GENERIC DRUG USER FEE AMENDMENT (GDUFA) 2012 AND IMPACTS ON GENERIC DRUG APPROVALS

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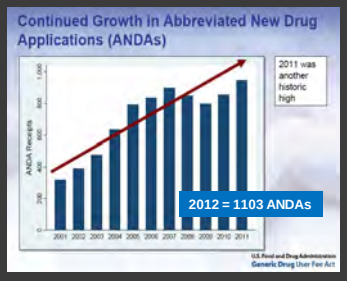
Overview of Presentation

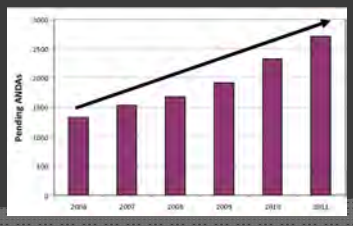
- State of ANDAs pre-GDUFA
- GDUFA & its Purpose
- Major Program Goals
- Who are Impacted?
- Types of Fees
- Sponsor Responsibilities
- Major Changes for DMF Holders
- Conclusions

Disclaimer: The messages and views presented are based on the author's own experience and interpretations of regulations and guidance documents.

Pre-GDUFA

ANDA and DMF Receipts ANDA Backlogs





Source: Generic Drug User Fee Act, Presented to the Drug, Chemical & Associated Technologies Association, by Russell Wesdyk, FDA, OPS

Pre-GDUFA State of ANDAs

- Severe and Continuing Backlog
  - 800-900 New ANDAs / ~800 PASs /~350 new Type-II DMFs **Per Year**
  - >2,500 application backlog
- Changing conditions
  - Increasingly complex products
  - Shift to foreign manufacturing
  - Increase focus on product quality
- Result: **Severe approval delays; ~31 months median approval time**

Pre-GDUFA State of ANDAs

Continuous Increase in
- New ANDAs
- Amendments
- ANDA Supplements (PAS)

- Global Manufacturers
- Complex Products

FDA Resources
(Review/ Inspection)

Public Health Need
Access to Affordable Generic Drugs

Industry's Need
For quicker access to markets

Pre-GDUFA State of ANDAs

Finding a Solution – A joint effort between FDA and Industry / Stake Holders

- Negotiations with API and FDF trade associations
  - Many all-day sessions using highly transparent processes
- Multiple open public stakeholder meetings
  - Many public meetings & stakeholder updates

Generic Drug User Fee Amendment (GDUFA)

"The Generic Drug User Fee Amendments of 2012 (GDUFA) is designed to speed access to safe and effective generic drugs to the public and reduce costs to industry. The law requires industry to pay user fees to supplement the costs of reviewing generic drug applications and inspecting fees."

GDUFA 2012

- Part of the Food and Drug Administration Safety and Innovation Act (FDASIA) signed into law on July 9, 2012
- GDUFA is Similar to other User Fee Acts (UFAs)
  - PDUFA (Prescription Drug) since 1992
  - MDUFA (Medical Device) since 2002
  - ADUFA (Animal Drug) since 2003
  - AGDUFA (Animal Generic Drug) since 2008
- Allows FDA to collect user fees to establish systems, and hire personnel to enhance efficiency in review, inspection and related areas
- Starting Date: FY2013 (Oct 1, 2012)
- FDA has published performance goals and procedures

GDUFA: Overall Purpose

"To help FDA ensure that participants in the U.S. generic drug system comply with U.S. quality standards, and to increase the likelihood that American consumers get timely access to low cost, high quality generic drugs"

Focused on three key aims:

- Access
- Safety / Quality
- Transparency

GDUFA Aims: Access

- Expedite the availability of low cost, high quality generic drugs
  - Reduce the (ANDA, Amendments, PAS) submission review and approval to a shorter and more predictable time frame

GDUFA Aims: Quality

- Increase the safety and quality of the drugs by applying same standards globally
  - Bring foreign facility inspections on par with domestic inspections; every 2 years
  - Apply risk-based approach

GDUFA Aims: Transparency

- Identify all facilities involved in the manufacture of generic drugs and their ingredients
  - Protect American public in today's complex global supply environment
  - Improve FDA's communications and feedback with industry to expedite product access

GDUFA Implementation

- This is a **Transformational Change**
- Reaching the desired state is not an over-night process
- 5 year plan (1st GDUFA cycle: 2013-2017)
- GDUFA Performance Goals – FDA/Industry joint proposal
  - First 2 years – Preparation to launch an effective program
    - Hire staff / Establish systems etc
  - Years 3, 4 and 5: Ramp up the efforts to reach program goals by 2017

GDUFA Major Performance Goals

- Application metrics*: Review and act on 90% of complete electronic ANDAs within 10 months.
- Backlog metrics: Review and act on 90% of all ANDAs, ANDA amendments and ANDA PASs by the end of FY 2017.
- CGMP Inspection metrics: Conduct biennial cGMP inspections of generic API & Finished Dosage Form (FDF) manufacturers and achieve parity of inspection frequency between foreign/domestic firms in FY 2017.
- Efficiency Enhancements: Implement various efficiency enhancements (next slide)
- Regulatory Science: Continue and begin various regulatory science initiatives to support science/risk based approaches

NOTE: No performance metrics goals for first 2 years; incremental changes after that to reach the target by 2017

GDUFA Major Performance Goals…

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Original ANDA	Expedite review of paragraph IV and maintain pre-GDUFA productivity		60% in 15 months	75% in 15 months	90% in 10 months
Tier 1 first major amendment	Maintain pre-GDUFA productivity		60% in 10 months	75% in 10 months	90% in 10 months
Tier 1 minor amendments (1st – 3rd)	Maintain pre-GDUFA productivity		60% in 3 months*	75% in 3 months*	90% in 3 months*
Tier 1 minor amendments (4th – 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 Oct 1st, 2012	Act on 90% by end of FY 2017				
Controlled correspondences	Maintain pre-GDUFA levels		70% in four months**	70% in two months**	90% in two months**

*10 months if inspection required

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

Source: OGD Director's Update: K. Uhl, MD, 2013

GDUFA Major Performance Goals…

- Efficiency Enhancements
  - ANDA Review
    - Issue complete response (CR) letters (include all disciplines)
    - Improved communication during review to address simple deficiencies
    - Opportunity to clarify CR issues/questions in a T-con (30 min) ; Sponsor must request for T-con in writing within 10 business days of CR letter
  - DMF Review – Similar to ANDA
  - cGMP Inspections
    - Biennial inspections & achieve parity of inspection frequency
    - Evaluate potential utilization of foreign government regulatory inspections
  - Others
    - API/FDF facility database
    - Electronic data submission standards

Who Are Impacted by GDUFA?

- ANDA sponsors
- Type II (API) DMF holders
- Manufacturers
  - API manufacturers
  - Finished Dosage Form (FDF) manufacturers

What are the Impacts

- Self Identification
- Payment of Fees
  - Timing of payment
  - Right amount
- Communication with Agency
  - During review / After Complete Response
- Electronic Submission Standards (eCTD)
  - For ANDA (& DMF)

FY 2013 User Fees

- Total User Fees: $299 Million/year (inflation adjusted)
  - One time Backlog fee: $50 Million
  - Remaining $249 Million from Applicants and Facilities
    - Facility fee (70%; ~ $174 Million)
      - FDF Manufacturers (56%; ~ $139 Million)
      - API Manufacturers (14%; ~ $35 Million)
    - Application fee (30%; ~ $75 Million)
      - ANDA/PAS (24%; ~ $60 Million)
      - DMF (6%; ~ $15 Million)

Backlog Fee (One Time -2013)

- **Applied to**: Pending ANDAs (original ANDAs not withdrawn, tentatively approved, or approved by 9/28/12); and submissions prior to 10/1/12, that were not accepted for review
- **Fee was published in Federal Register**
- **Penalty for non-payment**:
  - The person/affiliate will be placed on publicly available arrears list
  - Will impact all future ANDA or supplements from the person or affiliate

Facility Fee (Annual)

- **Applies to**: active pharmaceutical ingredient (API) and finish dosage form (FDF) producers (2 fees if facility does both)
- **Amount**: Determined based on self-identification statistics
  - Facilities that manufacture or intend to manufacture, package into primary container/closure, repackage to different primary container/closure, BE/BA/bioanalytical/in vitro BE sites, contract testing sites required to self identify
  - Higher fee for foreign facilities
- **Fee to be published in Federal Register** each year
- **Payment Due:** 45 days after publication in Federal Register
- **Penalty for non-payment:**
  - ANDA/PAS referencing the non-paying facility will be "refused to receive"
  - Facility will be placed on publicly available arrears list
  - All FDFs and APIs manufactured in non-paying facility will be misbranded

ANDA and PAS Fee (For each filing)

- **Applies to**: abbreviated new drug application (ANDA) or a prior approval supplement (PAS) submitted on or after 10/1/12
  - PAS fee is ~50% of ANDA fee
  - No fee for CBE supplement
  - If CBE supplement changed to PAS, fee required
- **Fee to be published in the Federal Register each year**
- FY 2014-2017 will be published no later than 60 days before October 1; Fee due on the date of submission
- **Application will be refused to receive:** if the fee is not paid within 20 days of due date
  - 75% fee will be refunded if ANDA or PAS is refused to receive for scientific reason
  - No refund if the application is refused for fee payment reasons (DMF/Facility/Backlog, etc.)

DMF Fee (One Time per DMF)

- **Applies to:**
  - Type II DMFs that cover the manufacture of API for use in ANDA (ANDA applicant may pay fee)
  - DMF, irrespective of when submitted, referenced in ANDA after 10/1/12 by initial LOA
- One-time fee per DMF, irrespective of number of LOAs
- **Fee to be published in the Federal Register each year**
- **Payment due:** when the first ANDA is submitted that references DMF
  - Fee can be paid prior to a LOA
  - When fee is paid, DMF undergoes Completeness Assessment (CA)
    - DMFs passing CA will be placed on publicly available list of "Available for Reference" on FDA's website
    - CA Guidance issued (Draft); carefully review the new checklist
- **Penalty for non-payment:** ANDA referencing that DMF will be Refused to Received – ANDA applicant will be notified and given 20 days to pay

2013 Generic Drug User Fees

- Facility fee
  - Domestic FDF facility: $175,389
  - Foreign FDF facility: $190,389
  - Domestic API facility: $26,458
  - Foreign API facility: $41,458
- Filing fee
  - Original ANDA $51,520
  - PAS $25,760
  - Original DMF $21,340
- ANDA Backlog Fee $17,434 (per application)

2014 Generic Drug User Fees

- Facility fee
  - Domestic FDF facility: $220,152
  - Foreign FDF facility: $235,152
  - Domestic API facility: $34,515
  - Foreign API facility: $49,515
- Filing fee
  - Original ANDA: $63,860
  - PAS: $31,930
  - DMF: $31,460

NOTE: Severe Penalty for Non-Payment of GDUFA fees

Refuse to Receive an ANDA/PAS for:

- Failure to pay the GDUFA ANDA or PAS fee within 20 calendar days of submitting the application
- Referencing a Type II DMF (API) that is not on the public *available for reference* list because of non-payment of the GDUFA DMF fee
- Use of a facility that is on the facility arrears list for failure to pay the GDUFA facility fee(s)
- Affiliation with owner of a facility on the facility arrears list
- Listed on the backlog arrears list
- Affiliation with an entity on the backlog arrears list

Sponsor Responsibilities

- The FDA review metric goals under GDUFA will only apply to ANDA submissions made electronically, following the eCTD (electronic Common Technical Document) format
- That means, all ANDA applications have to be in eCTD format to realize the GDUFA benefits
- Ensure fee payments are made promptly and accurately
- Plan and be ready for timely follow up (within 10 business days) after CR letter
- Ensure that your Type II (API) DMF holders are fully compliant with all of their GDUFA requirements

Big Change for DMF Holders

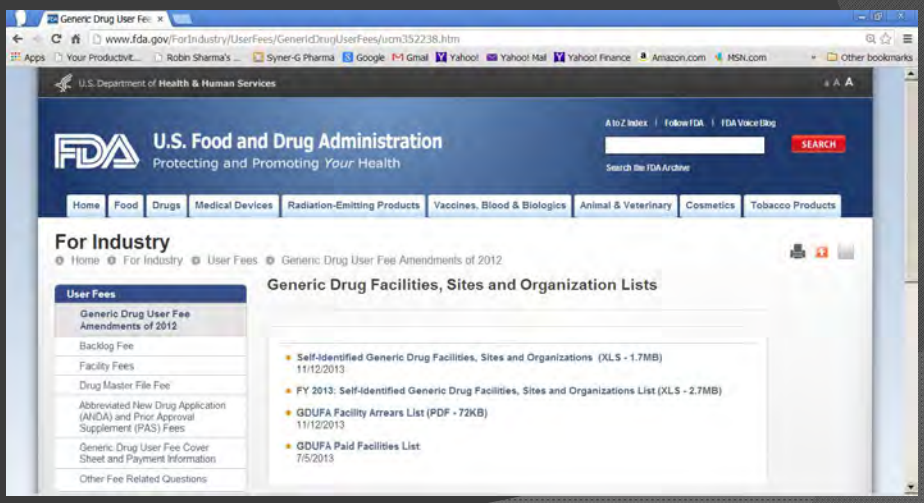
- Now there is a User Fee for DMF filing
- "Available for Reference" Status
  - Fee should be paid on time
  - Must meet FDA's completeness assessment (CA) requirements
  - Passing DMFs posted on FDA website "available for reference"
- ANDA can be accepted for filing only if the Type II DMFs included are in the "available for reference" list
- Each Active Ingredient requires a separate DMF
- Each manufacturing process for a given API requires a separate DMF

What About Legacy DMFs?

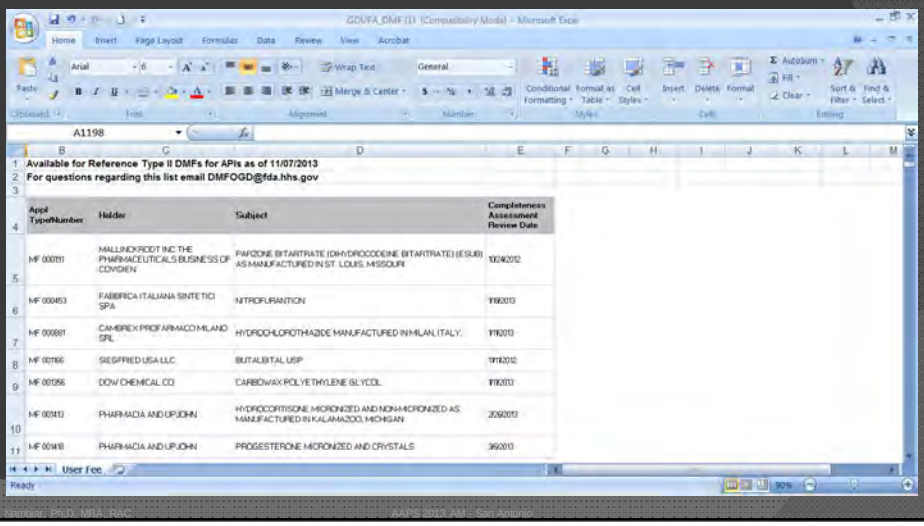
- DMFs reviewed prior to 10/1/12 still have to pay fee when referenced in an ANDA submission after 10/1/12
- If there are large number of amendments to a DMF, the FDA might require complete updated filing
- Major API CMC changes requiring DMF updates will trigger PAS by ANDA sponsor and will incur PAS fee
- Paper DMFs are still accepted, however:
  - Complete eCTD filing requirement is coming in the near future
  - ANDAs referencing Type II DMFs in eCTD will benefit the smoother review to meet metrics goals
  - Legacy paper DMFs upgraded to eCTD will benefit ANDA applicants significantly

FDA – GDUFA Page

GDUFA – Self Identified Sites



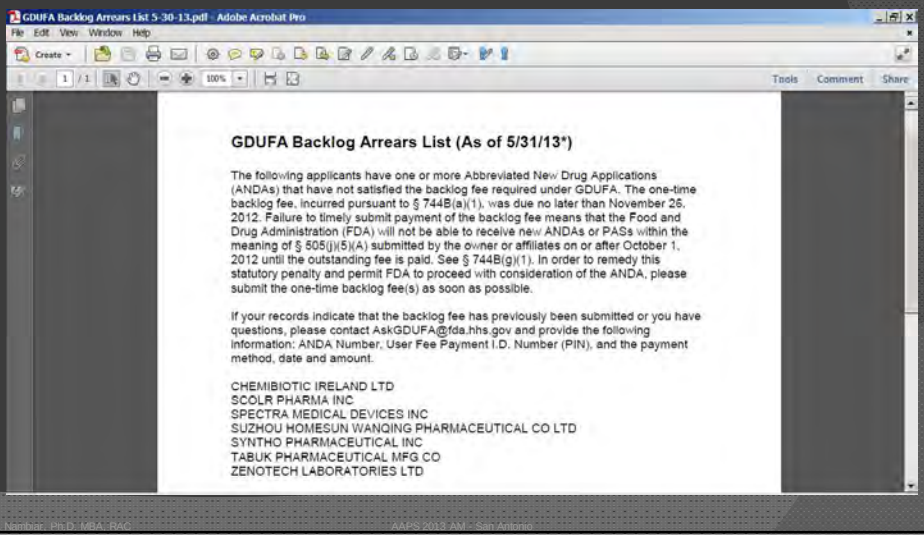
GDUFA –List of DMFs Available for Reference



Available for Reference Type II DMFs for APIs as of 11/07/2013
For questions regarding this list email DMFOGD@fda.hhs.gov

Appl Type/Number	Holder	Subject	Completeness Assessment Review Date
MF 000191	MALLINCKRODT INC THE PHARMACEUTICALS BUSINESS OF COVIDIEN	PAPZONE BITARTRATE (DIHYDROCODEINE BITARTRATE) (ESUB) AS MANUFACTURED IN ST. LOUIS, MISSOURI	10242012
MF 000453	FABBRICA ITALIANA SINTETICI SPA	NITROFURANTOIN	1192013
MF 000881	CAMBREX PROFARMACO MILANO SRL	HYDROCHLOROTHIAZIDE MANUFACTURED IN MILAN, ITALY.	1192013
MF 00166	SIEGFRIED USA LLC	BUTALBITAL USP	1112012
MF 00186	DOW CHEMICAL CO	CARBOWAX POLYETHYLENE GLYCOL	1192013
MF 00413	PHARMACIA AND UPJOHN	HYDROCORTISONE MICRONIZED AND NON-MICRONIZED AS MANUFACTURED IN KALAMAZOO, MICHIGAN	2262013
MF 00418	PHARMACIA AND UPJOHN	PROGESTERONE MICRONIZED AND CRYSTALS	362013

GDUFA – Backlog Arrears List



GDUFA Backlog Arrears List (As of 5/31/13*)

The following applicants have one or more Abbreviated New Drug Applications (ANDAs) that have not satisfied the backlog fee required under GDUFA. The one-time backlog fee, incurred pursuant to § 744B(a)(1), was due no later than November 26, 2012. Failure to timely submit payment of the backlog fee means that the Food and Drug Administration (FDA) will not be able to receive new ANDAs or PASs within the meaning of § 505(j)(5)(A) submitted by the owner or affiliates on or after October 1, 2012 until the outstanding fee is paid. See § 744B(g)(1). In order to remedy this statutory penalty and permit FDA to proceed with consideration of the ANDA, please submit the one-time backlog fee(s) as soon as possible.

If your records indicate that the backlog fee has previously been submitted or you have questions, please contact AskGDUFA@fda.hhs.gov and provide the following information: ANDA Number, User Fee Payment I.D. Number (PIN), and the payment method, date and amount.

CHEMIBIOTIC IRELAND LTD
SCOLR PHARMA INC
SPECTRA MEDICAL DEVICES INC
SUZHOU HOMESUN WANQING PHARMACEUTICAL CO LTD
SYNTHO PHARMACEUTICAL INC
TABUK PHARMACEUTICAL MFG CO
ZENOTECH LABORATORIES LTD

Conclusions

- GDUFA is here and active as of 10/1/12
- FDA has prior experience in implementation of other User Fee Acts but GDUFA is complex-- anticipate “growing pains”
- First 2 years, no metrics goals; incremental changes after that to reach the target by 2017
- cGMP inspections impact foreign FDF/API manufacturers
- Penalties for non-payment of user fee are significant
- Major changes for Type II DMFs; New process including Completeness Assessment will affect new and legacy DMFs
- Be vigilant, proactive and compliant to benefit from GDUFA

References

- GDUFA
  http://www.fda.gov/forindustry/userfees/genericdruguserfees/default.htm
- GDUFA Performance Goals
  http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf
- GDUFA of 2012: Questions and Answers
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM316671.pdf
- Type-II DMF Completeness Assessment
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321884.pdf

Thank You

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