.

PDUFA VI Promotes Qualification and Use of Drug Development Tools

Developing new drugs is an incredibly risky process. The probability of an experimental drug compound progressing from Phase 1 trials to FDA approval was recently estimated to be 9.6% for all drug categories and 5.1% in oncology.⁸ A major driver of this low success rate is the uncertainty drug developers face when testing a new drug. It takes time and careful study to identify whether the patients selected for a clinical study are most likely to benefit from an experimental therapy and to

⁸ Clinical Development Success Rates 2006-2015. BIO, Biomedtracker, Amplion: 2016. Accessed at: <https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf> Accessed 3.19.17

determine how they respond to treatment. Questions such as: “Is a patient likely to develop side effects?” and “How far has the disease progressed?” and “Does a potential treatment target the correct disease pathway?” are routinely asked by drug developers and can be addressed efficiently through the use of biomarkers and other drug development tools.⁹ They help researchers answer these questions by providing rapid, reliable information on key metrics including drug safety, pharmacodynamics and drug response.

The FDA has a program to “qualify” certain biomarkers and other drug-development tools, which provides drug developers with the assurance that the methods they use have been scientifically vetted. This has the potential to rapidly speed the pace of drug development and prevent waste created by the case-by-case approach to biomarker qualification that the FDA has adopted in the past.¹⁰ The present PDUFA reauthorization package contains important provisions to enhance the biomarker qualification process. It instructs the FDA to publish two draft guidance documents on standards and taxonomy for biomarker qualification, as well as to convene a public workshop to engage the public on these topics.

By facilitating the development of new markers that can serve as intermediate indicators of safety or efficacy, the clinical testing process is improved. The use of validated biomarkers can help identify patients for which a drug is likely to work, offer early indicators of toxicity that help improve patient safety, and in some cases indicate that a drug will have a longer term benefit and allow for earlier access to promising new drugs. The resources provided in the PDUFA VI agreement will help create a process in which new biomarkers and other drug development tools can be accurately assessed and ensure their appropriate use.

⁹ Amur S, LaVange L, Zineh I, Buckman-Garner S, Woodcock J. Biomarker Qualification: Toward a Multiple Stakeholder Framework for Biomarker Development, Regulatory Acceptance, and Utilization. *Clinical Pharmacology & Therapeutics*. Volume 98 Number 1: July 2015.

¹⁰ Ibid.

PDUFA VI Enhances the Use of Real-World Evidence in Regulatory Decision-Making

Clinical trials are typically conducted in highly controlled populations to maximize the probability of success. However, once a drug reaches real-world populations, there may be unanswered questions about a drug's effect in patients with characteristics not represented in clinical trials. The collection of real-world evidence (RWE) allows for a greater understanding of drugs currently in use. Real-world evidence is gathered by processing data from electronic medical records (EMRs) and tracking patient outcomes over time. This type of evidence has the potential to supplement the knowledge gained from pre-market studies and can aid in regulatory decision-making. Under PDUFA VI, the FDA will engage patients, industry and academia to better understand how RWE can be collected and used to support high-quality evidence generation and regulatory decision-making. By allocating user-fee funding toward these programs, the FDA and other stakeholders will be able to identify limitations and explore different opportunities for the use of data collected from post-market experience with a drug.

For Additional Consideration

Effectively Communicating Scientific Advances

Rapid advancement in science and technology allows our understanding of new and current drugs continues to grow. In the years following FDA approval, new data about drug safety and efficacy emerges rapidly through post-market clinical studies and real-world experience captured in day-to-day medical practice. While new safety information is readily incorporated into drug labeling, new information about drug efficacy is often not submitted to FDA for labeling updates. Despite its absence on approved labeling, new information is quickly synthesized by clinical guideline developers, which is then used to inform clinical practice. This drives the high rate of off-label prescribing, which has become commonplace; indeed between one half and three quarters of all oncology prescribing is done off

label.¹¹ That off-label use is based on varying levels of supportive evidence. One study found that 27% of off-label uses were backed by strong evidence, with the remaining uses lacking strong scientific support.¹²

After reviewing collections of drug-related information published by clinical-guideline developers, called compendia, we found additional evidence of off-label use. When we compared drug compendia to existing FDA drug labels, we found that compendia recommended additional uses beyond the scope of those described in product labels for 79% of oncology drugs. Of the additional uses recommended by compendia, 91% were recommended by uniform consensus among the physicians developing the guidelines and recognized as acceptable uses by the four largest private insurers.

The variance between FDA labels and drug compendia indicates that there is a significant opportunity to improve how emerging scientific evidence can be incorporated into product labels. Currently, sponsors can submit a supplemental new drug application to modify a product label with additional efficacy claims. However, there may be instances when the efficacy profile of a drug has evolved but no supplemental application to the label was ever submitted. This typically happens when incentives to submit additional information are limited, such as when a drug has gone off patent and faces generic competition, or when a drug is no longer actively marketed.

Because PDUFA VI tasks the FDA and other stakeholders with exploring uses of post-market evidence, we believe that such information needs to be scientifically rigorous to appropriately inform patient and

¹¹ Mullins CD, Montgomery R, Abernethy AP, Hussain A, Pearson SD, Tunis S; American Society of Clinical Oncology. Recommendations for clinical trials of off-label drugs used to treat advanced-stage cancer. *J Clin Oncol*. 2012 Feb 20;30(6):661-6.

¹² Radley D, Finkelstein S, Stafford R. Off-label Prescribing Among Office-Based Physicians. *Arch Intern Med*. 2006 May 8;166(9):1021-6.

practitioner decisions. When post-market data presents compelling evidence for a new use of an approved product, the FDA could play a greater role in evaluating the relevant data to update the product label, as appropriate. This would allow independent experts at FDA to adjudicate between uses backed by strong evidence and those backed by less persuasive evidence, and to establish a standard by which post-market evidence should be evaluated.

Restoring the relevance of FDA-approved labels is an important public health goal. While other high quality sources of clinical prescribing information exist, FDA labels remain the sole source of information carrying the weight of a scientific agency with decades of experience reviewing drug efficacy data. Ensuring that processes are in place to modify outdated product labels can help ensure that use of the product is supported by the highest quality of evidence possible, and that patients and physicians can have confidence in supplemental uses of approved drugs.

Current Challenges to the FDA

Despite opportunities afforded by PDUFA VI, the passage of the 21st Century Cures Act, and the enormous contributions of this committee, I would be remiss to state that the FDA and the people who rely on it are optimally positioned at present. Even so, proposed cuts to biomedical research will put the brakes on the engine of discovery, abandon progress on new tools to enhance product evaluation, impede opportunities for new businesses in the biotech sector, and most perilously, jeopardize the development of new medicines for patients desperate for progress. Holding the FDA budget authority at stagnant levels prevents progress on agency functions that are not applicable to user fees. These include critical functions of the agency such as drug-safety surveillance programs, oversight of drug compounding facilities, review of product advertising material, oversight of over-the-counter medicines,

and conduct of scientific programming. Compounded with the constraints of the federal hiring freeze, the FDA will be hamstrung. The ramifications will be felt for years to come.

Among the challenges that have been exacerbated in the current environment is the implementation of the FDA Oncology Center of Excellence (OCE). The 21st Century Cures Act included a directive for the agency to establish an initiative to coordinate activities within the three current medical product centers around one or more major disease areas.¹³ To begin this work, the FDA established the OCE in recognition that cancer has evolved to require multimodal technologies for optimal management. For example, drugs are being developed with increased frequency to treat cancer using genetic information to guide their use. This can involve review divisions of CDER for the drug product, or CBER in instances of cell-based gene therapy or vaccines, and CDRH for a diagnostic. Housing these functions and expertise within the OCE can enhance collaborative interactions and streamline administrative processes, facilitating rapid and thorough development and application review. Ultimately, this type of coordination will add efficiencies to the development of new technologies, bring a uniform approach to assessing benefits and risks, and allow cutting-edge treatments to reach patients as quickly as possible. But reaching this goal has been stymied by the current environment. The reality of lagging funding, the potential of a detrimental budget future, and the presence of a hiring freeze place this transformational opportunity at significant risk. As Congress resolves the budget for FY18, clarification that funds dedicated to the cancer moonshot can be transferred to the FDA for the OCE would provide important core support.

Despite challenges ahead that may weigh progress down, scientific advancement has brought us to a time of great opportunity. For the people who currently depend on safe and effective medicines, for

¹³ PL 114-255. The 21st Century Cures Act. Title III Subtitle G Sec 3073: Establishment of Food and Drug Administration Intercenter Institutes.

those who are holding strong for the breakthroughs to come, and for every future patient, there isn't time to waste. The work that will be made possible through innovative policy like the 21st Century Cures Act will catalyze progress and improve lives and health of Americans. Building on these advancements, we urge Congress to swiftly pass this sixth reauthorization of PDUFA. In addition, to fully capitalize on this progress, and ensure that patients and physicians have access to the highest quality post-market evidence, new processes should be developed to maintain more up-to-date drug labels. Finally, for the programs of this proposed user fee agreement to succeed, the full budget for the FDA must be robust, and the capacity at which the agency can maintain and hire the best scientific minds must be unencumbered.

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About Friends of Cancer Research



Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy and regulation that speed life-saving treatments to patients. www.focr.org

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