ADVANCES IN THE REVIEW OF GENERIC DRUG APPLICATIONS BY UNITED STATES FOOD AND DRUG ADMINISTRATION, A REGULATORY PERSPECTIVE IN THE ERA OF GDUFA (GENERIC DRUG USER FEE AMENDMENT 2012)

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REVIEW ARTICLE

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ABSTRACT

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. The United States - Food and Drug Administration (U.S. FDA) has its own regulatory strategy to approve and allow generic drugs in to the market, which is named as Generic Drug Submission Review. FDA would like to slash the review time of generic drug application without compromising the quality and efficacy of proposed generic drugs for the intended use and to make them available to consumers in short time as possible. FDA has introduced Generic Drug User Fee program to supplement appropriate funding for resource management to ensure that consumers continue to receive the significant benefits offered by generic drugs. The purpose of this article is to present a concise overview about Generic Drug User Fee program and the recent advances in Abbreviated New Drug Application (ANDA) review process.

Keywords: FDA, FDASIA, ANDA, GDUFA, Generic Drug Submission.

INTRODUCTION

A generic drug is a drug defined as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use". (1) It has also been defined as a term referring to any drug marketed under its chemical name without advertising. For most of the consumers, generic drugs are important options that allow greater access to get health care in economical way compared to branded drugs. The generic drugs are nothing but the copies of brand-name drugs and are therapeutically equivalent to brand drugs. (2)

Since 1984, the Food and Drug Administration (FDA) has approved more than 8,000 generic equivalents of brand-name drugs. Generic drugs typically costs 50 to 70 percent less than their brand-name counterparts, resulting in cost savings for consumers and the U.S. Nation's health care system. In the year 2011, approximately 78 percent of the more than three billion new and refilled outpatient prescriptions dispensed in the United States were filled with generics. In the last decade alone, generic drugs have provided more than $824 billion in savings to the U.S. Nation's health care system. (3) Recognizing the critical role that generic drugs play in providing more affordable, therapeutically equivalent medicine, FDA would like to slash the review time of generic drug application without compromising the quality and efficacy of generic drugs for the intended use and to make available to consumers in short time as possible. In order to bring the generic drugs more and more into the market in short time through effective review process, FDA has introduced Generic Drug User Fee program to supplement appropriated funding for resource management to ensure that consumers continue to receive the significant benefits offered by generic drugs.

GENERIC DRUG APPROVAL PROCESS

In general to get marketing approval for a generic drug from U.S. Food and Drug Administration include various junctures such as finding basis for submission, getting drug substances from approved DMF vendors, finished product development, clinical /bioequivalence-bioavailability studies, plant inspection, dossier writing and finally submission to authorities. The diagram (Figure

1) illustrates the various elements involved in obtaining regulatory approval for generic product. (4)

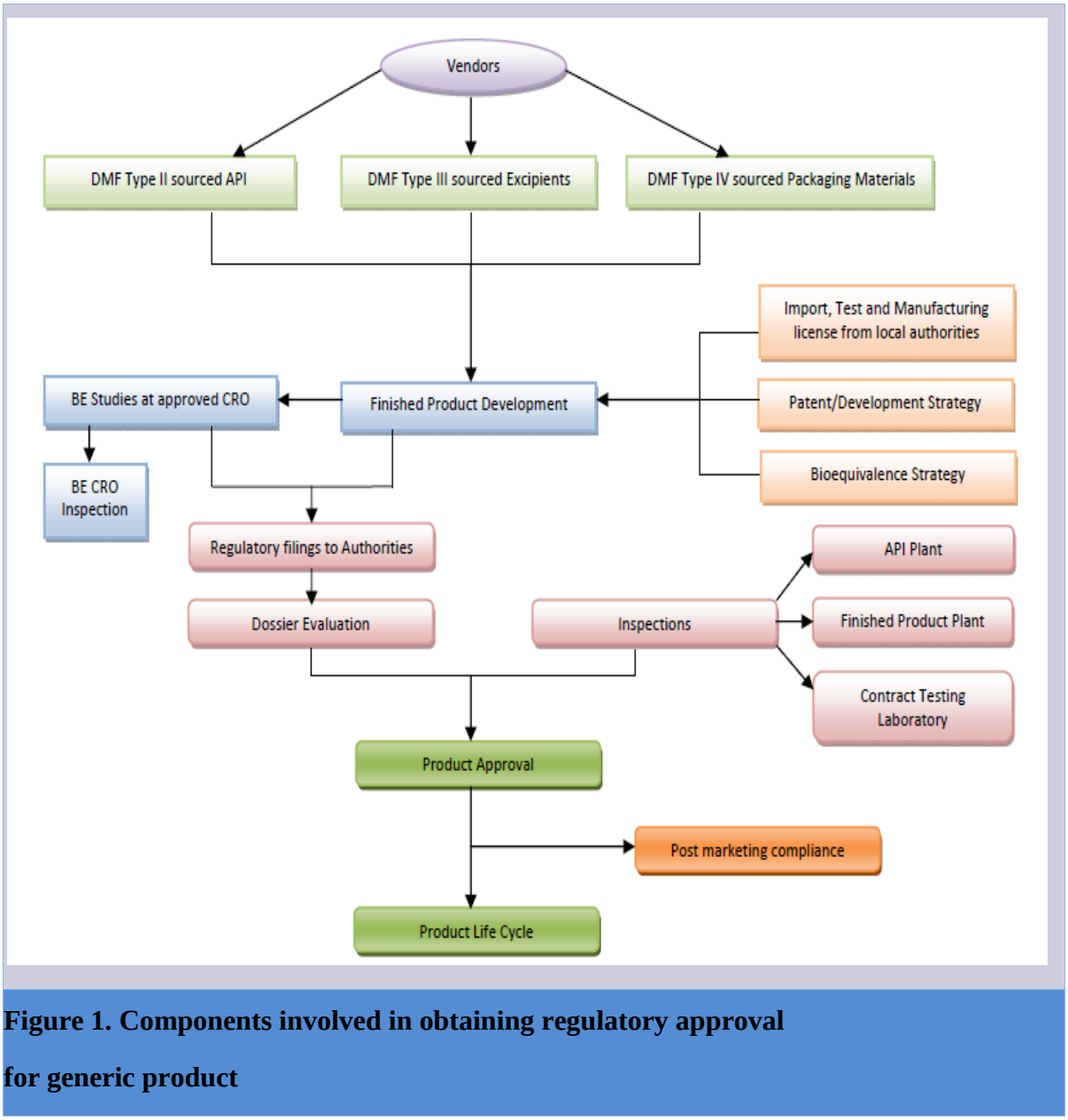

Figure 1. Components involved in obtaining regulatory approval for generic product

The review of generic product application will be initiated after submission of dossier to the regulatory authority. During review, if any deficiency arises generic applicant must be ready to provide responses with scientific rationales. Upon completion of scientific review of the application and after arriving to a conclusion that the submitted generic application is therapeutically equivalent to the reference listed drug upon which the generic application was based, agency will issue an approval letter for the generic product to introduce in to the market.

In Generic Drug Submission Review (5) the general responsibilities of the agency's designee and detailed activities are as follows:

Table 1: General Responsibilities

(a)	Review of the Generic submission.
(b)	Inspection of Facilities associated with the generic drugs.
(c)	Product lifecycle monitoring

Table 2: Detailed Activities

(a)	Review of generic drug submissions, including review of drug master files referenced in such submissions.
(b)	Issuance of letters for related generic drug submissions- i. Approval letters for abbreviated new drug applications or supplements to such applications ii. Complete response letters with in detailed specific deficiencies, and where appropriate the actions necessary to place such applications in condition for approval.
(c)	Issuance of letters related to Type II active pharmaceutical drug master files- i. Letters with in detailed specific deficiencies in such submissions, and where appropriate, the actions necessary to resolve those deficiencies ii. The document that no deficiencies need to be addressed.
(d)	Inspections related to generic drugs.
(e)	Monitoring of research conducted in connection with the review of generic drug submissions and drug master files.
(f)	Monitoring post-market safety activities with respect to drugs approved under abbreviated new drug applications or supplements, including the following: i. Collecting, developing, and reviewing safety information on approved drugs, including adverse event reports (AERs). ii. Developing and using improved adverse-event data-collection systems, including information technology systems. iii. Developing and using improved analytical tools to assess potential safety problems, including access to external data bases. iv. Implementing and enforcing section 505(o) (relating to post approval studies and clinical trials and labeling changes) and section 505(p) (relating to risk evaluation and mitigation strategies) insofar as those activities relate to abbreviated new drug applications. v. Carrying out section 505(k)(5) (relating to adverse-event reports and post market safety activities).
(g)	Regulatory science activities related to generic drugs.

In order to complete the review of generic applications more significantly faster and to make the generic drugs available to patients quickly, congress has introduced an act popularly known as Food and Drug Administration Safety and Innovation Act (FDASIA) by giving authorities to U.S. FDA to collect user fee for generic drugs applications through Generic Drug User Fee program. This designed Generic Drug User Fee program is expected to provide significant value to small companies and first time entrants in the generic market who will get benefit significantly from associated 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.

FOOD AND DRUG ADMINISTRATION SAFETY AND INNOVATION ACT (FDASIA) (5)

The Food and Drug Administration Safety and Innovation Act (FDASIA), signed into law on July 9, 2012; expands the FDA's authorities and strengthens the agency's ability to safeguard and advance public health by:

Table 3: Expanded FDA's Authorities

(a)	Giving the authority to collect user fees from industry to fund reviews of innovator drugs, medical devices, generic drugs and biosimilar biological products.
(b)	Promoting innovation to speed patient access to safe and effective products.
(c)	Increasing stakeholder involvement in FDA processes.
(d)	Enhancing the safety of the drug supply chain.

Table 4: FDASIA Table of Contents

TITLE I	Fees relating to Drugs
TITLE II	Fees relating to Devices
TITLE III	Fees relating to Generic Drugs
TITLE IV	Fees relating to Biosimilar Biological Products
TITLE V	Pediatric Drugs and Devices
TITLE VI	Medical device regulatory improvements
TITLE VII	Drug Supply Chain
TITLE VIII	Generating Antibiotic Incentives now
TITLE IX	Drug approval and Patient access
TITLE X	Drug Shortages
TITLE XI	Other Provisions

Table 5: User fee established for

(a)	Certain applications in the backlog as of October 1, 2012 (only applicable to financial year (FY) 2013).
(b)	Certain types of applications and supplements associated with human generic drug products.
(c)	Certain facilities where APIs and FDFs are produced.
(d)	Certain type II API DMFs associated with human generic drug products.

The Food and Drug Administration Safety and Innovation Act (FDASIA) has been designed including the following parts under different titles:

Under sections 744A and744B of the FD&C Act (21 U.S.C. 379j–41 and 379j–42), as added by GDUFA [in Title III of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144), which was signed by the President on July 9, 2012], and as further amended by the FDA User Fee Correction Act of 2012 (Public Law 112-193) (signed by the President on October 5, 2012), user fee have been established for the following which are associated with human generic drug product submission.

GENERIC DRUG USER FEE AMENDMENTS OF 2012 (GDUFA) (5)

GDUFA (Public Law 112-144, Title III) was signed into law by the President of United States on July 09, 2012. GDUFA was designed to speed the delivery of safe and effective generic drugs to the public and reduce costs to industry. GDUFA enables FDA to assess user fees to support critical and measurable enhancements to FDA's generic drugs program.

This legislation has been brought by FDA at a critical time. The public health success of generic drugs has also created a significant challenge. In pre-GDUFA time due to limited resources, FDA was not able to keep pace with an increasing number of applications requiring review. There were about more than 2,500 applications for new generic drugs seeking approval by the year 2012. However, with the enactment of the Generic Drug User Fee Amendments of 2012 (GDUFA), for the first time ever, FDA receives funding from the generic drug industry to ensure the timely access to safe, high-quality, and effective generic drugs. Further, with received funding additional resources will be allocated by the agency to reduce the backlog of pending applications, to slash the average time required to review generic drug applications without compromising the review quality and also increasing the risk-based inspections in order to bring the generic

drugs into the market and to the patients more quickly.

For the purpose of the designed FDASIA and GDUFA program the following definitions have been considered for few important terms being used in the Act:

Abbreviated new drug application (ANDA)

An application submitted under section 505(j), an abbreviated application submitted under section 507 (as in effect on the day before the date of enactment of the Food and Drug Administration Modernization Act of 1997), or an abbreviated new drug application submitted pursuant to regulations in effect prior to the implementation of the Drug Price Competition and Patent Term Restoration Act of 1984; and does not include an application for a positron emission tomography drug.

Active pharmaceutical ingredient (API)

A substance, or a mixture when the substance is unstable or cannot be transported on its own, intended
(i) to be used as a component of a drug; and (ii) to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or

A substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become a substance or mixture described in above paragraph.

Finished dosage form (FDF)

A drug product in the form in which it will be administered to a patient, such as a tablet, capsule, solution, or topical application;

A drug product in a form in which reconstitution is necessary prior to administration to a patient, such as oral suspensions or lyophilized powders; or

Any combination of an active pharmaceutical ingredient with another component of a drug product for purposes of production of a drug product described in above two paragraphs.

Facility

A business or other entity (i) under one management, either direct or indirect; and (ii) at one geographic location or address engaged in manufacturing or processing an active pharmaceutical ingredient or a finished dosage form; and does not include a business or

Other entity whose only manufacturing or processing activities are one or more of the following: repackaging, relabeling, or testing.

Generic drug submission

It means, an abbreviated new drug application, an amendment to an abbreviated new drug application, or a prior approval supplement to an abbreviated new drug application.

Type II active pharmaceutical ingredient drug master file

It means, a submission of information to the agency by a person that intends to authorize the Food and Drug Administration to refer the information to support the approval of a generic drug submission without the submitter having to disclose the information to the generic applicant.

Pending Application

The original ANDA that has not been withdrawn or tentatively approved or approved by September 28, 2012.

Solicited Amendment

A submission made by an applicant in response to a complete response letter (CR) issued by FDA. Solicited amendments are classified as either Tier 1 or Tier 3.

Major Amendment

Major amendments contain a substantial amount of new data or new information not previously submitted to or reviewed by FDA, requiring, in FDA's judgment, a substantial expenditure of FDA resources. The first solicited major amendment is classified as Tier 1; any solicited major amendment subsequent to the first is classified as Tier 3.

Minor Amendment

FDA review of a minor amendment requires, in FDA's judgment, fewer FDA resources than are necessary to review a major amendment, but more than are necessary to review the information submitted in response to an ECD. The first through fifth solicited minor amendment are classified as Tier 1; any solicited minor amendment subsequent to the fifth minor amendment is classified as Tier 3.

Easily Correctable Deficiency (ECD)

FDA review of information submitted in response to an ECD requires, in FDA's judgment, a modest expenditure of FDA resources.

Unsolicited Amendment

A submission made by an applicant on their own initiative and not in response to FDA's CR letter. Unsolicited amendments are categorized as either delaying or non-delaying. All delaying unsolicited amendments are classified as Tier 1 amendments. All non-delaying unsolicited amendments are classified as Tier 2 amendments.

Delaying Amendment

Delaying amendments address actions by a third party that would cause delay or impede application review or approval timing and that were not a factor at the time of submission. Unsolicited amendments that are in response to a delaying action or that FDA would eventually solicit are classified as Tier 1 delaying amendments. Delaying amendments do not add to the count of major or minor amendments for the purpose of classification.

Non-delaying Amendment

Non-delaying amendments are unsolicited amendments that contain information that is not requested by FDA and is not the result of changes to the RLD or USP monograph, changes to the RLD labeling, a REMS and REMS modification, or generic approval requirements reflected in citizen petition responses issued by FDA.

Administrative Amendment

Administrative amendments are routine in nature and do not require scientific review. Requests for final approval with no scientific changes to the ANDA, patent amendments, and general correspondence submitted by applicants are generally considered administrative amendments. Administrative amendments do not affect the goal dates for the application and, as a result, are considered neither Tier 1, Tier 2, nor Tier 3 amendments.

GDUFA GOALS & TARGETS (3, 5)

GDUFA is five year program with the goal of self fund generation, establishing a hiring authority for all GDFA-related positions, building and maintaining new data bases as necessary for facilities, fee assessments in collaboration with Industry. This five year GDUFA plan has been subdivided into cohort 1 to cohort 5 considering each financial year as one cohort. The summary of FDA's commitments phase-in over the five year period is presented below:

Table 6: Commitment phase-in over the five year period

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Hire and train new staff	25% of total	50% of total	25% of total		
Type II DMF completeness assessment - conduct and publish list	→	→	→	→	→
Enhances refuse to receive standards for ANDAs and related submissions	→				
Respond to appeals for ANDAs	Within 30 days of receipt				
ANDA teleconference requests			Close-out 200	Close-out 250	Close-out 300

Type II DMF teleconference requests		Limit one per DMF holder per month not to exceed ANDA teleconference levels
Risk-adjusted biennial cGMP surveillance inspections of generic API and generic finished dosage form manufacturers		Parity of inspection frequency between foreign and domestic firms

Table 7: New classification of Amendments under GDUFA

	Solicited Amendment Goals	Unsolicited Amendment Goals
Tier 1	1st Major: 10 months 1st – 3rd Minor: 3 months* 4th – 5th Minor: 6 months*	Delaying action or otherwise would eventually be solicited: 3 months*
Tier 2	N/A	Amendment not arising from "delaying action": 12 months
Tier 3	≥ 2nd Major: No goal ≥ 6th Minor: No goal	N/A
*10 months if inspection required		

Table 8: Targeted performance goals in five years of GDUFA program (apply only to electronic submissions)

Submission type	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Original ANDA	Expedites review of paragraph IV and maintain pre-GDUFA productivity		60% in 15 months	75% in 15 months	90% in 10 months
Tier 1 fist major amendment	Maintain pre-GDUFA productivity		60% in 10 months	75% in 10 months	90% in 10 months
Tier 1 major amendments (1st to 3rd)	Maintain pre-GDUFA productivity		60% in 3 months*	75% in 3 months*	90% in 3 months*
Tier 1 major amendments (4th to 5th)	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
Tier 2 amendment	Maintain pre-GDUFA productivity		60% in 12 months*	75% in 12 months*	90% in 12 months*
Prior approval supplements	Maintain pre-GDUFA productivity		60% in 6 months*	75% in 6 months*	90% in 6 months*
ANDA amendment, and PAS in backlog on October 1st, 2012	Act on 90% by end of FY 2017				
Controlled correspondences	Maintain pre-GDUFA productivity		70% in 4 months**	70% in 2 months**	70% in 2 months**

*10 months if inspection required ** One additional month added to goal if clinical division input required

Table 9: Types of User Fee that FDA authorized to collect

(a)	One time Backlog Fee for pending abbreviated new drug applications (only applicable to financial year (FY) 2013).
(b)	Drug Master File Fee.
(c)	Abbreviated New Drug Application and Prior Approval Supplement Filing Fee.
(d)	Generic Drug (FDF) Facility Fee and Active Pharmaceutical Ingredient Facility Fee.

Table 10: Summary of User Fee details since FY 2013 to FY 2015 under GDUFA

Fee Type	Who incurs the Fee?	Payment frequency	FY 2013	FY 2014	FY 2015
Backlog Fee	An applicant whose original ANDA was pending on Oct. 1, 2012 without a tentative approval	Once	$17,434	NA	NA
DMF Fee	A Type II active pharmaceutical ingredient (API) DMF holder whose DMF is referenced by an initial letter of authorization in a generic drug submission on or after Oct. 1, 2012	Once for each API DMF, no later than when first letter of authorization is submitted	$21,340	$31,460	$26,720
ANDA Fee, and PAS Fee	An applicant submitting an ANDA or PAS on or after October 01, 2012	Once at the time of ANDA or PAS submission	**ANDA:** $51,520 **PAS:** $25,760	**ANDA:** $63,860 **PAS:** $31,930	**ANDA:** $58,730 **PAS:** $29,370
Facility Fees for API and FDF	The owner of a facility identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce one or more generic drug finished dosage form (FDF) and/or APIs.	Annually	**API:** Domestic $26,458 Foreign $41,458 **FDF:** Domestic $175,389 Foreign $190,389	**API:** Domestic $34,515 Foreign $49,515 **FDF:** Domestic $220,152 Foreign $235,152	**API:** Domestic $41,926 Foreign $56,926 **FDF:** Domestic $247,717 Foreign $262,717

In accordance with the commitment letter (3), FDA agreed to certain performance goals and procedures for the review of amendments submitted electronically to original ANDAs and

PASs filed on or after October 1, 2014. The performance goals do not apply to amendments submitted on or after October 1, 2014, if they amend original ANDAs or PASs submitted before October 1, 2014. For purposes of FDA's performance goals, FDA has classified the amendment into different Tiers with different goal date for completion of review. Each Tier has corresponding performance metric goals, ranging from a 3-month review clock to no goal date, depending on the amendment's classification.

USER FEE DETAILS UNDER GDUFA (5, 6)

The Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended by the Generic Drug User Fee Amendments of 2012 (GDUFA), as further amended by the FDA User Fee Correction Act of 2012, authorizes FDA to assess and collect user fees for the following:

The detailed information presented as follows:

One-time Backlog Fee for pending abbreviated new drug applications (7-9)

Under GDUFA, each person that owns an abbreviated new drug application that is pending on October 1, 2012, and that has not received a tentative approval prior to that date, were subjected to a backlog fee for each such application (section 744B(a)(1)(A) of the FD&C Act). The backlog fee has been assessed one time only, for financial year (FY) 2013, and no backlog fee was assessed in subsequent years.

Under section 744B(a)(1)(B) of the FD&C Act, the backlog fee has been calculated by taking the exact number of pending abbreviated new drug applications in the backlog that have not received tentative approval as of October 1, 2012. The established **backlog fee was $17,434** only for financial year (FY) 2013.

For financial year (FY) 2013, the backlog fee for each pending application was due on November 26, 2012 i.e., within 30 days after publication of (section 744B(a)(1)(D) of the FD&C Act) Federal Register Notice dated October 25, 2012.

The person that owns an original ANDA that fail to pay the backlog fee has been placed on publicly available arrears list, and FDA has not received a new ANDA or supplement submitted by that person, or any affiliate of that person, within the meaning of 505(j)(5)(A) of the Federal Food, Drug and Cosmetic Act, until the outstanding fee paid.

FDA has also published a notice for the benefit of generic manufacturers saying that those generic manufacturers who no longer seeking approval of their application can withdraw their pending application before September 28, 2012 to avoid paying a fee.

Drug Master File Fee (9-12)

Under GDUFA, the DMF fee was owed by each person that owns a type II active pharmaceutical ingredient drug master file that was referenced, on or after October 1, 2012, in a generic drug submission by an initial letter of authorization.

This is a one-time fee for each individual DMF. If a person has paid a drug master file fee for a Type II active pharmaceutical ingredient drug master file, the person shall not be required to pay a subsequent drug master file fee when that Type II active pharmaceutical ingredient drug master file is subsequently referenced in generic drug submissions.

Based on the number of DMFs referenced to ANDAs and PASs every year, FDA has estimated to collect the DMF fee in FY 2013, 2014 & 2015 as follows:

Table 11: Details of DMF Submission fee

Fiscal Year	DMF Fee (USD)
2013	21,340
2014	31,460
2015	26,720

The established Fee for financial year (FY) 2015 will remain effect through September 30, 2015. Fees for financial years (FYs) 2015-2017 will be adjusted for inflation and other factors,

including the projected number of DMFs that FDA expects to be referenced for the first time in a given year based on experience. The fees details will be published in Federal Register no later than 60 days before the start of each fiscal year (October 1st to September 30th).

DMF fees will be incurred at the time of submission of a generic drug submission for all Type II API DMFs referenced for the first time by an initial letter of authorization on or after October 1, 2012. In general, fees will be due on the date the first generic drug submission is submitted that references the associated type II API DMF.

DMF holders may also pay the fee in advance of a first reference in order to have their DMF subjected to an initial completeness assessment by the Agency. This would allow their DMF to be included on a publicly-available list of DMFs that have paid their fee and not failed in the initial completeness assessment.

GDUFA requires Type II API DMFs to undergo initial complete assessment (CA) to ensure that the DMF is complete. (13) Although the requirement for an initial CA for Type II API DMFs is new, the elements of the initial CA have been used previously by FDA to evaluate DMFs. DMFs that have paid the fee and been found to be complete in accordance with the criteria for an initial CA set out in the checklist of guidance will be identified on FDA's public web site as available for reference in support of a generic drug submission. This initial CA does not replace the full scientific review, which will be performed to determine the adequacy or inadequacy of the information contained in the DMF to support an ANDA review decision.

For a generic drug submission to reference a Type II active pharmaceutical ingredient drug master file, the drug master file must be deemed available for reference in the Agency's website. A drug master file shall be deemed available for reference if:

(a) The person that owns a Type II active pharmaceutical ingredient drug master file must pay the DMF fee as required under GDUFA.

(b) The drug master file has not failed initial completeness assessment by the reviewer, in accordance with criteria set forth in the guidance.

If above criteria (a) and (b) were met, then the DMF will be made publicly available on the Internet web site of the Food and Drug Administration in the list of drug master file numbers available for reference.

If DMF holder failed to pay the DMF Fee then the DMF will be deemed not available for reference. Once the DMF fee becomes due, no generic drug submission submitted on or after October 1, 2012, referencing the DMF will not be received unless the fee is paid and the DMF is deemed available for reference.

Abbreviated New Drug Application and Prior Approval Supplement Filing Fee (9-12)

Under GDUFA, each applicant that submits, an abbreviated new drug application or a prior approval supplement to an abbreviated new drug application on or after October 1, 2012 shall be subjected to a fee for each such submission.

These fees are due on the date of submission of the ANDA or PAS. In certain circumstances, a partial refund (75 percent of the fee paid) may be possible to the applicant, if the reason for refusal of application is not related to failure to pay fees.

Based on the number of ANDAs and PASs received in each FY year, FDA has estimated to collect the ANDA and PAS fee in FY 2013, 2014 & 2015 as follows:

The established Fee for financial year (FY) 2015 will remain effect through September 30, 2015. Fees for financial years (FYs) 2015-2017 will be adjusted for inflation and other factors, including the projected number of ANDAs & PASs that FDA expects in a given year based on experience. The fees details will be published in Federal Register no later than 60 days before the start of each fiscal year (October 1st to September 30th).

If ANDA sponsor failed to pay either ANDA or PAS fee within 20 calendar days of from the date of submission, those submission will not be received by the Agency. (14)

Table 12: Details of ANDA and PAS submission fee

Fiscal Year	ANDA Fee (USD)	PAS Fee (USD)
2013	51,520	25,760
2014	63,860	31,930
2015	58,730	29,370

Table 13: Types of facilities

Generic Drug Facility	Each person that owns a facility which is identified or intended to be identified in at least one generic drug submission that is pending or approved to produce one or more finished dosage forms of a human generic drug shall be assessed an annual fee for each such facility.
API Facility	Each person that owns a facility which produces, or which is pending review to produce, one or more active pharmaceutical ingredients identified, or intended to be identified, in at least one generic drug submission that is pending or approved or in a Type II active pharmaceutical ingredient drug master file referenced in such a generic drug submission, shall be assessed an annual fee for each such facility.
Facilities producing both APIs and FDF	Each person that owns a facility identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce both one or more finished dosage forms subject to above referred Generic Drug Facility and one or more active pharmaceutical ingredients subject to above referred API facility shall be subject to fees under both such clauses for that facility.

An abbreviated new drug application or prior approval supplement that was submitted on or after October 1, 2012, and that the agency considers not to have been received, or that has been withdrawn, shall, upon resubmission of the application or a subsequent new submission following the applicant's withdrawal of the application, be subject to a full fee in respective Financial year of submission as per GDUFA Program.

Those ANDAs that include information about the production of active pharmaceutical ingredients other than by reference to a DMF need to pay an additional fee (i.e., DMF fee) that is based on the number of such active pharmaceutical ingredients and the number of facilities proposed to produce those ingredients.

Generic drug facility fee and active pharmaceutical ingredient facility fee (5, 9)

Facilities identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce a finished dosage form (FDF) of a human generic drug or an active pharmaceutical ingredient (API) contained in a human generic drug shall be subject to fees as follows:

In order to calculate the Annual FDF and API facility fee, FDA has designed a unique process called "self identification" of facilities in order to populate total number of facilities in one database. In this database the facilities will be categorized based on the type of business operations. Thus self identified number of

facilities will be considered for deciding the Facility fee for that financial year.

Self identification of facilities and laboratories (11, 12, 15-18)

The Food and Drug Administration (FDA) has notified generic drug facilities, and certain sites and organizations identified in a generic drug submission, that they must provide identification information to FDA. This information is required to be submitted to the FDA annually under the Generic Drug User Fee Act Amendments of 2012 (GDUFA) included in the Food and Drug Administration Safety and Innovation Act (FDASIA).

Table 14: Details of Self identification Process

<table>
<tr><td>Who is required to self-identify?</td><td>(a) Facilities identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce a human generic FDF or API, or both.
(b) A site or organization identified in a generic drug submission that is one or more of the following:
• A site in which a bioanalytical study is conducted
• A clinical research organization
• A contract analytical testing site
• A contract repackager site</td></tr>
<tr><td>What type of information must be submitted?</td><td>The information required to be submitted is identified in GDUFA SPL Industry Technical Specification Information document available at www.fda.gov/gdufa.
In brief the following information is required to submit:
(a) Name and contact information for both the registrant owner and the facility, if they are different, must be submitted.
(b) Type of business operation
(c) Data Universal Numbering System (DUNS) number(s) - DUNS number is a unique nine-digit sequence provided by Dun & Bradstreet, Inc.
(d) Facility Establishment Identifier (FEI) - FEI is a unique identifier designated by FDA to assign, monitor, and track inspections of regulated firms.
(e) Business entities will also be asked if they manufacture drugs other than generics.</td></tr>
<tr><td>Time period for self identification</td><td><table><tr><th>Fiscal Year</th><th>Self –Identification submissions received during the following dates</th></tr><tr><td>2013</td><td>Oct. 1, 2012 - Dec. 3, 2012</td></tr><tr><td>2014</td><td>May 1, 2013 - June 1, 2013</td></tr><tr><td>2015</td><td>May 1, 2014 - June 1, 2014</td></tr><tr><td>2016</td><td>May 1, 2015 - June 1, 2015</td></tr><tr><td>2017</td><td>May 1, 2016 - June 1, 2016</td></tr></table></td></tr>
<tr><td>What is the penalty for failing to self-identify?</td><td>(a) Under GDUFA, if a facility fails to self-identify, all FDF or API products manufactured at the facility and all FDFs containing APIs manufactured at the facility will be deemed misbranded.
(b) It is a violation of Federal law to ship misbranded products in interstate commerce or to import them into the United States. Such a violation can result in prosecution of those responsible, injunctions, or seizures of the misbranded products.
(c) Products that are deemed misbranded because of failure of the facility to self-identify are subject to being denied entry into the United States.</td></tr>
<tr><td>Which facilities have</td><td>Facilities identified, or intended to be identified, in at least one generic drug submission that is pending or approved to produce a human generic FDF or</td></tr>
</table>

to pay the facility fee?	***API*, *or both*.**

Based on the collated data of facilities (API and FDF) from self identification process the facility fee has been decided for FY 2013, 2014 & 2015 as follows:

Table 15: Details of Facility Fee [API and FDF]

Fiscal Year	FDF Facility Fee (USD)		API Facility Fee (USD)	
	Domestic (in USA)	Foreign	Domestic (in USA)	Foreign
2013	26,458	41,458	175,389	190,389
2014	34,515	49,515	220,152	235,152
2015	41,926	56,926	247,717	262,717

Table 16: Human Generic Application that require Form FDA 3794

(a)	Abbreviated new drug application (ANDA) or applicable amendment
(b)	Prior approval supplement (PAS) or applicable amendment
(c)	Type II active pharmaceutical ingredient (API) drug master file (DMF) that is referenced on or after October 1, 2012, in a generic drug submission to the FDA and for which the DMF fee has not already been paid
(d)	Generic drug facility which is identified or intended to be identified in at least one generic drug submission that is pending or approved to produce a finished dosage form (FDF) of a human generic drug or an API contained in a human generic drug
(e)	Backlog ANDA which is pending on October 1, 2012 (applicable only for financial year (FY) 2013), and that has not received a tentative approval prior to that date

For fiscal year 2013, the due date for payment of facility was within 45 days after the publication of the Federal Register notice dated January 17, 2013. For each of subsequent fiscal year i.e., 2014 through 2017, the fee will be due on the first business day on or after October 1 of each fiscal year (for all identified facilities).

The established Fee for financial year (FY) 2015 will remain effect through September 30, 2015. Fees for financial years (FYs) 2015-2017 will be adjusted for inflation and other factors, including the number of facilities that have self-identified each year. The fees will be published in the Federal Register approximately 60 days before the start of each fiscal year.

If a facility manufactures both generic FDFs and APIs, then under GDUFA, such a facility will incur both annual FDF and annual API facility fees.

If any personnel failed to pay the facility fee then there would be several consequences for failure to pay a facility fee. The facility will be placed on a publicly available arrears list if the fee is not fully paid within 20 days of the due date. No new generic drug submission referencing the facility will be received until the fee is paid. Furthermore, all FDFs or APIs manufactured in the non-paying facility and all FDFs containing APIs manufactured in such a facility will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to pay facility fees are subject to being denied entry into the United States.

Generic Drug User Fee Cover Sheet - Form FDA 3794 (19)

Per the Generic Drug User Fee Amendments of 2012 (GDUFA), Form FDA 3794 is required to be completed for each of the following human generic drug user fees:

FDA's review of a generic drug submission cannot begin until all applicable user fee obligations have been satisfied. A completed GDUFA Cover Sheet (Form FDA 3794)

provides the necessary information to determine the total user fee amount required and to help the agency track payments.

User Fee Payment Options and Procedures (19, 20)

To make a payment of the fee for DMF or ANDA or PAS or Facility, one must complete a Generic Drug User Fee Cover Sheet (form FDA 3794), available on the FDA Web site (http://www.fda.gov/gdufa) and generate a user fee payment identification (ID) number. Payment must be made in U.S. currency drawn on a U.S. bank by electronic check, check, bank draft, U.S. postal money order, or wire transfer.

The Office of Financial Management (OFM) is responsible for the financial management of the user fee programs. OFM maintains an account receivable system used for user fee invoicing, collections, reporting, and data maintenance.

Exemptions from GDUFA (21)

Positron Emission Tomography (PET) drug manufacturers are the only human generic drug manufacturers excluded from payment of GDUFA fees. They are, however, required to self-identify. FDA also requests that all drug manufacturers, including generic PET manufacturers, submit a user fee cover sheet with any new FDA submissions. PET manufacturers should complete a generic drug user fee cover sheet for $0.

Efforts from FDA to realize the GDUFA effective implementation

FDA has conducted several public meetings to collect the feedback and released several guidance documents with the agency's expectations as reference documents to generic drug industries. The summary of efforts and documents released/published by FDA since 2010 to till date in order to bring the GDUFA program in reality and to improve the existing review process of generic drug submission have been tabulated below (22):

Table 17: List of Documents/Guidance's/Notices/Rules released by FDA till February 2015

Title of Document	Action	Docket/ Document Number	Published Date
Generic Drug User Fee; Public Meeting; Request for Comments	Notice	FDA–2010–N–0381	August 09, 2010
Generic Drug User Fee; Public Meeting; Request for Comments	Notice	FDA–2010–N–0381	April 29, 2011
Generic Drug User Fee; Public Meeting; Request for Comments	Notice	FDA–2010–N–0381	July 22, 2011
Generic Drug User Fee; Public Meeting	Notice	FDA–2010–N–0381	December 08, 2011
Food and Drug Administration Safety and Innovation Act (FDASIA)	An Act	S. 3187 (Public Law 112-144)	July 09, 2012
Agency Information Collection Activities; Proposed Collection; Comment Request; Generic Drug User Fee Cover Sheet; Form FDA 3794	Notice	FDA–2012–N–0748	July 26, 2012
Draft Guidance for Industry on Generic Drug User Fee Amendments of 2012: Questions and Answers; Availability	Notice	FDA–2012–D–0880	August 27, 2012
Draft Guidance for Industry on Self-Identification of Generic Drug Facilities, Sites, and Organizations; Availability	Notice	FDA–2010–D–0881	August 27, 2012
Generic Drug User Fee Amendments of 2012; Public Meeting; Request for Comments	Notice	FDA–2012–N–0882	August 27, 2012

Notice of Opportunity To Withdraw Abbreviated New Drug Applications To Avoid Backlog Fee Obligations	Notice	FDA–2012–N–0879	August 27, 2012
Draft Guidance for Industry on Initial Completeness Assessments for Type II Active Pharmaceutical Ingredient Drug Master Files Under the Generic Drug User Fee Amendments of 2012	Notice	FDA–2012–D–1010	October 02, 2012
Generic Drug Facilities, Sites and Organizations - Self Identification Process	Notice of Requirement	FDA–2012–N–1006	October 02, 2012
FDA User Fee Correction Act of 2012	An Act	H.R.6433 (Public Law 112-193)	October 05, 2012
Generic Drug User Fee—Abbreviated New Drug Application, Prior Approval Supplement, and Drug Master File Fee Rates for Fiscal Year 2013	Notice	FDA–2012–N–0007	October 25, 2012
Generic Drug User Fee—Backlog Fee Rate for Fiscal Year 2013	Notice	FDA–2012–N–0007	October 25, 2012
Generic Drug User Fee—Active Pharmaceutical Ingredient and Finished Dosage Form Facility Fee Rates for Fiscal Year 2013	Notice	FDA–2013–N–0007	January 17, 2013
Generic Drug Facilities, Sites, and Organizations - Self Identification Process	Notice	FDA–2013–N–0391	April 16, 2013
Generic Drug User Fee Amendments of 2012; Regulatory Science Initiatives Public Hearing; Request for Comments	Notification of public hearing	FDA–2013–N–0402	May 09, 2013
Generic Drug User Fee-Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final dosage Form Facility, and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2014	Notice	FDA–2013–N–0007	August 02, 2013
Draft Guidance for Industry on Generic Drug User Fee Amendments of 2012: Questions and Answers (Revision 1); Availability	Notice	FDA–2012–D–0880	September 10, 2013
Draft Guidance for Industry on Abbreviated New Drug Application Submissions-Refuse-to-Receive Standards; Availability	Notice	FDA–2013–D–1120	October 1, 2013
Draft Guidance for Industry on Generic Drug User Fee Amendments of 2012: Questions and Answers (Revision 1);	Notice; reopening of the comment period.	FDA–2012–D–0880	November 27, 2013
Draft Generic Drug User Fee Act Information Technology Plan; Availability for Comment	Notice	FDA–2013–N–1615	December 26, 2013
Improving the Quality of Abbreviated New Drug Application Submissions to the Food and Drug Administration; Establishment of a Public Docket	Notice	FDA–2014–N–0032	January 23, 2014

Guidance for Industry; Providing Regulatory Submissions in Electronic Format—Receipt Date; Availability	Notice	FDA–2007–D–0077	February 7, 2014
Draft Guidance for Industry on Abbreviated New Drug Application Submissions; Content and Format of Abbreviated New Drug Applications; Availability	Notice	FDA–2014–D–0725	June 12, 2014
Draft Guidance for Industry on Abbreviated New Drug Application Submissions; Amendments and Easily Correctable Deficiencies Under the Generic Drug User Fee Amendments; Availability	Notice	FDA–2014–D–0902	July 11, 2014
Draft Guidance for Industry on Abbreviated New Drug Application Submissions—Prior Approval Supplements Under the Generic Drug User Fee Amendments of 2012; Availability	Notice	FDA–2014–D–0901	July 11, 2014
Generic Drug User Fee - Abbreviated New Drug Application, Prior Approval Supplement, Drug Master File, Final Dosage Form Facility, and Active Pharmaceutical Ingredient Facility Fee Rates for Fiscal Year 2015	Notice	FDA–2014–N–0007	August 1, 2014
Generic Drug User Fee Amendments of 2012; Public Hearing on Policy Development; Request for comments	Proposed Rules	FDA–2014–N–1168	August 19, 2014
Draft Guidance for Industry on Controlled Correspondence Related to Generic Drug Development; Availability	Notice	FDA–2014–D–1167	August 27, 2014
Guidance for Industry on Abbreviated New Drug Application Submissions- Refuse-to-Receive Standards; Availability	Notice	FDA–2013–D–1120	September 17, 2014
Draft Guidance for Industry on Abbreviated New Drug Application Submissions - Refuse To Receive for Lack of Proper Justification of Impurity Limits; Availability	Notice	FDA–2014–D–1292	September 17, 2014
Proposed Criteria for ‘‘First Generic’’ Submissions for Purposes of Abbreviated New Drug Application Review Prioritization Under the Generic Drug User Fee Amendments;	Notice; establishment of public docket; request for comments	FDA–2014–N–1741	November 19, 2014
Abbreviated New Drug Applications and 505(b)(2) Applications;	Proposed Rule	FDA–2011–N–0830	February 6, 2015
Generic Drug User Fee Amendments of 2012; September 2014 Public Hearing on Policy Development; Reopening of Docket; Request for Comments	Notice; reopening of docket; request for comments	FDA–2014–N–1168	February 6, 2015

After GDUFA implementation, a generic applicant has to comply with all requirements of GDUFA apart from the general requirements to prepare an Abbreviated New Drug Application i.e., getting drug substances from approved vendors, finished product development, clinical studies, plant inspection, dossier writing and finally submission to authorities. The diagram

(Figure 2) illustrates the various elements involved in obtaining approval for a generic product post GDUFA.

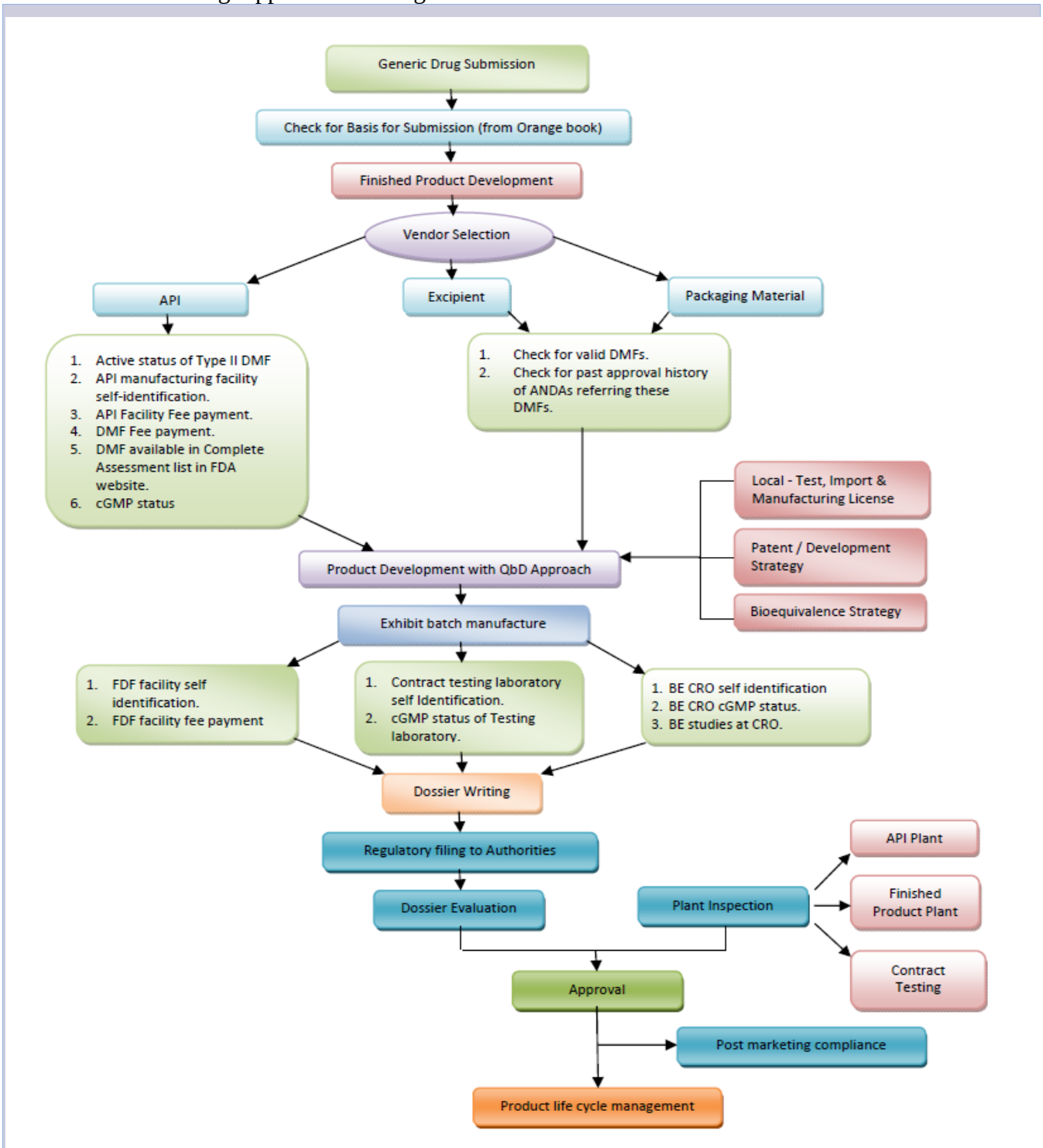

Figure 2. Components of Regulatory Filing post GDUFA implementation

Comparison of few elements in the requirements and review process of Generic drug Application pre and post GDUFA implementation are tabulated below:

Table 18: Comparison of elements of ANDA review Pre and Post GDUFA implementation

Element	Pre GDUFA	Post GDUFA
Self Identification of facilities and Laboratories	Not in place.	Required to identify all the facilities annually.
Facility Fee (API and FDF)	Not in place.	Required to pay the fee annually.
DMF Fee (for Active pharmaceutical ingredient)	Not in place.	Required to pay at once.
DMF Complete Assessment	Not in place.	Completeness Assessment of Type II DMF is mandatory in order to take up the ANDA for review (CA must be completed before ANDA submission date)
Deficiency letter	Issuing of Deficiency letters division wise i.e., CMC, DBE, Microbiology and Labeling.	Complete Response Letter by collecting deficiencies from all divisions i.e., CMC, DBE, Microbiology, Labeling and Inspections and other miscellaneous.
Amendment categories	Major, Minor Amendment	Tier system introduced with terminology of Solicited and Unsolicited Amendments with defined review goals
	Telephone Amendment	Information Request and Easily correctable deficiencies and in future FDA is planning to introduce Real time communication for resolving the minor deficiencies in minimum time to meet review goal
Goal Date for Approval	Not specified.	Goal date will be specified in the acceptance letter by OGD.
Typical review time for Generic Drug Application approval	The current median time for review of a new generic drug application is 31 months depending on the application quality and patent strategy.	FDA aspires to reduce the review time substantially; tentatively minimum 10 months and maximum may be 33 months depending on the application quality and patent strategy, litigation etc.
Limitation of number of Amendments during under review of ANDA (CMC Changes)	No limitation for Amendments, can propose changes during Amendment filing.	As number of Amendments increases, review time for application will be extended and may not be approved as per the given Goal date. So, good quality of Application will be approved early as per goal date.
PAS Submission	No Fee is incurred, and the review time of the application is not defined and the approval time ranges from 12 month to 24 months.	PAS Fee will be incurred. However, clear goal date for approval of the application will be defined (6 month or 10 months depending necessity of facility inspection).

Control Correspondence	Response for control correspondence has no time limitation.	Targeted to respond minimum 2 months and maximum 4 months (if inputs required from Clinical division).
cGMP Inspections	Frequency of Inspection has not been defined.	FDA will conduct risk-adjusted biennial cGMP surveillance inspections of generic API and generic finished dosage form (FDF) manufacturers.
Refuse to Receive standards (23)	Not in place	A guidance document has been released by FDA recommending to follow for the preparation of a good quality application in order to get the approval early i.e., goal date given by FDA.
Penalty to Refuse to Receive	No specific penalty defined.	Penalty would be in terms of Fee i.e., If FDA refuse to receive the application other than the reason of fee payment, then only 75% of the paid fee be refunded to the applicant.

CONCLUSION

The implementation of GDUFA program is yielding good improvements in FDA's division of Office of Generic Drugs (OGD) i.e., advancing/improving the review pattern of a generic application without compromising quality and efficacy for intended use of generic product. Further, FDA is planning to increase the staff to assess the Risk based quality approach and making every effort to allow the generic drugs in to the market for availability of patients/customers. Thus, the implementation of Generic Drug User Fee program benefits customers economically and benefits generic industries in facilitating early launch of generic products into the market.

Benefits to the consumers:

(a) **Access** - GDUFA will expedite the availability of low-cost, high-quality generic drugs by bringing greater predictability and timeliness to the FDA review process.

(b) **Quality** - GDUFA will help in increasing the safety and quality of the drugs required by the customers. Further, it helps in establishing a system to assure the high quality standards of generic drug manufacturing facilities (both foreign and domestic) at the same consistent level with very frequent inspections i.e., once every two years using a risk-based approach.

(c) **Transparency** - Under GDUFA, all facilities involved in the manufacture of generic drugs and their ingredients, both domestic and foreign, must be identified. This mandated identification system enhances the transparency in knowing the number of facilities involved in the manufacture of Generic Drugs and help FDA to protect customers in today's complex global supply environment.

Benefits to Industry

(a) GDUFA will deliver greater predictability and timeliness to the review of generic drug applications, slashing review times and saving industry time and money.

(b) Under GDUFA, based on an agreement negotiated by FDA and representatives of the generic drug industry, FDA will further modernizes the generic drug approval program time to time and sets new performance goals for initiatives to encourage the sooner availability of generics in the market.

(c) The annual fee total for GDUFA represents only about one half of 1 percent of generic drug sales. This relatively small cost to the

industry could be offset by faster review times that bring products to market sooner.

ACKNOWLEDGEMENTS

I express my gratitude to my family members and Management of Daewoong Pharmaceutical Co. Ltd., India for supporting me in writing this article. The contents of this article are the sole responsibility of the authors and do not necessarily reflect the views of Daewoong Pharmaceutical Co. Ltd, India.

CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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