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Research Article

GDUFA: Implementation and the Latest Amendments

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ABSTRACT

The law which is designed to fasten the delivery of safer and effective generic drugs to public and improve on the predictability of the review process is called the Generic Drug User fee Act (GDUFA). GDUFA made sure that the ones participating in the U.S generic drug system meets the quality requirements of U.S and also increased the timely access to high quality generic drugs in lower cost to the American purchasers. Before the implementation of GDUFA due to the limited resources the FDA was not able to manage the review of increasing number of applications. But after the enactment of GDUFA User Fee Amendments in the year 2012 the FDA started getting funds from the generic drug industry in order to ensure that the public receives safe and effective generic drugs at all times. Further, to facilitate the timely access to reasonable generic medicines and to report the issues related to GDUFA, GDUFA II was signed into law on August 18, 2017. Then the FDA agreed to review procedures and goals for the preparation and conduct of post-Close Response Letter meetings.

Keywords: GDUFA, Amendments, GDUFA II.

INTRODUCTION

A drug product which is similar to a reference listed drug product or branded drug in case of its strength, quality, dosage form, route of administration, performance characteristics and use is known as a generic drug. It is also known as any drug marketed under its chemical name without advertising. Since 1984 the FDA has totally approved more than 8,000 generic drugs and these costs 50-70% lesser than its branded ones. And this benefited the consumers and Nation's health care system by reducing the costs. Out of more than three billion new and refilled outpatient prescriptions that was dispensed in the US around 78% of it were filled with generics in the year 2011. After realizing the importance of generic drugs in providing medicines which are therapeutically equivalent but in lesser cost, FDA decided to cut down the time for review of generic drug application without compromising the quality and efficacy of generic drugs for the intended use and also to make it available to consumers in a short period of time. In order to bring more and more generic drugs into the market in short time through effective review process, FDA introduced the Generic Drug User Fee program to get appropriate funding for resource management to ensure that consumers continue to receive the substantial benefits that is given by the generic drugs[1]. The Act was effective from 1 October 2012. The amounts were changed year-to-year, as the fee sources were variable. Due to the changes in the structure of the fee the generic manufacturers had to identify the international production facilities which helped to increase the transparency in the global supply environment. And this also led to establishment of consistent and biennial inspections of foreign and domestic generic pharmaceutical production facilities[2].

The Act helped the FDA by increasing the possibility of the consumers receiving high quality generic drugs at lower cost and also gave an assurance that the U.S generic drug system participants are complying with the quality standards of U.S. In order to make sure that consumers receive significant benefits offered by the generic drugs the program was designed to keep the individual fee amounts as low as possible. After the user fees was adopted, the expenses of bringing a product into the market had declined which resulted in reduced cost of the drugs. The public received health benefits due to this program along with this the generic companies and the first time entrants gets some additional benefits. These were benefited significantly from the certainty associated with performance review metrics that offer the potential to dramatically reduce the time needed to commercialize a generic drug when compared to pre-GDUFA review times. The user fee program and its performance metrics and fees provide benefits to the public and do not cause any disadvantage to the business sector[3].

When the first Generic Drug User Fee Act (GDUFA I) was implemented in 2013, the US FDA was experiencing a very large backlog of ANDAs and associated post-approval submissions. The FDA reported that it expected to receive approximately 750 ANDAs per year under GDUFA I and instead saw about 1,000 per year for at least the first 4 years. In the final year of GDUFA I, the agency projected to spend approximately $430 million, but noted

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Table 1: User Fees to be paid by Sponsors to FDA (Pre and post GDUFA)

Fee	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	FY 2018
ANDA Fee	$63,860	$63,860	$58,730	$76,030	$70,480	$171,823
PAS Fee	$31,920	$31,920	$29,370	$38,020	$35,240	-
DMF Fee	$31,460	$31,460	$26,720	$42,170	$51,140	$47,829
API domestic	$34,515	$34,515	$41,926	$40,867	$44,234	$45,367
API foreign	$49,515	$49,515	$56,926	$55,867	$59,234	$60,367
FDF domestic	$220,152	$220,152	$247,717	$243,905	$258,646	$211,087
FDF foreign	$235,152	$235,152	$262,717	$258,905	$273,646	$226,087

that more than $493 million is needed each year to maintain their current performance goals.

Renewal terms were agreed upon between FDA and the Generic drug industry in 2016, and changes agreed upon for GDUFA II. It included new performance goals to further reduce backlogs and review times and modified the fee structures to provide relief to small businesses[4].

Objective

The objective is to study the pre and post GDUFA implications on the pharmaceutical sponsors and also to collate the changes in the latest amendment of GDUFA.

DISCUSSION

GDUFA fees for fiscal year 2013

The fee amounts of the fiscal year 2013 was issued by the FDA after giving notices in the Federal Register on 25 october 2012. The FDA will notify 60 days prior to the start of fiscal year, the fees due in the Federal Register. The FDA on 2 October 2012 published notices of requirements in the Federal Register, with the guidance on how industry should identify itself with the FDA and how to decide on what information organizations are required to be submitted. The identification information for the fiscal year 2013 had been submitted to FDA by 3 December 2012. Identification information have to be filed, updated, or reconfirmed by 1 June of the preceding fiscal year for each successive fiscal year. The facilities fees for FY 2013 was published by FDA by 13 January 2013, which will allocate approximately USD 174 million in total fees between facilities making active pharmaceutical ingredients (APIs) and finished dosage forms (FDFs). Due to the increased costs of inspections the facilities which are located outside the US and its territories had to pay higher fees. The differences in the costs was announced with the publication of the facility fees and will be adjusted in the coming years[2].

Penalties for lack of compliance

GDUFA imposed heavy penalties on those who fail to make timely payment of the required fees like the generic drug manufacturers and facilities. In case the fees is not paid the DMF will not be available for the reference. And as the DMF fee becomes due none of the generic drug submission which have referenced the DMF will be accepted. Same is with the facility fees too, in case you fail to pay the facility fee the FDA will not accept any new generic submission in reference to that facility until the fees is paid. And such facility will be placed on an official register of defaulters[2].

RTF

When an application is sent and they find one or more important components to be missing in it a Refuse to file

A Refuse to file letter will be sent to the applicant in case one or more necessary components is found to be missing in the application. The applicant will be notified that the application will not be filed till it is complete and then ask them to produce the missing information. Until the FDA gets the requested data from the applicant and the application is found acceptable and complete, no review of the application will be done further[2].

Backlog fee

In case of a person who owns a original ANDA which is pending and has not been approved on that date will be required to pay a backlog fee for that ANDA. The determination of the backlog is based on the number of original ANDAs pending.

DMF Fee

The DMFs that covers the manufacture of an API (Type II API DMFs) for use in generic drug application are supposed to pay fees. There was no distinction made by GDUFA between the DMFs which were submitted before & after October 1, 2012. The DMFs which was reviewed before the implementation of GDUFA had to pay one-time fees in case the DMF is referenced in a new generic drug submission. In case of generic drug submission which made in reference to a DMF whose fees is due will not be received till the fees is paid.

A notification will be given to the ANDA applicants that reference a DMF for which the fee is due and has not been paid. The notification will have the information of why the DMF holder failed to satisfy user fee obligation. In situations were the DMF fee is not paid within 20 calendar days of the notification, the ANDA referencing the DMF will not be received.

Management Priorities and Accomplishments

GDUFA includes several management and statutory requirements that are critical to enabling progress toward performance goals for the human generic drug program. These priorities include enhancing the efficiency of the review process, increased and expedited hiring, decreasing the backlog of applications, ensuring consistency and frequency of inspections for domestic and foreign sites, improving transparency, establishing databases and IT systems and advancing regulatory science initiatives.

Human Resources

FDA committed to hiring and training the staff necessary to achieve GDUFA program goals with incremental hiring goals established for FY 2013 and FY 2014. In FY 2015, FDA met the mandated human resources goal by hiring the final 25 percent of overall GDUFA program hires nearly

GDUFA I vs. GDUFA II Fee Structure:

Fee Category	GDUFA I		GDUFA II	
1-time Fees :				
ANDA Application	✓	24%	✓	33%
DMF Application	✓	6%	✓	5%
Annual Program Fees :				
API Facility	✓	14%	✓	7%
FDF Facility	✓	56%	✓	20%
CMO Facility	Same as FDF		✓	One-third FDF
ANDA Holder	N/A		✓	35%
Small (1-5 ANDAs)	N/A		✓	One – tenth Large
Medium (6-19)	N/A		✓	Four– tenths Large
Large (20+)	N/A		✓	Full Fee

11 months ahead of schedule. FDA has continued to add resources to the GDUFA program with a total of 1192 hires by the end of FY 2015[6].

Prior approval supplements

If the Prior approval supplements are received, it goes to the inspection in two different timelines of 6 & 10 month goal & in situations where it is not received the review clock will be stopped.

The section 506A of the FD&C Act and § 314.70 of FDA regulations provides the following reporting categories of changes to an approved application:

Major Change

a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product is known as a major change as these factors may relate to the effectiveness or safety of the drug product. In this type of change a submission of Prior Approval Supplements (PAS) and approval by FDA will be required before the distribution of the drug product.

Moderate Change

a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product is known as a moderate change as these factors may relate to the safety or effectiveness of the drug product. Depending on the nature of the change two types of supplements must be submitted to FDA:

a. Changes Being Effected in 30 Days (CBE-30 supplement): This supplement involves the moderate changes that requires the submission of the supplement to FDA at least 30 days before the distribution of the drug product.

b. Changes Being Effected (CBE-0 supplement): A CBE-0 supplement involves moderate changes that will allow distribution to occur as soon as FDA receives the supplement.

Minor Change

a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product is called a minor change as these factors may relate to the safety or effectiveness of the drug product. The applicant will have to describe minor changes in its next annual report[7].

Generic drug submission

The Generic drug submission is a term which is used for an ANDA submission, an amendment which is made to a ANDA or a PAS to an ANDA. If the fee has not been paid by the applicant for the API which has been manufactured in its own facility then they will have to pay the API related fee. The fee amount will differ based on the number of APIs referenced in the application and on the number of facilities in which the number of APIs have been manufactured. In situation were the ANDA references more than one facility as manufacturing each of the API, the applicant will have to pay the API-related fee for each of such facility.

Process for paying GDUFA user fees

The process for payment is as follows:

• The one who has to pay the fees need to enter all the required information on FDA's website to generate a GDUFA user fee payment cover sheet.

The cover sheet is designed in order to provide the minimum necessary information to verify if a person has satisfied all relevant user fee obligations.

The cover sheet has to be submitted to FDA electronically that will generate a receipt along with a user fee payment identification (ID) number to assist in tracking payment.

Payment can be done online by credit card or Automated Clearing House (ACH) electronic cheque or send payment by cheque, bank draft, U.S. postal money order, or wire transfer. Cover sheets has to be submitted with generic drug submissions and DMFs.

Positron Emission Tomography (PET) drug manufacturers are the only human generic drug manufacturers who are excluded from payment of GDUFA fees. However, they are required to self-identify. PET manufacturers will have to complete a generic drug user fee cover sheet for $0[5]

The success of the GDUFA program showed how the FDA, industry and other stakeholders can work together to achieve the goal. By the implementation of GDUFA the affordable generic medicines are accessible at all times. Over the last few years the generic industry, the application numbers for the generic medicines and the number of foreign facilities making the generic drugs has grown substantially. Due to which the GDUFA program became under-resourced over the period of time.

GDUFA II

The Generic Drug User Fee Amendment (GDUFA II) was into effect from October 1, 2017. It created a new fee for abbreviated new drug application (ANDA) holders to smooth the FDA funding from unpredictable ANDA submission fees. It also removed the Prior Approval Supplement (PAS) fees and reduced the active

pharmaceutical ingredient (API) and finished dosage form (FDF) facility fees, making the funding provided by the ANDA holder fees even more important.

The FDA has created a tiered fee system to account for the size of the business. Small ANDA holders (1-5 approved ANDAs) will pay one-tenth of the large ANDA holder fee, medium ANDA holders (6-19 approved ANDAs) will pay four-tenths of the large ANDA holder fee, and large ANDA holders (20+ approved ANDAs) will pay the full ANDA holder fee. The full ANDA fee has yet to be determined, and it will depend on the number of small, medium, and large ANDA holders.

Proposed GDUFA II Recommendations

For the purpose of reauthorization of GDUFA that is thefor the making of GDUFA II meetings and discussions were conducted with the regulatory industry, consultation from the stakeholders were taken for preparing recommendations to congress. The first reauthorization process for the GDUFA started with the public meeting which was held on June 15, 2015. The meeting included presentations which were given by the FDA and the various stakeholder groups like consumer group, patient advocates, regulatory industry, health professionals and academic researchers.

Once the meeting was over on June 2015, FDA continued with discussions with the generic industry along with the consultations from the stakeholders. The enhancements which were given in the GDUFA II were the issues which were addressed by the stakeholders, the generic industry, and various challenges faced by the FDA. This led to the improvement in the review program, and also set up new submission review performance goals, expedited the drug development process for the complex products and proposals to enhance the regulatory science and facility assessments. The recommendations which are made is described in the GDUFA II commitment letter.

Submission Review Performance Goals

The submission review performance goals of GDUFA program is very complex in nature. There are different review goals for the different tiers and cohorts of submissions. The very first cohort was the pre-GDUFA "backlog". The FDA had promised to take an action on 90% of the pending ANDAs by the end of fiscal year 2017. Yet none of the ANDAs received goal dates and also there were no goals set up for the subsequent amendments which were submitted in response to first action taken by the FDA on backlog ANDAs. The next cohort consisted of the ANDA submitted in the Years 1 & 2 of the program (Year 2013 & 2014). These cohort too did not receive any goal dates. FDA agreed to maintain the levels of productivity in years 1 and 2 like the pre-GDUFA times. The next three cohorts were the ANDAs submitted in the year 2015, 2016 & 2017. These cohorts got the goal dates, which became rigorous for each cohort. There was also an effective sixth cohort, as a practical matter : In the course of GDUFA implementation , FDA informally committed to assign "Target Action Dates" to "pre-Year 3" ANDAs and ANDA amendments, which had not obtained any formal goal dates under GDUFA. Target Action Dates were aspirational deadlines for action on these submissions.

For GDUFA II program, FDA has proposed two major changes to the submission review goals:

For the purpose of simplifying and improving review efficiency and to reorganize the program administration it required the ANDAs and their amendments to be in a single, consolidated, review goals scheme to ensure that no submissions are left behind.

As per the GDUFA II program the priority submissions had faster review goals. For an ANDA submission 10 months is the time taken for standard review whereas for a priority review, 8 months is the time taken from the date of submission. They will consider a submission to be a public health priority depending on the CDER's Manual of Policies and Procedures (MAPP), then they will put the submission for a priority review. Regarding a pre-submission facility correspondence the applicant will submit the correspondence 2 months before the actual ANDA is submitted, then it will be checked for its completeness an accuracy. The reason to submit a pre-submission facility correspondence is to provide the agency some time to plan for high volume of the facility assessments which effects the approval of the ANDA. The submission performance goals and procedure which is proposed are given in the section I of the proposed commitment letter.

Original ANDA Review Program Enhancements

The GDUFA I had made enhancements in it based on the issues related to the review efficiency and the transparency in communications like the continuous communications of deficiencies which can be easily corrected and then the adoption of the complete response letters (CRLs). But these enhancements failed to meet the expectations of the industry and thus the industry expressed concern over this matter. Taking this into consideration the FDA further started developing and refining the ANDA review and communication procedures during the 2nd and 3rd year GDUFA I. Discussions made on these issues were resolved and put into GDUFA II and given in the proposed Commitment Letter. ANDA review enhancements given in the GDUFA II are more specific and programmatic when compared to GDUFA I. They have completely refined and enhanced the efficiency of review process of the ANDA from the start to finish.

The ANDA review program begins with the submission of the ANDA in the GDUFA II program. The FDA the strives to receive the ANDA within 60 days from the date of ANDA submission. The Agency will then issue MAPP procedures for filing reviewers on communication in case of minor technical deficiencies and also on deficiencies which were resolved with the information in the original submission of the ANDA. This is done to give an opportunity for resolution within 7 calendar days. If that deficiency is solved within the 7 calendar days then that deficiency cannot be taken as a basis for refuse to receive. Such ANDA enhancements are given in Section II of the proposed commitment letter.

DMF Review Program Enhancements

GDUFA II proposes enhancements for the current DMF review procedures. Along with issuing of the review comments for the DMF of an ANDA, the review

comments submitted to the DMF holder will also be issued. The commitment letter proposed gives the procedures and timelines for the teleconferences to clarify the deficiencies found in the first DMF cycle review. After the DMF undergoes a complete scientific review and found to have no issues related to the referencing ANDA the FDA will issue a First Adequate Letter. Next the DMF will go through an complete review for which the ANDA referencing have already been approved or tentatively approved, then the FDA will issue an No Further Comments Letter.FDA would issue a guidance regarding post-approval changes to a Type II DMF and submission mechanisms for ANDA applicants who reference it by the year 2019. These enhancements will be set forth in section IV of the proposed Commitment Letter.

Enhanced Accountability and Reporting

In order to enhance the productivity and performance the FDA proposed to build the internal capacity by the regular assessment towards the GDUFA II goals. They also focused on different methodologies and the timely reporting of the GDUFA II metrics, efficient administration and reporting of the user fee resources. Several activities were conducted by the FDA in order to develop the resource management planning and a modern time reporting approach for GDUFA II[8].

CONCLUSION

GDUFA fees will help in increasing the ability of the Agency to perform significant program functions and to reduce the costs, considering the reduced review timelines and GDUFA II further reduce review cycle times, and may impose additional financial impact on the industry.

Depending on the new fees the FDA establishes consistent & biennial inspections of foreign & domestic generic pharmaceutical production facilities. And also increase the transparency in the global supply environment which will require the generic manufacturers to identify international production facilities.

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