Generic Drug User Fee Proposal Summary

CORE ELEMENTS OF GENERIC DRUG USER FEE PROPOSAL

- SAFETY - Ensure all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard and inspected by the FDA on an biennial basis
- ACCESS - Expedite the availability of low cost, high quality generic drugs by decreasing the median review time of applications and supplements
- TRANSPARENCY - Enhance the FDA's ability to protect Americans in the complex global supply environment by identifying, tracking and requiring the registration of all contributors involved in each drug product sold in the US

GENERIC DRUG USER FREE PROPOSAL SHOULD <u>NOT</u>:

- Delegate FDA inspectional responsibilities to third parties
- Tie fees (including application specific fees) to an artificial timeframe for application review because not all applications or supplements can or should be treated equally and because generic applicants uniquely experience various Hatch Waxman delays that prevent launch even after the application review is complete
- Encourage different application treatment or different safety standards based solely on the U.S. or non-U.S. location of an establishment

PROPOSED FEE STRUCTURE

- Establishment Registration Fee
- Inspection Fee
- Application Fee

PROPOSED SELECT KEY PERFORMANCE METRICS

- Decrease median application review times to reach 12 months within 3 years, including pending applications
- Biennial inspections for all facilities, foreign and domestic, with prompt agency wrap-up or follow-up
- Improved reviewer to application ratio, increase in staffing, including reviewers and inspectors
- Prompt feedback to applicant requests and transparency regarding application status

CORE ELEMENTS OF GENERIC DRUG USER FEE PROPOSAL

1. **Ensure all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard and inspected by the FDA on an biennial basis**

   - To create an effective user fee program that provides resources to be used in a meaningful way, we must focus on the critical issues facing our government and the US pharmaceutical consumer – access to needed drugs with the knowledge that those drugs are safe and effective regardless of where they are made, where the API is sourced, where clinical work is done, and where packaging and storage takes place.

   - Establishment Registration Fees and Inspections Fees will help the FDA to address global supply chain challenges and ensure all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard so that consumers can rely on the safety of the medications they consume.

2. **Expedite the availability of low cost, high quality generic drugs by decreasing the median review time of applications and supplements**

   - Traditional user fee proposals focused solely on how to provide additional resources to the FDA so that the agency can expedite the application approval process and eliminate the backlog of applications will not work for generics given the unique Hatch-Waxman generic drug approval system.

   - Under a solely application based user fee structure, generics will consistently be "paying to wait" given the unique Hatch-Waxman generic drug approval system. Unlike a branded product, which can obtain approval and launch immediately following FDA's scientific review, the approval and launch of generic drugs is subject to months, sometimes years of additional delays following the FDA's review.

   - The user fee model should encourage the appropriate review and approval of ANDAs and not simply create a cookie cutter approach that treats all applications alike and fails to recognize legal distinctions between applications such as first to file ANDA v. subsequent ANDAs, and/or significance of a particular product, such as one that meets an unmet medical need, a first generic, or an orphan drug. It is critical that the safety of our drug supply is never compromised for the sake of speed. Make no mistake, we believe in timely access to life-saving medications is very important. However, a user fee model that only looks at the timing of the approval process for an application misses a more critical point - SAFETY.

   - A generic user fees program should require a review tailored to each individual application while ensuring the good quality standing of each and every establishment - domestic and foreign - involved in the development and manufacture of each and every drug sold in the U.S., so that every American can have faith in the quality, safety and effectiveness of any pharmaceutical product they consume.

- Even without the variables commonly uniquely experienced by generic applicants under Hatch Waxman, a user fee system tied to the certainty of an artificial timeframe is still flawed because not all applications can or should be treated equally.

- While making sure the FDA has the resources to conduct timely and efficient reviews is important to all of us, it's also paramount that the agency have the flexibility to conduct more or less time-intensive reviews based upon the quality of the application filed.

- An application fee will also supplement Agency resources by ensuring that FDA has continuous supplemental resources to match review demand by hiring and training the number of reviewers necessary to ultimately achieve median review times of 12 months within 3 years.

- A reduction in the Median Review Times of Applications and Supplements as proposed in the Performance Metrics Summary below will address pending applications as well as new applications going forward.

- We must also develop a user fee model that prohibits differences in application treatment based solely on the U.S. or non-U.S. location of an establishment.

3. Enhance the FDA's ability to protect Americans in complex global supply environment by identifying, tracking and requiring the registration of all contributors involved in each drug product sold in the US

- An establishment registration fee should not only provide much needed resources to the FDA, it would also give the Agency the ability to identify and track all contributors involved with each drug product by creating an accurate database of sites around the world that play a part in making the pharmaceuticals U.S. consumers ingest.

- An application fee will also supplement Agency resources of making sure all approved applications are maintained and reviewed annually and provide additional resources associated with monitoring adverse events, annual report reviews, promotional materials review, and other post approval commitments made by application holders.

THE GENERIC DRUG USER FREE PROPOSAL SHOULD <u>NOT</u>

- Delegate FDA inspectional responsibilities to third parties

- Tie fees (including application specific fees) to an artificial timeframe for application review because not all applications or supplements can or should be treated equally and because generic applicants uniquely experience various Hatch Waxman delays that prevent launch even after the application review is complete

- Encourage different application treatment or different safety standards based solely on the U.S. or non-U.S. location of an establishment

Establishment Registration Fee

Purpose:

- The establishment fee acts like a business license or registration tied simply to the act of participating in and benefiting from the U.S. pharmaceutical market which is regulated by the FDA. The creation of such a fee will supplement existing FDA funds to assist FDA in carrying out its responsibility of ensuring the safety, efficacy and security of the U.S. drug supply and provide additional resources necessary to support the increasing complex global drug supply environment.
- Requiring all participants in the U.S. pharmaceutical market register with the FDA will also give the Agency the ability to identify and track all contributors involved with each drug product, and provide information to create an accurate database of sites around the world that play a part in making the pharmaceuticals that U.S. consumers consume.
- Funds derived from the annual establishment fee will also allow FDA to increase the number of agency staff, including inspectors and application reviewers, among others and would also allow agency to invest in continual improvement measures (ie, system to track and monitor the time an application spends in the review queue in active and inactive status, as well as review times by division, by individual, by application, and by applicant).

Scope:

- An establishment registration fee will be required for any facility that seeks to participate in the process of researching, developing, manufacturing, supplying active ingredients for or performing clinical or other laboratory work in support of a pharmaceutical product to be sold in the U.S.
- The following participants would be required to register and pay an establishment fee: finished dose manufacturers, API suppliers, bioanalytical labs, clinical labs, contract analytical labs, contract research organizations, packagers/repackagers

Mechanics:

- Establishment Registration fee paid annually by any facility that wants to participate in the research, development, clinical, packaging, and supply of ingredients for and/or manufacturing of a product to be sold in the U.S.
- Self policing mechanism: Facility cannot submit a DMF or an application unless the applicant and/or all of the facilities the applicant is utilizing to support the application has paid annual establishment registration fee
- Foreign registered establishments will not experience import delays except for good cause shown. If an import hold or delay is imposed at the border involving an FDA registered establishment's product, FDA must provide notice of the concerns within 24 hours of imposing an import delay or hold and shall take action to resolve or request further information within 48 hours of receipt of additional information.
- Foreign registered establishments will be permitted to import more than one shipment at a time to receive the forecasted quantities needed prior to approval under FDA's Pre-Launch Activities Import Request Program
- Fees vary according to the type of facility and scope of its pharmaceutical manufacturing role.
    - FDF manufacturer: $100,000
    - API manufacturers: $50,000
    - Packagers and Re-packagers: $25,000
    - Bio Clinical Sites and Bio-Analytical Laboratories: $12,500
- A facility that performs more than one function identified above at the same site will not be charged twice
- FDA will maintain a publicly accessible database to allow others to verify registration status and license number
- Sunset provision - Fee amount, scope and associated metrics to be reevaluated in five years
- Performance Metrics Summary- See attached Chart

Inspection Fee

Purpose:

- The purpose of an Inspection Fee is to provide FDA with additional resources to ensure that all establishments, regardless of whether they are located in the US or outside the country, comply with U.S. quality standards.
- An Inspection Fee would be charged on an inspection-by-inspection basis to help cover expenses associated with carrying out an onsite agency inspection of an FDA facility. Inspection fees would supplement FDA funding in order to ensure that all facilities, foreign and domestic, are inspected at least one every two years. Biennial inspections should be legally required for Foreign Establishments, not just domestic, as provided under current law.
- Inspection fees will also provide additional resources to ensure timely administrative follow-up after an inspection occurs.

Scope:

- An inspection fee should be required of any facility that seeks to participate in the process of researching, developing, manufacturing, supplying active ingredients for or performing clinical or other laboratory work in support of a pharmaceutical product to be sold in the U.S and requires FDA inspection.
- An inspection fee should be assessed for all inspections (including, for example, preapproval product inspections, new site inspections, GMP inspections, for cause inspections, 483 related follow-up inspections, etc).

Mechanics:

- An Inspection Fee would be paid at the time of inspection. The Inspection Fee would be based, at least in part, on the type of establishment inspected and must also be designed to promote the effective use of FDA resources including travel costs as well as scope and length of an inspection.
- Fee will be charged to the site being inspected with the understanding that the inspected site has discretion to pass through costs as appropriate.
- The Inspection Fee would also account for the estimated amount of time and related expenses any particular inspection takes, and account for the additional staffing, additional travel and interpreter related expenses involved in conducting foreign inspections. The proposed inspection fees are as follows:
  - Foreign establishments: $30,000 per inspection
  - Domestic establishments: $15,000 per inspection
- Performance Metrics Summary- See attached Chart

Application Fee

Purpose:

- An application fee is a fee intended to supplement FDA's costs associated with conducting review of abbreviated new drug applications and provide the Agency with additional resources necessary to hire and train an appropriate number of reviewers to achieve the median review times outlined below. Because the fee will be assessed on an each application submitted, the fees generated will ensure that FDA has continuous supplemental resources to match review demand. The fees will also supplement post approval associated resources needed to make sure all approved applications are maintained and reviewed annually as well as monitoring adverse events, annual report reviews, promotional materials review, and other post approval commitments made by application holders.

Scope:

- This fee will be paid by each ANDA applicant at the time the application is submitted to the FDA for review. The fee would be assessed on all ANDAs that are pending approval at the time of the effective date and on all ANDAs submitted after the effective date going forward.

Mechanics:

- An Application Fee would be paid at the time of ANDA submission. The same application fee shall be applied regardless of the product type.
- Performance Metrics Summary- See attached Chart

PROPOSED USER FEE PERFORMANCE METRICS

Application Median Review Times* (review times include both pending applications and new submissions)

*Median review time is irrespective of whether the application is blocked from approval as a result of a patent, exclusivity, 30 month stay, or court order

- Median review times of all applications reduced to at least 20 months within one year of effective date
- Median review times of all applications reduced to at least 16 months within two years of effective date
- Median review times of all applications reduced to at least 12 months within three years of effective date and each year thereafter

Prior Approval Supplement Median Review Times (review times include both pending applications and new submissions)

- Median review times of all supplements reduced to at least 12 months within one year of effective date
- Median review times of all supplements reduced to at least 9 months within two years of effective date
- Median review times of all supplements reduced to at least 6 months within three years of effective date and each year thereafter

Inspections

- All domestic and foreign establishments GMP inspected at least once every two years, starting within two years of effective date
- Foreign registered establishments will not experience import delays except for good cause shown. If an import hold or delay is imposed at the border involving an FDA registered establishment's product, FDA must provide notice of the concerns within 24 hours of imposing an import delay or hold and shall take action to resolve ore request further information within 48 hours of receipt of additional information.
- Foreign registered establishments will be permitted to import more than one shipment at a time to receive the forecasted quantities needed prior to approval under FDA's Pre-Launch Activities Import Request
- Inspector team to provide inspection report to headquarters within two weeks of inspection
- Office of Compliance must review inspection report and provide any feedback within two weeks of receipt
- Office of Compliance must review 483 responses, issue close out action/Establishment Inspection Report and update Office of Compliance internal inspection status database within two weeks of receipt of 483 responses or seek additional information within two weeks following receipt of reply
- FDA shall expedite and prioritize inspections for facilities associated with an application that is otherwise approvable except for an outstanding inspection. Such inspection must occur within 30 days of date ANDA is expected to become otherwise approvable.
- When an applicant adds a new site of manufacture or any other change requiring an inspection including those identified in FDA's Post Approval Changes Guidance, including first time site registrants, FDA shall expedite and prioritize such inspections to occur within 30 days of receipt of notice of such change by the applicant

Controlled Correspondence Response, Notification of Issues Identified during the Review and Planned Review Timelines

- Median complete response time to controlled correspondence request for feedback reduced to at least 120 days within one year of effective date
- Median complete response time to controlled correspondence request for feedback reduced to at least 90 days within two years of effective date
- Median complete response time to controlled correspondence request for feedback reduced to at least 60 days within three years of effective date and each year thereafter
- For at least 90% of all applications, FDA will report substantive review issues identified that could impact approval (or lack thereof) to the applicant within 10 business days following the date that is six months after ANDA submission and again every three months thereafter until approval/disapproval by telephone, conference, facsimile, secure email, or other expedient means and also inform the applicant of the planned timeline to complete review, including a date by which the applicant will receive feedback from the review division regarding open matters, including, for example, labeling, food studies, etc.

Guidance Development and Outstanding Regulation Development

- Within two years following effective date, FDA will develop guidances on the following topics: Specificity regarding post approval changes that, based on a risk based approach, do not require supplement approval
  Within two years following effective date, FDA shall publish proposed regulations interpreting the 180 day forfeiture provisions provided in 21 USC 355(j)(5)(D)(i) and finalize such regulations within three years following effective date
- Within 30 days of effective date, FDA shall update its agency policy and guidance documents to include biennial inspection requirement for foreign establishments

Formal Meetings

- Schedule and conduct at least 90% of Type A meeting requests (as defined in PDUFA plus meetings requested following issuance of FDA feedback that is different from standard practice or previous agency guidance/recommendation) within 60 days of request within two years of effective date
- Schedule and conduct at least 90% of Type B meeting requests (as defined in PDUFA plus meetings requested following issuance of FDA feedback that is different from standard practice or previous agency guidance/recommendation) within 60 days of request within two years of effective date

FDA Staffing and Resources

- Increase reviewer to application ratio
- Hire additional inspectors, reviewers, and develop and implement training to achieve application median review time metrics and to inspect all domestic and foreign establishments at least once every two years.

Establishment Registration Database

- Develop database of all FDA registered establishments and provide registration online verification lookup within 6 months of effective date, including a registration lookup for the public, a more detailed internal database for FDA's CDER and an internal database for use at US ports of entry for imported product

Annual Congressional Report

Within six months of the one year anniversary of the effective date and annually thereafter, FDA to report the following to Congress:

- Median review times of all applications (including those applications that are pending at the time of effective date) broken down by year
- Median review times of all supplements (including those supplement that are pending at the time of the effective date) broken down by year
- Number of GMP inspections conducted for domestic establishments during the reporting period, Number of GMP inspections conducted for foreign establishments during the reporting period,
- Number of domestic establishments with biennial inspection incomplete, Number of foreign establishments biennial inspection incomplete
- Number of 483 observations issued to domestic establishments during the reporting period, Number of 483 observations issued to foreign establishments during the reporting period
- Number of other enforcement actions (broken down by type) taken against domestic establishments resulting from GMP inspections during the reporting period, Number of other enforcement actions (broken down by type) taken against foreign establishments resulting from GMP inspections during the reporting period
- Number and amount of Establishment Fees received for the reporting period, broken down by type
- Number and amount of Inspection Fees received for the reporting period, broken down by type
- Number and amount of Application Fees received for the reporting period, broken down by type
- Number of active FDA registered establishments during the reporting period broken down by type, Number of first time registered FDA establishments during the

reporting period broken down by type, Number of repeat registered FDA establishments during the reporting period broken down by type

- Median complete response time to controlled correspondence request for feedback during the reporting period
- Percentage of applications that FDA provided timely notification of substantive issues identified
- Average time an application spends in the review queue in active and inactive status, as well as average review times by division
- Average application-to-reviewer ratio for the report period
- Summary of staffing initiatives, including hiring of additional staff (including inspectors and reviewers), and additional training initiatives
- Report on the number of new reviewer and inspector hires
- Summary any other actions taken by FDA during the reporting period to address each of the three core user fee goals:
  - Ensure all players, foreign or domestic, contributing to the U.S. drug system are held to the same quality standard and inspected by the FDA on an biennial basis
  - Expedite the availability of low cost, high quality generic drugs by decreasing the median review time of applications and supplements
  - Enhance the FDA's ability to protect Americans in complex global supply environment by identifying, tracking and requiring the registration of all contributors in each drug product sold in the US