

GDUFA II Public Meeting

October 21, 2016

Welcome

Mary Beth Clarke, Director, Office of
Executive Programs, CDER

Opening Remarks

Kathleen Uhl, Director, Office of
Generic Drugs, CDER

GDUFA II Background and Reauthorization Process

Keith Flanagan, Director, Office of
Generic Drug Policy, CDER

Agenda

- Why is there a GDUFA I?
- What is an UFA?
- Result of GDUFA I
- What is the statutory process for reauthorizing GDUFA?
- Why is the proposed GDUFA II very important?
- Main features of the proposed GDUFA II
- 4 major lessons learned & corresponding GDUFA II recommendations

Why is there a GDUFA I?

- Hatch-Waxman an extraordinary success:
 - Approximately \$1.68 trillion saved over 10 years
 - Approximately 9 in 10 prescriptions filled by generics
- But, FDA's generic drug program was chronically under-resourced, could not keep pace with growth of Industry
- Thus, GDUFA I was enacted - Title III of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)
- First-ever human generic drug user fee agreement
- Approximately \$1.5B in user fees over 5 years
- FDA's commitments phased in over 5 years

What is an UFA?

- User fee agreements are negotiated by FDA and Industry, then authorized by Congress and the President
- Industry pays agreed-upon fees
- FDA fulfills agreed-upon commitments

Result of GDUFA I

- Deep, foundational restructuring of FDA's generic drug program
- Metric goals to improve the speed and predictability of ANDA review
- Record output – IRs/DRLs, CRLs, TAs and APs
- Approximately 835 combined TA+AP in FY16 – greatly exceeds old record of 619 TA+AP in FY12
- Output will continue to increase
- Improved access to quality, affordable generic medicines
- To date, FDA has met or exceeded all of its negotiated GDUFA I commitments

What are the statutory procedures for reauthorizing GDUFA?

Pursuant to FFDCFA Section 744C(d) –

- ✓ Consultation with stakeholders
- ✓ Prior Public Input - public meeting conducted June 15, 2015
- ✓ Minutes of Negotiation Meetings on FDA website
- ✓ Periodic Consultation with patient and consumer advocacy groups
- ❑ Public Review of Recommendations – today’s meeting – FDA will consider “public views and comments, revise [the] recommendations as necessary.” **Docket open through November 16.**
- ❑ Transmittal of Recommendations - to Congress by January, 2017

Why is the proposed GDUFA II very important?

If GDUFA is not timely reauthorized, severe consequences:

- User fee program ends
- Severe disruption of FDA's generic drug program
- Staff layoffs, affecting reviewers and field inspectors
- Dramatically reduced program performance

If GDUFA is timely reauthorized:

- More efficient and effective ANDA review program
- Reduced cycles to ANDA approval
- Increased rate of ANDA approval
- Maintain and grow consumer access to generics

Main features of GDUFA II

- ANDA review goals
- ANDA review program enhancements
- DMF review program enhancements
- Enhanced pre-ANDA process for complex products
- Facility assessment enhancements
- Enhanced accountability and reporting
- Program size commensurate with ANDA workload
- Modifications to user fee structure
- Small business considerations

Lessons Learned and GDUFA II

GDUFA I Lesson #1

- GDUFA I ANDA review goals were extremely complex and arcane
- Widely differential treatment for different cohorts and “tiers” of submissions
- Adding another layer of complexity – informal “Target Action Dates” for thousands of submissions
- GOT US HERE - Organized ANDA workload, charted feasible path to current state
- BUT – difficult to operationalize
- AND – large gap between negotiated goals and stakeholder expectations

GDUFA II Recommendation

- All ANDAs and ANDA amendments fall within a single, consolidated review goals scheme
- Simplify and streamline program administration
- Improve review efficiency – focus more on ANDA review, less on administering complex scheme
- Reduce gap between goals and expectations
- Ted Sherwood to present details on Panel 1

Lessons Learned and GDUFA II

GDUFA I Lesson #2

- The GDUFA I Commitment Letter described ANDA review procedures at a high level of generality
- GDUFA I ANDA review procedures – when first operationalized by FDA - did not meet Industry's expectations, and were reportedly commercially disruptive
- Applicants sought more communication and transparency

GDUFA II Recommendation

- Proposed GDUFA II ANDA review procedures are much more specific and programmatic than corresponding features of GDUFA I
- Refine and enhance each stage of the ANDA review process, from start to finish
- More communication and transparency – in general and at key points in the process
- Roles and responsibilities, sequencing and timing prescribed
- More opportunities for applicants to address deficiencies in current review cycle
- Reduce number of cycles to approval
- Ted Sherwood to present details on Panel 1

Lessons Learned and GDUFA II

GDUFA I Lesson #3

- Complex products pose distinct scientific and regulatory challenges
- Applicants sometimes don't know what FDA expects – harder to develop approvable ANDA for submission
- After submission, multiple review cycles – tremendous back and forth between FDA and applicants
- Inefficient

GDUFA II Recommendation

- Enhanced pre-ANDA process for complex products
- “Front-load” work so ANDA can be “right the first time”
- FDA to issue a guidance on process: Improve review efficiency, mitigate operational risk, manage stakeholder expectations
- Targeted -- not a broad, open-ended invitation to consult with FDA
- Applicant still has primary responsibility to develop the ANDA
- Rob Lionberger to present details on Panel 1

Lessons Learned and GDUFA II

GDUFA I Lesson #4

- GDUFA I projected that FDA would receive approximately 750 ANDAs/year
- FDA planned and budgeted accordingly
- FDA actually received approximately 1,000 ANDAs/year – an extra 1.5 years of work
- In addition, thousands of submissions had no – or very modest – GDUFA I goals, but FDA still needed to review them – usually, multiple cycles
- Large gap - GDUFA I resources vs. workload/stakeholder expectations/public health needs

GDUFA II Recommendation

- Resources commensurate with overall ANDA workload
- Mary Beth Clarke to present details on Panel 2



Thank you

Landscape of the Generic Drug Industry & Small Business Perspective

Rob Berlin, Senior Policy Advisor,
Office of the Commissioner

Small Business Working Group

- Group provided a forum to discuss the characteristics of small businesses
- Group sought to define options for relief that could be presented to negotiators
 - Considered approaches to defining small business
 - Considered approaches to fee relief
 - Discussed practical impacts of proposals
- Two significant fee issues fell outside of small business group's mandate
 - Overall program costs
 - Split of fees between applications and facilities

Characteristics of ANDA Sponsors

- Most ANDAs are from large firms
- Sponsor only firms are smaller and more likely to be domestic
 - Note there is a shift over time toward consolidation and movement out of the U.S.
- Interesting distribution of applications based on number of ANDAs held by a company
 - Many submissions come from companies that already have a lot of ANDAs (100+)
 - Many come from entities with less than 10, or even 0

Characteristics of Facilities

- Most API and FDF facilities are part of large parent companies
- Sponsor-facility firms are larger than facility only firms
- CMOs are mostly small businesses

Issues for Consideration

- The first challenge came in defining small business
 - Number of employees?
 - Revenue?
 - Number of ANDAs?
- The generic drug industry includes a substantial number of small firms. However, most applications and facilities are part of large firms
- Setting parameters for small business relief was challenging because:
 - Apparent large number of small business entities in the industry
 - Remaining uncertainty about participant size
 - Verifying the criteria, especially for private companies

Conclusions

- The group concluded that traditional models of small business fee relief were not the best or most efficient way to address needed relief
- The work and discussions of the group fed into a broader fee discussion yielding the following (to be discussed in greater detail in Panel #2):
 - Tiered Program Fee
 - No Payment While Pending
 - CMO Discount

Questions

Panel 1: Proposed Pre-Market Review: Goals & Pre-ANDA

Rob Lionberger, Office of Generic Drugs

Ted Sherwood, Office of Generic Drugs

David Gaugh, Generic Pharmaceutical Association



Section I

Submission Review Performance Goals

Submission Review Performance Goals Metric

90% FOR ALL

A. Originals (& Amendments)

Submission Type	Goal
Standard Original	10 months (as is)
Priority Original	8 months w/PFC (NEW)

PFC = Pre-Facility Communication –
complete (all) facilities data package
submitted ≥ 2 months pre-ANDA submission

A. (Orig. &) Amendments (cont.)

Submission Type	Goal
Standard Major	10 months w/inspection 8 months no inspection
Priority Major	10 months w/insp. no PFC 8 months w/insp. w/PFC 6 months no inspection

A. (Orig. &) Amendments (cont.)

Submission Type	Goal
Standard Minor	3 months
Priority Minor	3 months

B. PAS (& PAS Amendments)

Submission Type	Goal
Standard PAS	10 months w/inspection 6 months no inspection
Priority PAS	10 months w/insp. no PFC 8 months w/insp. w/PFC 6 months no inspection

B. (PAS &) PAS Amend. (cont.)

Submission Type	Goal
Standard Major	10 months w/inspection 6 months no inspection
Priority Major	10 months w/insp. no PFC 8 months w/insp. w/PFC 4 months no inspection

B. (PAS &) PAS Amend. (cont.)

Submission Type	Goal
Standard Minor	3 months
Priority Minor	3 months

- Historic major & minor designations apply*

C. Unsolicited Amendments

1. Submitted during a cycle – later of the goal dates
2. Submitted between cycles – later of the goal dates applied at the time of the subsequent solicited amendment or goal date for the unsolicited amendment

D. DMFs

Complete initial assessment for 90% of Type II APIs (Active Pharmaceutical Ingredients) within 60 days of the later of the:

- A. DMF Submission
- B. DMF Fee Payment

E. Controlled Correspondence

Type	Goal
Standard	60 days (cont.)
Complex	120 days (longer)
Post Control T-cons	14 days (new)

(T-cons to provide clarity of ambiguities)

- Citizen Petition caveat – continued
- Post-AP controls – NEW!

F. GDUFA I “Bridging”

1. GDUFA I Goal Applications – honor existing goals
2. Backlog and GDUFA I non-Goal Applications – honor existing TADs
3. Missed or missing goals – NLT July 31, 2018
4. All new subs/amendments – GDUFA II

Section II
**Original ANDA Review Program
Enhancements**

A. ANDA Receipt

1. Strive to act within **60 days**
2. **IR industry response w/in 7 days** – expanded fixing of minor issues or data already in ANDA
 - MAPP Forthcoming by 10-1-17
3. **Notification of Standard or Priority review**

B. ANDA Review Transparency & Communication Enhancements

1. Issue discipline IRs and DRLs (Discipline Review Letters) at mid-point in the review
2. Continue IRs and DRLs during review
3. IRs and DRLs don't stop the clock or add to the goal period

B. Review Transparency & Communication (cont.)

4. If IR or DRL not responded to in time, CR will “generally” be issued
5. IRs and DRLs issued until late in the cycle
6. FDA will work through goal for imminent AP/TAs
7. FDA will act prior to the goal when done...

B. Review Transparency & Communication (cont.)

8. RPM to pass on high-level warnings of fatal flaw types of deficiencies when known
9. RPM to pass on knowledge of missed goal, nature of delay and est. response time
10. Authorized Rep. allowed ***periodic*** status requests of the RPM

B. Review Transparency & Communication (cont.)

11. CRLs to include basis for classifying major

12. Grant Post-CRL t-cons

- a. 90% scheduled w/in 10 days
- b. 90% held w/in 30 days
- c. All reasonable requests should be granted

C. Review Classification Changes

1. If change in classification from standard to priority, applicant shall be **notified within 14 days**
2. If an application was granted priority status, but no longer qualifies, applicant shall be **notified within 14 days** from receipts of the new amendment

C. Review Classification Changes (cont.)

3. Classification changes can occur anytime
4. Priority reviews will be retained through the current cycle, even if issue is resolved mid-cycle (e.g., shortage resolved)
(OGD traditionally works the ANDA through to TA or AP)

C. Review Classification Changes (cont.)

5. FDA will explain denials of priority status
6. Requests for t-cons : **90% w/in 30 days**

D. ANDA AP and TA

- Strive to AP (good) ANDAs on first cycle
- Strive to AP (good) first generics on earliest marketing date
- Strive to TA (good) ANDAs by forfeiture date

E. Dispute Resolution

1. Applicant may request at Division or signatory level
2. ORO Associate Director to facilitate & track
3. Formal Dispute Resolution may be requested after the Division level response (generally follow PDUFA Guidance)

E. Dispute Resolution (cont.)

4. Goal for 30 day resolution

Fiscal Year	Goal
FY 18	70%
FY 19	80%
FY 20 / 21 / 22	90%

5. Center Dispute Coordinator to track formal disputes

F. Other Rev. Prog. Aspirations

1. Aspire to continually improve the program
2. Absence of GDUFA II goal does not mean activity is not important or will not be done

Proposed Pre-ANDA Program for Complex Products

- “Complex Product” is a defined term in the proposed GDUFA II Commitment Letter.
 - products with complex active ingredients, formulations, routes of delivery or dosage forms
 - complex drug-device combinations
 - other products where complexity or uncertainty concerning the approval pathway or other alternative approach would benefit from early scientific engagement

Proposed Pre-ANDA Program for Complex Products

- Pre-ANDA Program for Complex Products includes:
 - Meetings
 - Guidance
 - Regulatory Science
 - Controls
 - IID improvements

Proposed Pre-ANDA Program for Complex Products: Meetings

- **Product development meetings**
 - Scientific exchange on specific issues (e.g., a proposed study design) or questions
 - FDA provides targeted advice for an ongoing ANDA development program
- **Pre-submission meetings**
 - Give applicant opportunity to discuss and explain content and format of an ANDA to be submitted
 - Does not include substantive review of summary data or full study reports
- **Mid-review-cycle meetings**
 - Post-submission, after the last key discipline has issued its IR/DRL, FDA schedules a t-con with applicant to discuss current concerns with the ANDA and next steps

Proposed Pre-ANDA Program for Complex Products: Meetings

- **Guidance on Meetings**
 - FDA would issue a guidance concerning the program, setting forth meeting policies and procedures.
- **Integrated Meeting Track**
 - Applicant granted a product development meeting also has the option of a pre-submission meeting and the option of a mid-review-cycle meeting.
- **Goals**
 - Metric goals for FDA to grant/deny and to conduct product development and pre-submission meetings
 - No cap on number of meetings

Proposed Pre-ANDA Program for Complex Products: Guidance

- Product-specific guidance identify the methodology for developing drugs and generating evidence needed to support generic approval
- For NCE NDAs (non-complex)
 - FDA would issue product-specific guidance: for 90% of NCE NDAs approved on or after October 1, 2017, at least 2 years prior to the earliest lawful ANDA filing date
- For complex products
 - there are meetings for complex products without guidance
 - FDA would strive to issue product-specific guidance for complex products as soon as scientific recommendations are available
- For other products
 - based on requests from the regulated industry
 - public health priorities as set forth in CDER MAPP 5240.3, as revised

Proposed Pre-ANDA Program for Complex Products: Other Aspects

- Controlled correspondence enhancements, including separate review goals for complex controls
- Regulatory science enhancements
- Inactive Ingredient Database enhancements
- Safety Determination Letter enhancements

Proposed Pre-ANDA Program for Complex Products: Overview

- Clarify regulatory expectations for prospective applicants early in product development
- Help applicants develop more complete submissions
- Promote a more efficient and effective review process
- Reduce the number of review cycles necessary to obtain ANDA approval of complex products

Questions

Break

Panel 2: Proposed New Fee Structure

Mary Beth Clarke, Office of Executive Programs

Donal Parks, Office of Management

John DiLoreto, Bulk Pharmaceuticals Task Force

David Gaugh, Generic Pharmaceutical Association

Gil Roth, Pharma & Biopharma Outsourcing Association

Program Size Commensurate with Overall ANDA Workload

- GDUFA I assumed that FDA would receive approx. 750 ANDAs per year.
- ANDAs are the primary workload driver of the program.
- Over the first 4 years of GDUFA, ANDA receipts have averaged approx. 1,000 per year.
- To address the increased workload, FDA hired additional staff and is projected to spend about \$430 million in user fee funds in the final year of GDUFA I.
- In order to maintain current productivity and implement proposed GDUFA II improvements, FDA and Industry agreed that user fees should total \$493.6 million annually, adjusted each year for inflation.

Modification to User Fee Structure

Introduction of ANDA Holder Program Fee

- For program stability, user fee collections must be predictable.
- Application volume can fluctuate from year to year.
- There is a relatively stable universe of ANDA sponsors.
- To maintain a predictable fee base and better align fee responsibility with program costs and fee-paying ability, FDA and Industry propose to shift the burden more towards annual program fees.
- Sponsors with one or more approved ANDAs would pay an annual fee.

Modification to User Fee Structure

Changes to Facility Fees

- Facilities will continue to pay annual fees as they did in GDUFA I except that:
 - Facilities with both FDF and API operations will pay only the FDF fee (instead of both, as under GDUFA I)
 - CMOs will pay one-third of the FDF fee (more on this later)

Elimination of Supplement Fees

- In GDUFA I, ANDA sponsors making changes to an already approved ANDA through a PAS were required to pay a PAS application fee (even if the PAS was requested by the FDA).
- The number of PAS submissions is unpredictable.
- The new ANDA program fee is meant to be an investment in the program, and include what were PAS fees.

Small Business Considerations

New in GDUFA II

- No facility or ANDA sponsor would be charged an annual fee until an ANDA in which it is listed is approved.
- Annual program fee would have three tiers based on number of approved ANDAs owned by a firm and its affiliates: large (20+), medium (6 – 19), and small (1 – 5).
- Contract Manufacturing Organizations (CMOs are hired by ANDA sponsors to manufacture their generic drugs) would pay one-third of the annual facility fee paid by manufacturers that produce their own ANDAs.

Modification to User Fee Structure

ANDA Ownership Determination Process

FDA must publish FY18 fees in August of 2017. In order to meet that deadline, FDA will be posting information about its process on its website to clarify who will pay the new generic application program user fee (aka ANDA holder fee).

- December 2016: FDA publishes list of approved ANDAs
- February 2017: Sponsors may let FDA know about any errors in its database about approved ANDAs owned by them or their affiliates
- March 2017: FDA identifies unclaimed ANDAs and publishes revised list with tiers
- April 2017: Sponsors may submit corrections to list
- June 2017: FDA publishes corrected list
- August 2017: FDA publishes FY18 fees

GDUFA I v. GDUFA II Fee Structure

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

Proposed Accountability and Reporting Enhancements

Internal capacity development

FDA will:

Build internal capacity to enable improved productivity and performance through

- regular assessment of progress towards GDUFA II goals
- consistent methodologies for timely reporting of GDUFA II metrics, AND
- transparent and efficient administration, allocation and reporting of user fee resources.

Third party evaluation and recommendations

FDA will:

Conduct activities to develop a resource management planning function and a modernized time reporting approach to GDUFA II.

- The Agency would obtain through a contract with a third party an evaluation of options and recommendations for a new methodology to accurately assess changes in resource needs of the generic drug program and how to monitor and report on those needs going forward.
- The report would be published for public comment.
- Upon review of the report and comments, FDA would implement robust methodologies for assessing resource needs of the program and tracking resource allocation across the program.

Program Evaluation

FDA will:

Conduct activities to evaluate the financial administration of the GDUFA II program to help identify areas to enhance operational and fiscal efficiency, and to enhance transparency of how GDUFA program resources are used.

Proposed Accountability and Reporting Enhancements

Robust Program Performance Reporting

FDA would expand and enhance GDUFA program performance reporting

- monthly
- quarterly
- annually

This would enable the regulated industry, patients and consumer groups, and other stakeholders to better gauge the generic drug program's performance.

Questions

Lunch

Panel 3: Facilities

Ashley Boam, Office of Pharmaceutical Quality

Ann Marie Montemurro, Office of Regulatory Affairs

John DiLoreto, Bulk Pharmaceuticals Task Force

Proposed Facility Assessment Enhancements

Background

- FDASIA eliminated longstanding, minimum surveillance inspection frequency requirements and directed FDA instead to inspect drug facilities globally on the basis of risk.
- The transition to a new paradigm has been commercially disruptive for Industry, which over time had developed expectations and business processes based on the old model.
- While facility assessment cuts across multiple FDA drug programs, GDUFA II contains several facility-related enhancements targeted to generic industry specific challenges.

Proposed Facility Assessment Enhancements

U.S. API manufacturers

To mitigate export-related challenges identified by U.S.-based active pharmaceutical ingredient manufacturers, FDA would:

- issue a guidance explaining the risk-based site selection model used to prioritize facilities for surveillance inspections;
- undertake outreach to foreign regulators on the risk-based site selection model; AND
- support the export of safe and effective pharmaceutical products by the U.S.-based pharmaceutical industry, including through the issuance of communications conveying the current compliance status of U.S. manufacturing facilities to foreign regulators.



Proposed Facility Assessment Enhancements

ANDA Sponsors

To mitigate ANDA sponsor concerns regarding the transparency and speed of facility assessment and its impact on ANDA approvability and product launch, FDA would:

- Communicate to the applicant when outstanding facility issues have been identified on an inspection that could prevent approval of an ANDA or PAS through an IR, DRL, or CRL
- Communicate to the facility owner final inspection classifications that do not negatively impact approvability of any pending application within 90 days of the end of the inspection
- Provide updates to and seek feedback from Industry stakeholders concerning facility assessment

To enhance transparency concerning the compliance status of GDUFA self-identified facilities and sites, FDA would update its existing, publicly available database.

*Includes facilities involved in any manufacturing activities subject to CGMP inspection and for sites involved in the conduct or analysis of bioanalytical or clinical bioequivalence/bioavailability studies conducted to support an ANDA



Proposed DMF Review Program Enhancements

Targeted improvements to review of Drug Master Files (DMFs)

- DMF review comments submitted to the DMF holder would be issued at least in parallel with the issuance of review comments relating to the DMF for the ANDA.
- Procedures and timelines for t-cons/email exchange to clarify DMF first cycle review deficiencies.
- Once a DMF has undergone a complete review and has no open issues related to the review of the referencing ANDA, FDA would issue a First Adequate Letter.
- Once a DMF has undergone a complete review and the ANDA referencing it has been approved or tentatively approved, FDA would issue a no further comment letter.
- By FY19, FDA would issue a guidance on post-approval changes to a Type II DMF and submission mechanisms for ANDA applicants who reference it.

Questions

Open Public Comments by Registered Speakers

Closing Remarks