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GENERIC DRUG USER FEE: AN OVERVIEW

Darshit S. Patel*, Abhishek R. Patel and Narendra A. Patel

Astron Research Limited, Ahmedabad, Gujarat, India

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Correspondence to Author:

Dr. Darshit S. Patel

Team Leader-Regulatory Affairs, Astron Research Limited, Premier House-1, S.G. Highway, Bodakdev, Ahmedabad-380054, Gujarat, India

E-mail:darshit_patel@astron-research.com

ABSTRACT

The globalization of generic drug manufacturing, supply and testing, and a growing workload that has far outpaced USFDA's resources has created new challenges. USFDA & Industry propose generic drug user fee to address the need for globalization of the inspection process, and to speed the timely review of generic product applications. The Generic Drug User Fee (GDUF) proposal is agreed by generic industry & USFDA and is focused on three key aims: safety, access, and transparency. Under the program, USFDA will receive nearly $1.5 billion over five years in supplemental funding through generic industry user fees in order to help the agency expedite access to generic drugs, enhance drug quality and safety and ensure inspection parity of both foreign and domestic manufacturing sites. GDUF also will help accelerate the market entry of additional manufacturers of drugs currently in short supply and improve quality, consistency, and availability within the supply chain, further helping to mitigate drug shortages. The GDUF new legislation is a milestone for the generic giants and a major win for American health care consumers.

INTRODUCTION:

Generic Drug [1, 2]: A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in USFDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book).

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug. According to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. Even more billions are saved when hospitals use generics.

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Key Functions in the Generic Drug Review [3]: All of the key functions listed below must be conducted in order to ensure the safety, efficacy, and quality of each generic drug. CDER's OGD responsible for conducting reviews of generic drug applications. The overall Generic Drug Review includes efforts from other offices within CDER and Office of Regulatory Affairs (ORA) to accomplish the key functions mentioned below.

- **Generic Application Review**: The basic requirements for approval of generic drugs are the same as for new drug approvals, although the generic drug manufacturer does not need to repeat the safety and efficacy studies conducted by the developer of the original product. Prior to approval, generic drug sponsors are required to demonstrate bioequivalence - that the active ingredient in a generic product is absorbed at a rate and extent similar to the brand name product. Medical reviewers from the OGD often consult with reviewers from the Office of New Drugs (OND) to address clinical questions regarding the referenced brand-name drug.

- **Pre Approval and Bioequivalence Lab Inspections:** As with new drug products, before an application for a generic drug product can be approved, USFDA must inspect the product manufacturing facility to ensure that manufacturing and development facilities meet USFDA's standards for good manufacturing practices. In addition, USFDA inspects the laboratories where bioequivalence studies were conducted to ensure the accuracy and integrity of the data submitted in the generic drug application.

- **Regulatory Policy:** USFDA frequently receives citizen petitions for or against an upcoming FDA action on a generic drug application. A citizen petition is a vehicle that stakeholders outside of FDA may use in order to suggest that USFDA take – or refrain from taking – an action. FDA has received numerous petitions asking USFDA not to approve particular generic drugs unless certain criteria set forth in the petition are met. In most cases, the petitions raise scientific issues relating to the standards for approval of the applications. CDER must evaluate and respond to each of these citizen petitions.

- **Researches into Bioequivalence Technologies:** Some types of drugs are very difficult for generic companies to duplicate. This is attributed, in part, to utilization of novel delivery technologies to which the human body's reactions are highly variable (for example, patches worn on a patient's skin, injections, etc.) In cases like these, FDA is eager to understand how to assess bioequivalence as a way to encourage development of generic alternatives, opening the doors to lower prices and better access to drugs for patients.

Generic Drug User Fees (GDUF) [4]: An important responsibility of USFDA is to assess generic drug applications. Generic drugs currently are used to fill more than two-thirds of all prescriptions dispensed in the United States and they provide important cost-effective alternatives to the American public. Nonetheless, despite increasing productivity on the part of USFDA's OGD, the number of applications awaiting USFDA action has been steadily increasing, and the median time for review of such applications has grown (the current average approval time is 31 months).

Similar to user fees for brand name human drugs, animal drugs, generic animal drugs, and medical devices, the intent of a generic drug user fee program would be to provide additional revenues so that USFDA can hire more staff and improve systems to support the generic drug review process. USFDA believes the supplementary revenues from generic drug user fees would allow the Agency to review generic drug applications in a timely manner and will provide flexibility, adequacy, and predictability in the funding of USFDA's review of generic drug applications.

Although the last several administration budgets contain a generic drug user fee program, new legislation would be needed to put such fees into place. At this time, generic drugs for humans are the largest category of preapproval products regulated by USFDA and generic drug applicants do not currently pay any type of user fee. USFDA believes that the predictability, flexibility, and adequacy of a funding stream from user fees and the accompanying ability to

more efficiently review generic drug applications would benefit the public health, USFDA, and the generic drug industry.

GDUF will focuses on three key aims: [5]

- **Safety:** Ensure that industry participants, foreign or domestic, who participate in the United States generic drug system are held to consistent high quality standards and are inspected biennially, using a risk-based approach, with foreign and domestic parity.

- **Access:** Expedite the availability of low cost, high quality generic drugs by bringing greater predictability to the review times for abbreviated new drug applications, amendments and supplements, increasing predictability and timeliness in the review process.

- **Transparency**: Enhance FDA's ability to protect Americans in the complex global supply environment by requiring the identification of facilities involved in the manufacture of generic drugs and associated active pharmaceutical ingredients, and improving FDA's communications and feedback with industry in order to expedite product access.

Necessity of GDUF [3]: The growth in generic drug applications has outpaced USFDA resources, resulting in an application backlog and an increase in time to approval. Generic drugs are now increasingly complex, and product testing and manufacturing often occurs in overseas facilities. To keep pace with the increase in applications and to respond to changes in the industry, USFDA is proposing increased resources in the form of user fees. These fees will:

- Strengthen the USFDA generic drugs program
- Enhance the application review process
- Allow FDA to increase post-market safety and overseas inspection activities

With each new generic version of a brand-name drug that FDA approves, consumers have an additional option to save money on their prescription needs. The proposed user fee investments in USFDA's generic drug program will generate additional savings by bringing more generics to market sooner, which will benefit more American patients. Without these GDUF resources, USFDA will not be able to address the growing number of pending generic drug applications and ensure more timely availability of generic drugs. Without these improvements, patients may continue to struggle to afford medical treatments that they need and health care payers will face increased drug costs.

Delays in the availability of less-expensive generic drugs will result in higher costs for patients – some of whom may forego critical medicines if their drugs are unaffordable – leading to poorer health outcomes. Without the user fees, USFDA will not be able to respond to important changes in generic manufacturing, including the increasing complexity of some products and the shift to overseas manufacturing.

Type of Fees & Fee Revenue Amounts [6, 7]

Type of Fees: Beginning in fiscal year 2013, the USFDA will assess and collect fees in accordance with generic drug user fee act (GDUFA) program. GDUFA would establish three ongoing types of fees: drug master file [DMF]; application filing [abbreviated new drug application (ANDA) and prior approval supplement (PAS)]; and facility [generic drug (GDF) and active pharmaceutical ingredient (API)]. It would also establish a one-time backlog fee.

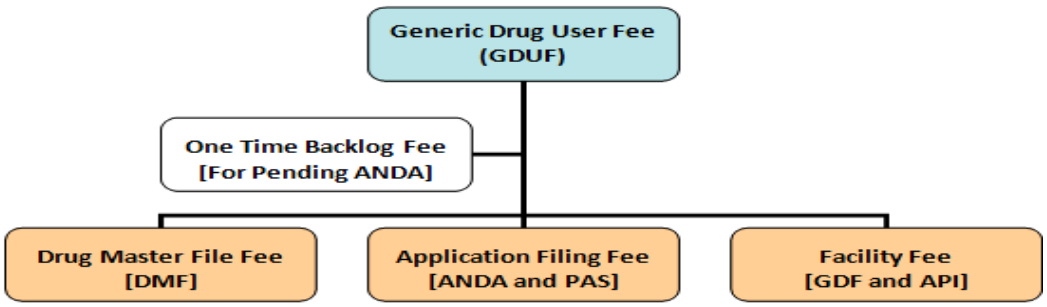

FIGURE 1: TYPE OF GENERIC DRUG USER FEE (GDUF)

One-Time Backlog Fee [Abbreviated New Drug Applications Pending on October 1, 2012]: Each person that owns a pending ANDA on October 1, 2012 that has not yet received tentative approval would be required to pay a one-time backlog fee. Backlog fees would total $50 million divided by the number of pending ANDAs. The fee required will be paid no later than 30 calendar days from the publication of the notice.

Drug Master File Fee: Each person that owns a Type II active pharmaceutical ingredient (API) DMF that is referenced on or after October 1, 2012 in a generic drug submission by any initial letter of authorization will be subject to a DMF fee. Once a person has paid a DMF fee for a Type II API DMF, the person shall not be required to pay a subsequent DMF fee when that Type II API DMF is referenced in additional generic drug submissions.

For fiscal year 2013, by October 31, 2012, the USFDA will publish notice in the Federal Register [FR] for amount of the drug master file fee. For each of fiscal years 2014 to 2017, the USFDA will publish notice in the FR for amount of the drug master file fee, 60 days before the start of each such fiscal year.

Upon payment of the DMF fee by DMF holders, USFDA will conduct a completeness assessment of Type II API DMF. Following a satisfactory completeness assessment, USFDA will deem the DMF available for reference, placing the DMF number in a publicly available list of Type II API DMF available for reference.

Application Filing Fee [Abbreviated New Drug Application (ANDA) and Prior Approval Supplement (PAS)]: Each applicant that submits, on or after October 1, 2012, an ANDA or a PAS to an ANDA will be subject to a fee.

For fiscal year 2013, by October 31, 2012, the USFDA will publish notice in the FR for amount of the application fee. For each of fiscal years 2014 to 2017, the USFDA will publish notice in the FR for amount of the application fee, 60 days before the start of each such fiscal year. The fees required by GDUFA will be due no later than the date of submission of the ANDA or PAS, except that, for fiscal year 2013, the fee will be due on the later of---

(i) the date of submission of the ANDA or PAS; or

(ii) 30 calendar days after publication of the notice, if an appropriations Act is not enacted providing for the collection and obligation of fees.

Refund of fee if ANDA is not considered to have been received -- The USFDA will refund 75 percent of the fee paid under GUDFA for ANDA or PAS to an ANDA that the USFDA considers not to have been received pursuant to Federal Food, Drug, and Cosmetic Act (FFDCA), section 505(j)(5)(A) as implemented in USFDA regulations, for a cause other than failure to pay fees.

Fee for an application the USFDA considers not to have been received, or that has been withdrawn -- An ANDA or PAS that was submitted on or after October 1, 2012 and that the USFDA considers not to have been received, or that has been withdrawn, will be subject to a new full fee under GUDFA upon resubmission of the application or a subsequent new submission following the applicant's withdrawal of the application.

Facility Fee [Generic Drug Facility Fee and Active Pharmaceutical Ingredient]: 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 of a human generic drug or an API contained in a human generic drug will be subject to this fees as follows:

1. **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 will be assessed an annual fee established under this for each such facility.

2. **Active Pharmaceutical Ingredient Facility**: Each person that owns a facility which produces, or which is pending review to produce, one or more API identified, or intended to be identified, in at least one generic drug submission that is pending or approved or in a Type II API DMF referenced in such a generic drug submission, will be assessed an annual fee established under this for each such facility.

3. **Facilities Producing Both Active Pharmaceutical Ingredients and Finished Dosage Forms**: 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 form and one or more active pharmaceutical ingredient will be subject to fees under both clauses for that facility.

   For fiscal year 2013, the fees required by this enacted act, will be paid within 45 calendar days of the publication of the notice except that if an appropriations Act is not enacted providing for the collection and obligation of fees, the fee will be due 30 calendar days after the date that such an appropriations Act is enacted.

   For each of fiscal years 2014 through 2017, such fees will be due on the later of— (I) the first business day after October 1 of each such year; or (II) the first business day after the enactment of an appropriations Act providing for the collection and obligation of fees for such year.

Fee Revenue Amounts: The total estimated revenue for all fees for FY2013 would be $299,000,000 ($299 million), of which $50,000,000 ($50 million) would be from the one-time backlog fee for pending applications. For each of FY2014 through FY2017, the total estimated revenue for the continuing fees would be $299 million.

Other than the one-time backlog fee, the relative proportion of each fee to the total annual amount would be:

- 6% (Six percentages) from drug master file fees;
- 24% (Twenty four percentages) from ANDA and prior approval supplement fees;
- 56% (Fifty six percentages) from generic drug facility fees; and
- 14% (Fourteen percentages) from API facility fees.

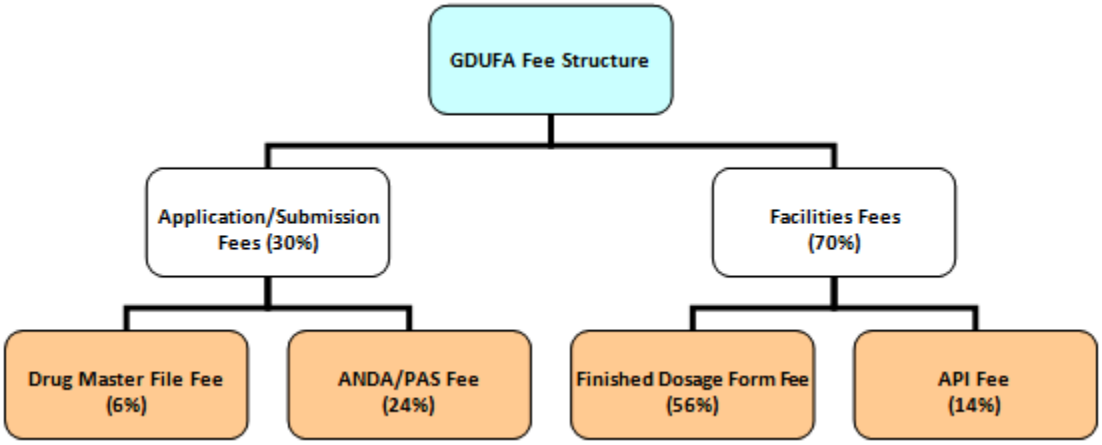

FIGURE 2: GDUFA FEE STRUCTURE

The fee for facilities located outside the United States would be $15,000-$30,000 higher than fees for facilities located in the United States, based on the difference in the cost of inspections as determined by the USFDA.

Effect of Failure to Pay Fees [6, 7]**:** The penalties for failing to pay GDUFA fees are particularly harsh under the proposed statutory language.

1. Failure to pay the ANDA backlog fee will result in placing the ANDA sponsor on an arrears list, "such that no new ANDAs or supplement submitted on or after October 1, 2012 from that person, or any affiliate of that person, will be received within the meaning of [FFDCA § 505(j)(5)(A)] as implemented in USFDA regulations, until such outstanding fee is paid." Proposed FFDCA § 744B(g)(1)

2. Failure to pay the DMF fee within 20 calendar days of the due date "will result in the Type II API DMF not being deemed available for reference." An affected ANDA "shall not be received within

the meaning of [FFDCA § 505(j)(5)(A)]" unless the fee "has been paid within 20 calendar days of the Secretary providing the notification to the sponsor of the [ANDA] or supplement of the failure of the owner of the Type II API DMF to pay the DMF fee . . . ." Proposed FFDCA § 744B(g)(2).

3. Failure to pay the required ANDA/PAS-application fee within 20 calendar days of the due date will result in the application not being received (FFDCA § 505(j)(5)(A)) until the fee is paid. Proposed FFDCA § 744B(g)(3).

ANDA receipt date is, of course, particularly important when 180-day exclusivity is at stake. And the proposed statute recognizes this at FFDCA § 744B(n), which states:

An ANDA that is not considered to be received within the meaning of [FFDCA § 505(j)(5)(A)] because of failure to pay an applicable fee under this provision within the time period specified in [FFDCA § 744B(g)] shall be deemed not to have been "substantially complete" on the date of its submission within the meaning of [FFDCA § 505(j)(5)(B)(iv)(II)(cc)]. An ANDA that is not substantially complete on the date of its submission solely because of failure to pay an applicable fee under the preceding sentence shall be deemed substantially complete and received within the meaning of [FFDCA § 505(j)(5)(A]) as of the date such applicable fee is received.

4. Failure to pay a facility fee within 20 calendar days of the due date will result in several penalties, included what might be the harshest penalty of all – misbranding. Specifically, proposed FFDCA § 744B(g)(4) states that failure to pay a fee will result in:

   a. identification of the facility on a publicly available arrears list, such that no new [ANDAs] or supplement submitted on or after October 1, 2012 from that person, or any affiliate of that person, will be received within the meaning of [FFDCA § 505(j)(5)(A)] as implemented in USFDA regulations;

   b. any new generic drug submission submitted on or after October 1, 2012 that references such a facility shall not be received, within the meaning of FFDCA § 505(j)(5)(A)] as implemented in USFDA regulations if the outstanding facility fee is not paid within 20 calendar days of the Secretary providing the notification to the sponsor of the failure of the owner of the facility to pay the facility fee as specified in [proposed FFDCA § 744B(a)(4)(C)]; and

   c. all drugs or APIs manufactured in such a facility or containing an ingredient manufactured in such a facility being deemed misbranded under [proposed FFDCA § 502(aa)].

The penalties in [proposed FFDCA § 744B(g)(4)] shall apply until the [facility] fee . . . is paid or the facility is removed from all generic drug submissions that refer to the facility.

Proposed FFDCA § 502(aa) would amend the statute to state that a drug shall be deemed to be misbranded:

If it is a drug, or an active pharmaceutical ingredient, and it was manufactured, prepared, propagated, compounded, or processed in a facility for which fees have not been paid as required by section [proposed FFDCA §744A(a)(4)] or for which identifying information required by section [proposed FFDCA §744B(f)] has not been submitted, or it contains an active pharmaceutical ingredient that was manufactured, prepared, propagated, compounded, or processed in such a facility.

Generic Drug User Fee Act Program Performance Goals [5, 8]: GDUFA will include performance goals that cover improvements over a broad range including review times, staffing, communications, and submission methods.

Major Program goals can be summarized as follows;

Backlog Metrics: FDA will review and act on 90 percent of all ANDAs, ANDA amendments and ANDA prior approval supplements regardless of current review status pending on October 1, 2012 by the end of FY 2017. (Currently, there are more than 2,000 applications and supplements in the backlog),

Application Metrics: By year five, USFDA will review and act on 90 percent of complete electronic ANDAs within 10 months after the date of submission. (Current average approval time is 31 months.)

cGMP Inspection Metrics: By year five, USFDA will conduct risk-adjusted biennial cGMP surveillance inspections of generic API and generic finished dosage form manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017.

Efficiency Enhancements: USFDA will implement various efficiency enhancements impacting review of ANDAs and DMFs, as well as inspections, upon enactment of the program (e.g., use of complete review/response letters; completeness assessment for DMFs intending to be referenced by ANDA sponsors; division level deficiency review; and first cycle deficiency meetings for ANDAs and DMFs).

Regulatory Science: USFDA will undertake various initiatives designed to enhance post-marketing safety, develop guidance for industry and mitigate regulatory science gaps in select generic regulatory pathways.

Current Status [7]**:** Bill S. 3187: Food and Drug Administration Safety and Innovation Act, A bill to amend the Federal Food, Drug, and Cosmetic Act to revise and extend the user-fee programs for prescription drugs and medical devices, *to establish user-fee programs for generic drugs* and biosimilars, and for other purposes.

Currently, this bill passed in the United States Senate & the United States House of Representatives and signed by the US President on July 9, 2012.

Bill S. 3187 Status:	
Introduced	May 15, 2012
Reported by Committee	May 16, 2012
Passed Senate	May 24, 2012
Passed House with Changes	Jun 20, 2012
Passed House	Jun 26, 2012
Signed by the President	Jul 09, 2012

Impact on the Generic Pharmaceuticals Industry [7, 9]: At present, Bill S. 3187: Food and Drug Administration Safety and Innovation Act, signed by the US President on July 9, 2012. This bill is publicized information about the user-fee programs for generic drugs.

Smaller companies seem to be quite concerned that they will be priced out of the market. Meanwhile, some companies with multiple manufacturing sites are worried that they will get hit hard by annual facility fees. It is possible that some companies may choose to consolidate manufacturing sites to avoid paying multiple fees.

Some manufacturers view the proposed user fees as anticompetitive due to the barrier of entry which it creates while others argue that faster and more predictable review times will speed up product launches thus benefiting the manufacturers. It is also possible that, at least initially, the increased number of global surveillance inspections will lead to additional warning letters and import bans which may prevent certain companies from selling their products into the US market. Therefore, the creation of additional drug shortages is another possible unintended consequence of GDUFA.

Going forward, companies will likely be selective about which active ingredients and finished dose forms they manufacture and may choose to stop production of some low margin products in light of having to pay user fees. Because the budget for GDUFA is fixed and based on a set amount of regulatory filings per year, a decrease in the number of DMF and ANDA submissions would result in higher user fees the following year, further contributing to the drug shortage problem. On the plus side, the quicker review times should make it possible for new players to enter the market if shortages loom.

CONCLUSION: At present, generic pharmaceuticals is the largest category of products that must be pre-approved and regulated by the USFDA. As healthcare costs continue to skyrocket, the USFDA needs stability and the funds to efficiently review drug applications as well as help the USFDA monitor the safety of foreign manufacturing facilities. GDUF changes USFDA generic review landscape with millions in new funds. GDUF is being viewed as a significant game changer within the industry.

The GDUF new legislation will likely favor the generic giants and those smaller players who possess excellent quality systems. The increased frequency with which USFDA inspects facilities will lead to improved and more consistent quality generic medicines which ultimately benefit U.S. consumers, although in the short term we should be prepared for additional drug shortages.

DISCLAIMER: The authors do not claim anything; the purpose of this review article is solely educational. This review article is built from our work and experience. It is not the official position of Astron Research Limited or its subsidiary companies policies and position.

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