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Prescription drug user fee act and its influence on review time and budget

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ABSTRACT
Before enactment of this act review time for a new drug application is unacceptably long, to overcome this problem PDUFA act was enacted by United States federal government. PDUFA act was legislated in 1992 and for every five years, it was amended with specific goals. PDUFA act is last amended as FDA Safety and Innovation Act in 2012. PDUFA act allowed FDA to collect three types of user fees from manufacturers, they are application fee, establishment fee and drug product fee. After the introduction of this act most of the times it reached its targets of review time and budget.
Key words: FDA, NDA, CBER, CDER, OTC, ANDA, Rx Drug, BLA, Review time, FD& C Act.

INTRODUCTION
The Prescription Drug User Fee Act (PDUFA) was enacted by United States federal Congress in 1992 and allowed FDA to collect fees from companies that produce human drug and biological products. After the passage of PDUFA, user fees have played an important role in facilitating the drug approval process.

PDUFA must be amended every five years, and was first renewed in 1997 (PDUFA II), 2002 (PDUFA III), 2007 (PDUFA IV), and 2012 (PDUFA V). PDUFA IV, amended in the Food and Drug Amendments Act of 2007, was with effective from September 2012.

PDUFA fees provided 52% of the Human Drugs Program funding for FY2012, accounted for more than 2,000 full-time equivalent employees. As each reauthorization deadline approaches, FDA For FY2012, 35% of FDA's total budget obtained from user fees, PDUFA revenue also contributed to the Biologics Program, and agency wide headquarters and rent budgets, industry groups, and most Members of Congress see PDUFA as must-pass legislation. Congress originally intended PDUFA to reduce the backlog of new drug applications at FDA and shorten the time from submission to decision. The general view is that PDUFA has succeeded. FDA has appointed review staff and reduced its review times.

FDASIA (Food and Drug Administration Safety and Innovation Act) appended 10 other titles that reauthorized medical device user fees, facilitated generic drug and biosimilar biological product user fees, and addressed pediatric drug research, medical

device regulation, pharmaceutical supply chain security, antibiotic development incentives, accelerate drug approval, drug shortages, and a set of miscellaneous provisions.

GERM OF PRESCRIPTION DRUG USER FEES

In the late 1980s, the median time for FDA to approve a new drug application (NDA) was 29 months. Pharmaceutical industry, consumers, and FDA agreed that the time from submission of a drug or biologics application to FDA's decision was inadmissible long. Patient advocates argued that delay in the review process will affect thousands of patient population.

Manufacturers argued that prolonged review times affected their ability to retrieve the costs of research and development. During PDUFA I consideration, FDA evaluated that each one month delay in a review's completion cost a manufacturer an average of $10 million.

The 1992 law came in to existence when the FDA commissioner David Kessler worked out a provision that met two industry demands: performance goals, which would set target completion times for various review processes; and the promise that these fees would supplement rather than replace funding that Congress appropriated to the FDA.

PDUFA and its reauthorizations

PDUFA I and the successive PDUFA II, PDUFA III, PDUFA IV, and PDUFA V authorized the collection of prescription drug user fees and the use of that revenue for specified activities (Fig 1).

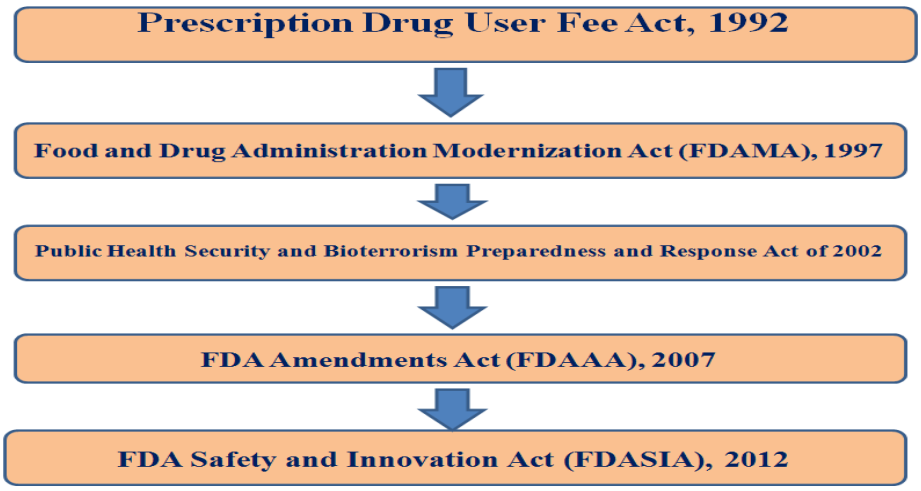

Fig 1: PDUFA and its reauthorizations

PDUFA I (Prescription Drug User Fee Act): allowed fee revenue to fund activities needed for the review of human drug applications and supplemental applications. In order to the actual review of applications, it included activities such as letters from FDA to applicants outlining inadequacy in their applications; manufacturing facility inspections as part of the pending approval applications; and observing of research necessary for the review of applications. All those activities fit within the time frame from when a manufacturer submits a new drug application (NDA) until the FDA makes its decision on that application.

PDUFA II (Food and Drug Administration Modernization Act (FDAMA): increased the scope of activities for which FDA could use prescription drug user fee revenue to include those related to the clinical trial phases of a new drug's development (from the IND to NDA submission).

PDUFA III (Public Health Security and Bioterrorism Preparedness and Response Act): increased the scope of activities for which FDA could use prescription drug user fee revenue to include both a drug's preclinical development period and 3 years into the post approval and marketing period. It allowed FDA to use PDUFA revenue for the collection, development, and review of post market safety information for up to 3 years post approval (those drugs approved beside October1, 2002).

PDUFA IV (FDA Amendments Act): Abolished the 3 year limitation on post approval activities, and again expanded the list of postmarket safety activities that the fees could support. New items on the list included developing and using adverse event data collection systems, including IT systems; developing and using improved analytical tools to judge potential safety problems, including access to external databases; implementing and enforcing new FFDCA requirements relating to post approval studies, clinical trials, labeling changes, and risk assessment and mitigation strategies; and managing adverse event reports.

PDUFA V (FDA Safety and Innovation Act (FDASIA): maintained the PDUFA IV purview of activities that PDUFA fees could support. The PDUFA V statutory language does not differ much from PDUFA IV. The accompanying FDA industry agreement on performance goals and procedures for FY2013 through FY2017 includes revised communication procedures and review timing goals during the application review process and addresses expanded FDA efforts in regulatory framework, drug development, drug safety, and information technology.

TYPE OF USER FEES

In order for these fees not to be viewed as taxes, the new law was intended to divide the fee burden across existing manufacturers. Segments were created which relied directly on the payment for real FDA services, including (a) the review of drug/biologic applications (application fee), (b) insuring safe manufacturing processes (establishment fees), and (c) monitoring adverse reports, recalls, labeling, etc. (product fees). These three segments insured that a company with a lot of product applications but few products on the market currently or with no existing manufacturing facility would not bear the entire burden of funding FDA review operations. Likewise, if a company marketed many products or maintained many facilities, it could afford to sustain FDA CDER and CBER operations more easily than a new company with few products. Therefore, the fees were divided into three segments, as summarized below.

Application Fees

Fees are evaluated for the submission of certain human drug or biological applications. Human drug applications include: new drug applications (NDAs), Pre-Licensing Applications and Establishment Licensing Applications for biologics which have been consolidated into Biological Licensing Applications (BLAs), and initial certification of antibiotic drugs. Also included are product efficacy and manufacturing supplements. Expressly excluded from application fees, and also from FDA performance commitments, were (a) over-the-counter drugs, which commonly do not require advance FDA approval (excluding for Rx-to-OTC switching, which do commonly contain clinical information and are included), (b) generic drug applications (ANDAs), (c) blood products, (d) in vitro diagnostics, and (e) large-volume parenterals.

Drug Establishment Fees

An Rx drug user fee was due from each corporation that owned an establishment in which at least one Rx drug (or biologic drug) was manufactured during the relevant fiscal year. If the drugs made in the facility are all subject to generic competition, no fee would result. So that the user fee would not be deemed a tax, the payer had to have at least one application pending for FDA review after September 1, 1992. FDA later interpreted this requirement to mean that if the other establishment fee criteria were met, an original application or supplement (with or without clinical data) that was pending after that date would initiate establishment fees for all qualifying establishments. Contract manufacturers that were not registrants on a FDA application were exempt from this fee.

Drug Product Fees

A separate annual fee was determined to each manufacturer based on the number of Rx drug products listed in the FDA's product registry. The fee is determined for each person named as an applicant on a human drug application, for each Rx drug (or biologic) listed on the FDA's product registration list. The applicant is required to have at least one application or supplement pending for agency review in the year the product fee was assessed (after Sept. 1, 1992). A listed product is exempted from the fee once it has generic competition. Innovator antibiotic drug products are subject to product fees. Generic antibiotic drug products (those that are not the first approval of a particular antibiotic drug) are not subject to product fees.

REVIEW TIME

PDUFA had put a target time frame for various types of applications, for standard review the target is 10 months, and for priority review target is 6 months.

WAIVERS OF USER FEES

Under section 736(d) of the Federal food Drug and cosmetic Act, a waiver may be granted for one or more fees where:

1. Fee exemption is necessary to protect the public health.
2. Evaluation of assessment of the user fees would present a significant barrier to innovation due to limited resources or other circumstances.
3. Prior to October 1, 2002, assessment of the fee for an application or a supplement filed under section 505(b)(1) pertaining to a drug product would be inequitable because an application for a product with the same active ingredient filed by another person under section 505(b)(2) could not be assessed user fees.
4. The FDA will waive the application fee for the first human drug application that a small business for review (section 736(d) (1) (E) of the FD&C Act). Small business entity is defined as a business that has fewer than 500 employees, including employees of affiliates. To be allowed as a waiver, the small business must submit a written request for the waiver. To qualify for waiving, reduction or refund of any fee, a written request must be presented not later than 180 days after the fee is due.

Drugs not considered as Prescription Drug Product

There are few drug products are not considered under prescription drug category they are:

1. Whole blood or blood component products for transfusion
2. A bovine blood product for topical application licensed prior September 1, 1992, an allergenic extract product, or an diagnostic biologic product licensed under section 351 of the PHS Act (Section 351 of the PHS Act provides the authority for regulating biological products.
3. A large volume parenteral drug product approved prior September 1, 1992
4. Later on October 1, 2002, any large volume parenteral drug product irrespective of when it was submitted (unless it is a large volume product intended for single dose injection for intravenous use or infusion).

PDUFA INFLUENCE ON FDA REVIEW TIME AND BUDGET

Influence on Review Time

The approval times for drugs and biologics applications provide a measure of PDUFA's effectiveness in meeting its primary goal: reducing the time between an innovator submission of an NDA and FDA's approval decision. FDA and industry experts have presented review time data in various ways, such as looking at all applications or differentiating between standard and priority review.

FDA presentation on December 2011 indicated that, as on September 30, 2011, the agency data indicated that the FDA had met or exceeded 10 out of the 12 specified performance goals for applications submitted in financial year 2010 and were, thus far in FY2011, meeting or exceeding 11 out of the 12 performance goals for FY2011 submissions. (Fig 2)

Influence on Budget

The Human Drugs total program level, the relative contributions of the two funding sources budget and user fees. In the first year of PDUFA contributions to the FDA budget, the fee revenue occupied for 9.7% of the Human Drugs Program total program level. For FY2012, fees provide 51.8% of the total. (Fig 3)

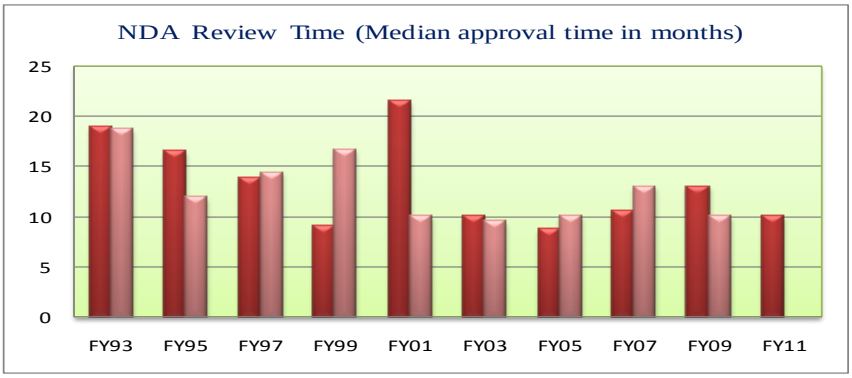

Fig:2 Median Approval Times, New Molecular Entities (NMEs) and New Biologic Entities (NBEs), by Fiscal Year

Source

FDA Center for Drug Evaluation and Research (CDER) data as of November 30, 2011, from John K.Jenkins, Director, Office of New Drugs, CDER, FDA. "CDER New Drug Review: 2011 Update," presentation at FDA/CMS Summit, December 8, 2011

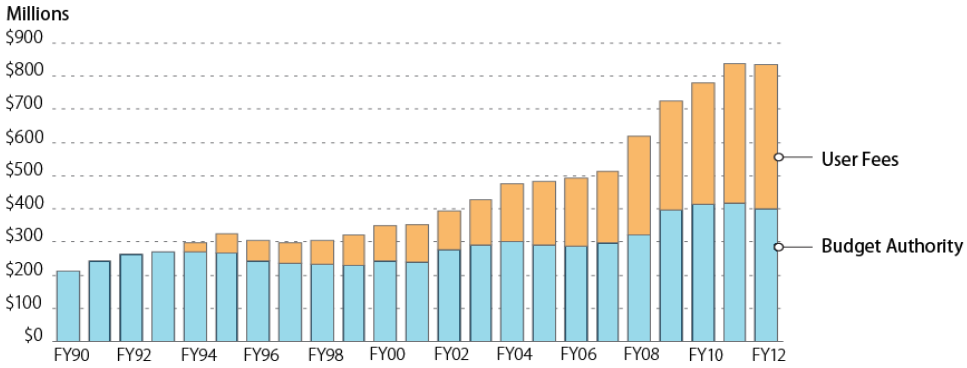

Fig 3: FDA Human Drugs Program Budget (By funding source)

From FY 1990 to FY 2012

Source: HHS Budget Office in response to Sec. 116 of the Continuing Resolution (CR)

CONCLUSION

There is a great need for innovation in the pharmaceutical industry because there are many diseases which doesn't have proper medication, but at the same time to avoid innovators from financial losses due to the time lapse in the review process. PDUFA act is a proper solution for this, where a defined time frame is allocated for each type of review category (i.e. Fastrack review, Priority review, Stander review). In 2010 FDA had met 10 out of 12 specified performance goals and, in 2011 met 11 out of 12 performance goals. For financial year 2012, PDUFA user fee has funded 51.8% of Human Drugs total program level.

Acknowledgement

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