FY 2015

PERFORMANCE REPORT TO CONGRESS

for the

Generic Drug User Fee Amendments

Food and Drug Administration
Department of Health and Human Services

Commissioner's Report

I am pleased to present to Congress the Food and Drug Administration's (FDA or the Agency) fiscal year (FY) 2015 annual performance report on the Generic Drug User Fee Amendments (GDUFA) of 2012. This report details FDA's preliminary accomplishments during the period of October 1, 2014 through September 30, 2015, (FY 2015) and updates FDA's performance for the previous years of GDUFA. This report marks the third year of GDUFA.

The passage of GDUFA brought high expectations for the timely review of human generic drug applications, creating parity between domestic and foreign firms, and reducing the backlog of human generic drug approval applications. Pursuant to GDUFA's design, FDA has restructured the generic drug program. The GDUFA restructuring through FY 2015, was a deep, foundational transformation which has prepared FDA to meet goal dates, starting in FY 2015, agreed upon in the Generic Drug User Fee Act Program Performance Goals and Procedures (GDUFA Commitment Letter).[1] The restructuring of the program included, among other things, the hiring and training of many new employees, reorganizing the Office of Generic Drugs (OGD) into a Center for Drug Evaluation and Research (CDER) "Super Office", establishing a new Office of Pharmaceutical Quality, replacing fragmented information technology systems with a new integrated system (i.e., CDER Informatics Platform), and substantially enhancing review and business processes. Now that FDA has successfully accomplished this transformation, there are still goals and challenges ahead to continue the modernization of the generic drug program. For example, GDUFA goal dates for FY 2015 Abbreviated New Drug Applications (ANDAs) went into effect on October 1, 2014. As such, an ANDA received on October 1, 2014, received a 15-month GDUFA goal date of December 31, 2015; therefore, it is too soon to report on FDA's final performance on its FY 2015 ANDA review goals. The Agency's efforts in restructuring the generic drug program in the first few years of GDUFA are already contributing to an increase in productivity (including taking actions on 82 percent of the backlog by the end of FY 2015) and FDA is confident it will meet its GDUFA goals.

FDA is committed to building on the successes of the first three years of the program to ensure that safe, effective, and high quality human generic drugs are accessible to the American public. I am proud of the significant progress FDA has made and look forward to even greater performance levels in the future.

Robert M. Califf, M.D.
Acting Commissioner of Food and Drugs

[1] http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

Acronyms

ANDA – Abbreviated New Drug Application

API – Active Pharmaceutical Ingredient

BE – Bioequivalence

CA – Completeness Assessments

CC – Controlled Correspondence

CBER – Center for Biologics Evaluation and Research

CDER – Center for Drug Evaluation and Research

CR – Complete Response

cGMP – Current Good Manufacturing Practices

DMF – Drug Master File

ECD – Easily Correctable Deficiency

eCTD – Electronic Common Technical Document

ESG – Electronic Submission Gateway

FDA – Food and Drug Administration

FDASIA – Food and Drug Administration Safety and Innovation Act

FD&C Act – Federal Food, Drug, and Cosmetic Act

FDF – Finished Dosage Form

FTE – Full-Time Equivalent

FY – Fiscal Year (October 1 – September 30)

GDUFA – Generic Drug User Fee Amendments of 2012

IR – Informal Request

IT – Information Technology

MAPP – Manual of Policies and Procedures

OGD – Office of Generic Drugs

OIP – Office of International Programs

ORA – Office of Regulatory Affairs

PAS – Prior Approval Supplement

PDUFA – Prescription Drug User Fee Act

RLD – Reference Listed Drug

RPM – Regulatory Project Manager

RTR – Refuse to Receive

Executive Summary

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA),[2] which included the authorization of GDUFA. GDUFA authorizes FDA to collect user fees for human generic drug activities and enables FDA to advance a safer, more efficient, and more affordable human generic drug review program. Furthermore, GDUFA enhances FDA's ability to protect Americans in the complex global supply environment by requiring the self-identification of facilities involved in the manufacture of generic drugs and associated active pharmaceutical ingredients (API) and by ensuring that foreign and domestic industry participants in the U.S. generic drug system are held to consistent, high-quality standards and are inspected with comparable rigor and frequency, using a risk-based approach. This self-identification requirement allows FDA to create an accurate inventory of facilities and organizations involved in the manufacture of human generic drugs.

FDA has made noteworthy advancements in the implementation of GDUFA. This annual report presents preliminary data on FDA's success in meeting FY 2015 review performance goals and commitments, and updates the review goals performance for FY 2013 and FY 2014.

FY 2015 GDUFA Performance

FDA's efforts to lay the foundation for a modern generic drug program have positioned the Agency to meet the FY 2015 GDUFA goals, which were agreed upon in the GDUFA Commitment Letter. It is too soon to determine whether FDA will meet all the GDUFA review goals for FY 2015. For example, the goal date for review of an ANDA that arrived on the last day of FY 2015, September 30, 2015, is December 29, 2016. However, FDA is confident that, given the Agency's efforts to transform the generic drug program, the GDUFA goals agreed to in the Commitment Letter will be met.

During FY 2015, FDA accomplished the following:

- Met/exceeded the GDUFA hiring goal.
- FDA exceeded the commitment to respond to 70 percent of GDUFA Year 3 Controlled Correspondence (CC) within 4 months of submission (if the control requires input from the clinical division, one additional month is added to the goal, making them due within 5 months of the submission). FDA has responded to 96 percent or more of controls within goal for those submitted through September 2015.

[2] https://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf

- FDA committed to review and act on 90 percent of all ANDAs, PASs, and amendments that were pending on October 1, 2012, (i.e., backlog) by the end of FY 2017, September 30, 2017. Through GDUFA Year 3, FDA has taken action on 82 percent of the backlog.
- FDA committed to review and act on 60 percent of GDUFA Year 3 PASs not requiring inspection within 6 months of submission. The Agency has not missed a goal date for FY 2015 PAS Submissions as of the end of FY 2015 (100 percent on time).
- As of September 30, 2015, the average time to approval for the FY 2015 PAS cohort is 96 calendar days. As more PASs in each cohort are approved, the average number of calendar days is expected to increase. The cohort numbers for each fiscal year will be updated and reported in future GDUFA Performance Reports.
- Issued 1,009 Complete Responses (CR). 170 are "CRs pending inspection" which are issued when the scientific review is done, but inspection and compliance work is not. This approach goes beyond FDA's GDUFA commitment to issue CR letters that include compliance status determinations. FDA began using CRs pending inspection following industry's request for more information. Issuing CRs in this manner allows companies to address non-inspection issues while inspections are pending. Essentially, it helps applicants correct their deficiencies more rapidly, and thus moves them closer to potential approval.
- At industry's request and beyond FDA's commitment, in FY 2015, FDA began communicating "information requests" (or IRs) from individual disciplines. This means that FDA alerted applicants to minor deficiencies as soon as practical, instead of waiting to consolidate them in a later CR letter. Similar to issuing CRs pending inspection, IRs help applicants move their submissions closer to approval in the current review cycle.
- Per the GDUFA Commitment Letter for review efficiency enhancements, FDA reviewers have continued to make every reasonable effort to communicate promptly to applicants easily correctible deficiencies (ECDs) found in the ANDA and have used this communication process during the review, including before and after the issuance of CRs.
- Performed 637 Type II API Drug Master File (DMF) Completeness Assessments (CAs).
- Continued to maintain the "Available for Reference Type II DMFs for APIs for Generic Drug Applications" list containing more than 3,000 Type II API DMFs that passed the CA and are available for reference. This list is publicly available.[3]
- Continued to advance scientific efforts under the regulatory research science program through a collaborative partnership with the regulated industry. FDA's efforts included holding an annual Regulatory Science Part 15 hearing to provide an opportunity for industry and other stakeholders to provide input on developing the annual list of

[3] http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls

regulatory science initiatives specific to generic drugs for the FY 2016 Regulatory Science Plan.

- Engaged in outreach efforts to educate and inform industry participants and other stakeholders about GDUFA. For example:
    - In October 2014, FDA speakers, along with industry, addressed a number of key current regulatory and technical issues impacting the generic drug industry at the Generic Pharmaceutical Association (GPhA) Fall Technical Conference.
    - In December 2014, FDA speakers provided their insights on real time communication during the Chemistry, Manufacturing, and Controls (CMC) review in a webinar hosted by GPhA.
    - In February 2015, senior leaders at FDA discussed GDUFA, the generic drug program, and quality culture at GPhA's annual meeting.
    - In April 2015, FDA staff discussed various topics along the dynamic continuum of the generic drug approval process with small businesses and others at the Regulatory Education for Industry (REdI) Generic Drugs Forum.
- Published multiple guidances and Manuals of Policies and Procedures (MAPPs) to clarify policies and procedures, including MAPP 5200.3 Rev. 1: Communications with Industry with respect to pre-GDUFA Year 3 Abbreviated New Drug Applications. This MAPP was revised following careful consideration of feedback provided by the generic drug industry. MAPP 5200.3 Rev. 1 will help ensure transparent and proactive communications with industry to support timely review and approvals.

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Introduction

The human generic pharmaceutical drug industry has saved the American health care system over $1.6 trillion over the 10-year period from 2005 through 2014[4] with over $254 billion just in 2014, under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Act.[5] Millions of Americans use generic drugs to treat a wide variety of medical conditions. FDA helps ensure that human generic drug products are thoroughly tested and shown to meet the statutory standards for approval, in most cases by proof that they contain the same active ingredients, are identical in strength and dosage-form, deliver the same amount of active ingredients to the site of action, and maintain the same strict standards of good manufacturing practice regulations as their brand name counterparts.[6]

On July 9, 2012, the President signed the Food and Drug Administration Safety and Innovation Act (FDASIA) into law, which included the authorization of the Generic Drug User Fee Amendments (GDUFA) for 5 years (FY 2013 through FY 2017). GDUFA authorizes FDA to collect user fees to support the review of applications and supplements for human generic drugs.

GDUFA provides FDA with supplemental funds to hire and train additional reviewers, investigators, and support staff, and to upgrade its information technology (IT) systems. The GDUFA legislation empowers FDA to better serve and protect public health by implementing management initiatives that are designed to increase the efficiency of the human generic drug program and improve the predictability of review processes. The GDUFA hiring initiative is a critical component to achieving GDUFA performance goals.

Historically, globalization of the human generic pharmaceutical industry challenged FDA's limited resources and impacted the Agency's oversight of domestic and foreign facilities and their supply chain entities. GDUFA's authorization of additional resources, as described above, allowed FDA to increase oversight of foreign and domestic facilities and commit to achieving risk-adjusted parity in inspections of foreign and domestic facilities.

GDUFA requires that human generic drug facilities and sites submit, update, or reconfirm their identification information on an annual basis. Self-identification is a key element in FDA's ability to deliver health safety and security. It is crucial in understanding the scope of the global supply chain for human generic drugs and in allowing FDA to determine the universe of facilities required to pay user fees. FDA will use the information obtained through the self-identification process to facilitate inspections and compliance. Enhanced safety of the supply chain will ultimately reduce risk.

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[4] Generic Pharmaceutical Association, Generic Drug Savings in the U.S. Seventh Annual Edition: 2015, available at: www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf

[5] www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf

[6] Some generic drugs are permitted, after grant of a suitability petition, to deviate in minor ways from the innovator they copy. See section 505(j)(2)(C) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Performance Presented in This Report

GDUFA performance goals cover a wide range of improvements including enhancing the efficiency of the review process, increasing and expediting hiring and training, decreasing the backlog of applications that were pending FDA decisions as of October 1, 2012, ensuring consistency and frequency of inspections for domestic and foreign sites, improving transparency, establishing databases and IT systems, and advancing regulatory science initiatives. This report details FDA's performance in the third year of GDUFA and presents the Agency's progress in accomplishing the program goals and enhancements detailed in the GDUFA Commitment Letter. Unless otherwise noted, all data are as of September 30, 2015.

The information below applies to FDA's implementation of GDUFA and its performance goals and provides some key terms and concepts used in this report.

- Several of the GDUFA performance goals are scheduled to be implemented incrementally from FY 2015 through FY 2017. Therefore, this report will include information on goals not discussed in previous reports.
- FDA will annually report GDUFA performance data for each fiscal year receipt cohort (defined as submissions received from October 1 to September 30). Some submissions received in one fiscal year may have associated goals requiring completion in subsequent fiscal years. In these cases, FDA's performance will be reported in subsequent fiscal year reports either after FDA takes an action or when the action required by a goal becomes overdue, whichever comes first.
- In order for a performance goal to be met, FDA must review the specified percentage of submissions within the review-time goal. For example, in FY 2015, in order to meet the goal for original ANDAs, FDA will need to review and act on 60 percent of original ANDAs within 15 months.
- To "act on an application" means that FDA will issue a complete response (CR) letter, an approval letter, a tentative approval letter, or a refuse to receive (RTR) letter.
- FDA may close out a request for a first cycle review teleconference by: (1) holding the teleconference; or (2) responding to questions in the applicant's teleconference request in writing in lieu of holding the teleconference.
- For applications and supplements submitted in response to an RTR action, the applicable performance goal is determined by the fiscal year in which the response is received, rather than the fiscal year in which the initial application or supplement that was refused-to-receive was submitted.
- Submission types with shorter review-time goals (e.g., PASs with 6-month goal dates in FY 2015, controlled correspondence with 4-month goal dates in FY 2015) tend to have a larger percentage of reviews completed by the end of the fiscal year, and their preliminary performance is a more reliable indicator of their final performance.

However, submission types (e.g., original ANDA submissions) with longer review-time goals (e.g., 15-month goal date in FY 2015) tend to have a smaller percentage of reviews completed, and their preliminary performance is a less reliable indicator of their final performance.

- Definitions of key terms used throughout this report can be found in Appendix A.

GDUFA Performance Goals and Commitments

The table below reflects the percentage of submissions that FDA must act on in order to meet the goal for that particular fiscal year. Goals are phased in incrementally over the 5-year authorization period with most goals beginning in FY 2015. Definitions of submission types can be found in Appendix A.

GDUFA Goals/Commitment Type	Review-Time Goal	FY 13	FY 14	FY 15	FY 16	FY 17
Original ANDA Review						
Original ANDA Submissions	15 months	--	--	60%	75%	--
Original ANDA Submissions	10 months	--	--	--	--	90%*
Amendment Review[†]						
Tier 1 - First Major Amendment	10 months	--	--	60%	75%	90%
Tier 1 - First through Third Minor Amendment	3 months	--	--	60%	75%	90%
Tier 1 - First through Third Minor Amendment requiring an Inspection	10 months	--	--	60%	75%	90%
Tier 1 - Fourth Though Fifth Minor Amendment	6 months	--	--	60%	75%	90%
Tier 1 - Fourth Though Fifth Minor Amendments requiring an Inspection	10 months	--	--	60%	75%	90%
Tier 2 Amendments	12 months	--	--	60%	75%	90%
PAS Review Time						
PASs not requiring inspections	6 months	--	--	60%	75%	90%
PASs requiring inspections	10 months	--	--	60%	75%	90%
Controlled Correspondence						
Controlled Correspondence	4 months	--	--	70%	--	--
Controlled Correspondence	2 months	--	--	--	70%	90%
Controlled Correspondence requiring input from clinical division	5 months	--	--	70%	--	--
Controlled Correspondence requiring input from clinical division	3 months	--	--	--	70%	90%
ANDA Review Efficiency						
30 Minute Teleconference	10 business days	--[‡]	--[‡]	200	250	300
DMF Review Efficiency						
30 Minute Teleconference	10 business days	--	--	[§]	[§]	[§]
Backlog						
Review and Act on ANDAs, ANDA amendments, and ANDA PASs that are pending on October 1, 2012	60 months	--	--	--	--	90%
Human Resources						
Incremental Staffing	Staff/Train	25%	50%	25%	--	--

* Ten month review cycle for 90 percent of applications submitted in year 5.
[†] Amendments may be submitted to either Original ANDAs or PASs.
[‡] FDA will aspire to hold teleconferences in FY 2013 and FY 2014 at a level similar to pre-GDUFA levels.
[§] One teleconference per DMF holder per month, with the number of teleconferences not to exceed the number of teleconferences for ANDAs.

GDUFA Preliminary Performance Summary

The table below presents GDUFA preliminary performance data for FY 2015. Upon evaluating preliminary performance for FY 2015, FDA has not missed a goal, has already met the goals for PASs not requiring inspections and the two CR goals, and has the potential to meet all goals. FDA will be able to report final performance for FY 2015 as goal dates for each category come to fruition. However, final performance will depend on the outcome of pending submissions and will be presented as a potential range.

GDUFA FY 2015 Preliminary Performance	Review Time Goal	Goal	Actions* Completed	Percent On-time†	Potential Range‡
I. Original ANDA Review Time Goals					
Original ANDA Applications	15 months	60%	89 of 509	100%	17% to 100%
II. Amendment Review Time Goals§					
Tier 1 - First Major Amendment	10 months	60%	--	--	--
Tier 1 - First through Third Minor Amendment	3 months	60%	0 of 2	Pending	0% to 100%
Tier 1 - First through Third Minor Amendment requiring an Inspecton	10 months	60%	--	--	--
Tier 1 - Fourth Though Fifth Minor Amendment	6 months	60%	--	--	--
Tier 1 - Fourth Though Fifth Minor Amendments requiring an Inspection	10 months	60%	--	--	--
Tier 2 Amendments	12 months	60%	0 of 1	Pending	0% to 100%
Tier 3 Amendments	--	--	--	--	--
III. PAS Review Time Goals					
PASs not Requiring Inspections	6 months	60%	238 of 352	100%	67% to 100%
PASs Requiring Inspections	10 months	60%	27 of 63	100%	43% to 100%
IV. PAS Amendment Review Time Goals§					
Tier 1 - First Major Amendment	10 months	60%	0 of 1	Pending	0% to 100%
Tier 1 - First through Third Minor Amendment	3 months	60%	7 of 13	100%	54% to 100%
Tier 1 - First through Third Minor Amendment requiring an Inspection	10 months	60%	--	--	--
Tier 1 - Fourth Though Fifth Minor Amendment	6 months	60%	--	--	--
Tier 1 - Fourth Though Fifth Minor Amendments requiring an Inspection	10 months	60%	--	--	--
Tier 2 Amendments	12 months	60%	--	--	--
Tier 3 Amendments	--	--	--	--	--
V. Controlled Correspondence					
Controlled Correspondence	4 months	70%	1019 of 1197	98%	83% to 98%
Controlled Correspondence requiring input from clinical division	5 months	70%	255 of 322	100%	79% to 100%

* Actions completed include any action taken regardless of whether or not it met the review time goal.
† Percent on-time represents the current percentage of actions FDA completed within the review time goal.
‡ Range represents the minimum (all pending become late) and maximum (all pending reviewed on time) performance.
§ Amendments are a work in progress. The dataset is preliminary and immature. We expect more robust reporting in future reports.

For the receipts in FY 2013 and FY 2014, the GDUFA Commitment Letter does not require FDA to report on any performance goals. The table below presents GDUFA's performance in terms of completed actions for FY 2013 and FY 2014 and preliminary FY 2015 performance.

GDUFA Performance	FY 13*	FY 14*	FY 15
Refuse to Receive for Failure to Pay Fees	62	39	6
Refuse to Receive for Technical Reasons	145	163	71
Number of CR Letters with inspection recommendations	394	166	10
Number of CR Letters without inspection recommendations	123	28	0
Number of Tentative Approvals	33	5	0
Number of Approvals	41	20	1
Number of PAS CR Letters	92	36	57
Number of PAS Approvals	222	165	206

* These figures represent the updated FY 2013 and FY 2014 GDUFA performance data. For goal-based metrics, the numbers will be final once the goal has been met or the goal date for everything that applies to the metric has passed; thus, prior year numbers are updated annually.

GDUFA Workload: Applications and Submissions Received

Under GDUFA, FDA agreed to issue timely CR letters generally reflecting full division-level reviews of all deficiencies (including inspections and consults) noted by relevant review disciplines. FDA also agreed to make every reasonable effort to communicate promptly with applicants to facilitate the timely revision of ECDs found in ANDAs and PASs and to clarify issues and answer questions on deficiencies used in the first cycle CR letter. FDA's communications are further discussed in the ANDA and DMF Review Efficiency Enhancements section of this report. These commitments are intended to reduce the number of ANDA review cycles.

The following table summarizes GDUFA workload for FY 2013, FY 2014, and FY 2015. The GDUFA application figures represent submissions that are subject to the review metrics. Submissions to FDA are tracked according to the fiscal year in which they are submitted. Since GDUFA afforded FDA a 2-year implementation period (i.e., FY 2013 and FY 2014) to hire and train new staff and establish the necessary infrastructure, FDA had no review time goals for ANDAs, PASs, or Amendments in fiscal years 2013 or 2014. The performance of the GDUFA review-time is measured against a goal for the first time in FY 2015; however, FDA did monitor the performance during the first 2 years to identify any areas where improvements were needed. When GDUFA was negotiated, the average number of ANDAs and PASs expected was established at approximately 750 each annually. As is reflected below, receipts for ANDAs significantly exceeded that expectation in FYs 2013 and 2014, and fell below expectations in FY 2015. It is also important to note that the table below shows a significant increase in PAS and CR receipts.

Review Workload for Applications and Submissions

GDUFA Workload	FY 2013*	FY 2014*	FY 2015
Original ANDAs			
Total Original ANDAs Submitted	1,057	1,598	522
ANDAs Submitted After RTR for Failure to Pay User Fees	44	37	20
ANDAs Submitted After RTR for Technical Reasons	75	112	101
ANDA Solicited Amendments			
Total Solicited ANDA Amendments Submitted	48	81	2
PASs			
Total PAS Submissions with Inspection Status Undetermined	321†	256†	414
PAS Solicited Amendments			
Total Solicited PAS Amendments Submitted	34	6	15
Controlled Correspondence			
Total Controlled Correspondence Submitted	953	1,087	1,197
Total Controlled Correspondence Requiring Input from Clinical Division	36	26	322

* These figures represent the final Fiscal Years 2013 and 2014 GDUFA workload data; prior years' numbers are updated annually.
† Inspection status for PASs submitted in FYs 2013 and 2014 was not established because there were no PAS review goals in those fiscal years.

Management Priorities and Accomplishments

GDUFA includes several management and statutory requirements that are critical to enabling progress toward performance goals for the human generic drug program. These priorities include enhancing the efficiency of the review process, increased and expedited hiring, decreasing the backlog of applications, ensuring consistency and frequency of inspections for domestic and foreign sites, improving transparency, establishing databases and IT systems and advancing regulatory science initiatives. This section details the status of these requirements.

Human Resources

FDA committed to hiring and training the staff necessary to achieve GDUFA program goals with incremental hiring goals established for FY 2013 and FY 2014. In FY 2015, FDA met the mandated human resources goal by hiring the final 25 percent of overall GDUFA program hires nearly 11 months ahead of schedule. FDA has continued to add resources to the GDUFA program with a total of 1192 hires by the end of FY 2015.

The following table shows how FDA met the GDUFA human resource goals.

Fiscal Year	New FTE Count as of End of Fiscal Year	Incremental Hiring Goal	Percent of Incremental Staff Hired*	Cumulative Percent Hired	Goal Met
2013	291	25%	31%	25%	Yes
2014	591	50%	64%	96%	Yes
2015	310	25%	34%	129%	Yes

*The percentage of incremental staff hires does not add up to 100 percent because FDA exceeded the GDUFA hiring goal.

Generic Industry Facility Self-Identification

To increase transparency into the complex, global, human generic drug industry and to enhance the safety of the supply chain, GDUFA requires facilities, sites, and organizations involved in the manufacturing of finished dosage forms (FDF) or active pharmaceutical ingredient (API) for human generic drugs to self-identify annually. This statutory requirement enables FDA to build an accurate inventory of facilities, sites, and organizations, improves the Agency's ability to target compliance issues and inspections, and expedites access to human generic drug products. In addition, facilities manufacturing FDFs and APIs for human generic drugs are required to pay an annual facility fee when the facility is referenced on a pending or approved human generic submission as of the fee due date of each applicable fiscal year.

The table below displays the number of facilities, sites, and organizations that submitted their self-identification information to FDA during the open periods for fiscal years 2013, 2014, 2015 and 2016. A detailed list of all GDUFA self-identified facilities, sites and organizations is available on FDA's GDUFA website.[7] There are no obvious year-to-year trends.

Fiscal year	Number of Facilities, Sites, and Organization	Self-Identification Reporting Period	Business Operations Reported for User Fees			
			Domestic FDF	Foreign FDF	Domestic API	Foreign API
2013	3,334	Oct 02, 2012 - Dec 03, 2012*	325	433	122	763
2014	3,604	May 01, 2013 - Jun 01, 2013	315	433	128	775
2015	3,335	May 01, 2014 - Jun 01, 2014	271	410	103	692
2016	3,641	May 01, 2015 - Jun 01, 2015	283	422	105	721

*For FY 2013, the open period was extended to allow generic manufacturers additional time to comply with self-identification requirements.

GDUFA Guidance and Procedural Development

FDA committed to increasing transparency in operations and enhancing communication on critical information for ANDA applicants and manufacturers. While not required by the GDUFA Commitment Letter, in FY 2015 FDA published many guidances and MAPPs, including:

- Draft Guidance for Industry How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD, December 2014[8]
- DRAFT Guidance for Industry *Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System,* Revision 1, May 2015[9]
- FINAL Guidance for Industry *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules,* June 2015[10]
- DRAFT Guidance for Industry *Request for Quality Metrics,* July 2015[11]
- DRAFT Guidance for Industry *Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class I and 3 Drugs,* August 2015[12]

[7] www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm
[8] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425662.pdf
[9] www.fda.gov/downloads/Drugs/.../Guidances/ucm070246.pdf
[10] www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm377938.pdf
[11] www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm455957.pdf
[12] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM456594.pdf

- FINAL Guidance for Industry *Controlled Correspondence Related to Generic Drug Development,* September 2015[13]
- DRAFT Guidance for Industry *Formal Dispute Resolution: Appeals Above the Division Level,* September 2015[14]
- Manual of Polices and Procedures 5200.3 Rev. 1: Communications with Industry with respect to pre-GDUFA Year Three Abbreviated New Drug Applications, August 2015[15]
- Published 154 new and 69 revised product-specific recommendations for generic drug development[16]

[13] www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm411478.pdf
[14] www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm343101.pdf
[15] www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM369599.pdf
[16] www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Technology Enhancements

FDA employed a number of significant technology improvements aimed at promoting the efficiency of the human generic drug review process; facilitating self-identification of generic manufacturers; strengthening surveillance and inspections; and managing user fee collection. FDA continues to devote resources to IT improvements that integrate human generic drug information across relevant Agency systems. The FY 2015 IT accomplishments are described below.

Subsequent to the initial pilot release of the CDER Informatics Platform in 2014, FDA has now implemented the modern informatics platform for the review of new and generic drugs while consolidating legacy systems and increasing operational efficiency. This platform further integrates drug review processes, institutes a managed inventory of facilities and sites, enables a more efficient facility inspection process, and supports the overall quality assessment of drug applications. It also helps FDA track GDUFA review performance goals and commitments to the public by managing work commitments throughout FDA in one place. Accomplishments of the new platform include the following:

- Since October 1, 2014, over 2,000 reviewers have successfully used the human drug informatics platform to:
    - Improve end-to-end review of original and supplemental ANDAs
    - Improve overall quality assessment for new drugs, generic drugs, and therapeutic biologics
    - Support manufacturing facility evaluation and inspection management
- Consolidated seven legacy systems, multiple access databases, and spreadsheets that advance regulatory review, pharmaceutical quality, and patient safety.
- Prioritized workload and optimized resource utilization leading to accelerated processing of ANDAs
- Published the first inactive ingredients dictionary since October 2013.[17]

Second, FDA committed to developing a Chemistry, Manufacturing and Controls (CMC) database to improve the efficiency of review and inspections. This was necessary because CMC data, which include important information about a company's manufacturing process, were previously dispersed in multiple databases and not easily accessible to FDA reviewers. To meet this goal, FDA built a single repository that indexes all CMC data into a single, easily searchable location. In practice, the CMC database streamlines FDA's operations and enhances our ability to review generic drug applications and manage other regulatory processes.

[17] www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm

Facilitating Standardized Electronic Submissions:

- FDA implemented the electronic Common Technical Document (eCTD) Module 1 (M1) update to support the submission of Promotional Labeling in eCTD format through FDA's Electronic Submissions Gateway (ESG), the organization of submission types and submission numbering, functionality for grouped submissions, and additional headings and metadata to improve submission processing and review.[18]

- FDA finalized the eCTD guidance document detailing submission requirements for the eCTD format. This guidance implements the electronic submission requirements of section 745A(a) of the FD&C Act for the electronic format of the content submitted in new drug applications (NDAs), abbreviated new drug applications (ANDAs), certain biologics license applications (BLAs), and certain investigational new drug applications (INDs) to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). [19]

- FDA finalized the eCTD guidance document detailing standardized study data requirements for the eCTD format. This guidance implements the electronic submission requirements of section 745(a) of the FD&C Act for study data contained in NDAs, ANDAs, BLAs, and INDs submitted to CDER or CBER by specifying the format for electronic submissions.[20]

[18] "Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, May 2015.
www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

[19] Guidance -
www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

[20] "Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Standardized Study Data*, December 2014
www.fda.gov/downloads/Drugs/.../Guidances/UCM292334.pdf

Backlog Summary

FDA is committed to reviewing and acting on 90 percent of the backlog of 2,866 original applications and 1,884[21] PAS submissions that were pending as of October 1, 2012, by the GDUFA-defined goal of September 30, 2017. In FY 2014, FDA issued first regulatory actions on approximately 65 percent of the backlog. FDA continues to make progress toward eliminating the backlog of applications. As of this September 30, 2015, FDA has issued a first action on approximately 82 percent of the GDUFA backlog applications since program launch. The table below shows FDA's progress toward meeting the backlog goal.

Cumulative Percent of Backlog Issued First Action

Submission Type	Backlog as of October 1, 2012	FY 2013	FY 2014	FY 2015
ANDA	2866	31%	60%	80%
PAS	1884	40%	73%	86%
Total	4750	34%	65%	82%

Review Time

Because implementation of GDUFA involves improvements in many areas, the efficiency and performance goals are phased in over the 5-year GDUFA program period. FDASIA requires FDA to report the following three metrics starting in FY 2013:

1. The average total time to full approval action of applications (original ANDAs and PASs) received in each fiscal year cohort.
2. The number of original ANDAs and PASs pending with FDA for more than 10 months on September 30, 2012.
3. Of these pending ANDAs and PASs, the number FDA has taken a final action on during the previous fiscal year.

The first metric requires FDA to report the average total time to full approval action for ANDAs and PASs[22] received during the respective fiscal year, including the number of calendar days spent during the review by FDA and the number of calendar days spent by the applicant

[21] The FY 2014 GDUFA Performance Report noted there were 1,879 PAS submissions. This figure has been adjusted as a result of data validation and cleanup.

[22] Section 715(a)(2) of FDASIA requires FDA to report on the total time for "applications for approval of a generic drug under 505(j), amendments to such applications, and prior approval supplements…" Pursuant to 21 CFR 314.98, applicants may amend an ANDA not yet approved to revise existing information or provide additional information. Amendments are not submissions separate from an original ANDA or PAS. FDA does not take action on amendments and therefore cannot report on the time to approval for amendments received in any fiscal year.

responding to a CR letter(s). The figures represented under each cohort are revised annually to incorporate updated results based on ANDAs and PASs approved in the previous fiscal year. The data are presented in the following two tables.

Average Calendar Days to Full Approval Action: Original ANDAs

	FY 2013	FY 2014	FY 2015*
First Cycle Approvals†			
Average Total Time to Approval	768	537	316
Multi-Cycle Approvals			
Average Total Time to Approval	730	568	--‡
Average Calendar Days Spent During Review by FDA	634	482	--‡
Average Calendar Days Spent by Applicant Responding to CR	96	86	--‡
Total Combined (First Cycle and Multi-Cycle)			
Combined Average Total Time to Approval	738	552	316

* FDA continued to focus its review efforts in FY 2015 on reducing the number of pending applications in the backlog that were received in previous fiscal years. Given the substantial backlog and the 15-month review goal for FY 2015 ANDAs, only one ANDA submitted in FY 2015 was approved.

† First cycle approvals may include applications for which ECDs and IRs were issued in order to help applicants correct deficiencies in the current review cycle. This reduces the need for additional review cycles; however, it may add to the total review time for first cycle approvals.

‡ There are no multi-cycle approvals to report yet for FY 2015, but as FY 2015 goal dates come to fruition, there may be multi-cycle approval numbers reported for FY 2015 in future reports

Average Calendar Days to Full Approval Action: PASs

	FY 2013	FY 2014	FY 2015
First Cycle Approvals*			
Average Total Time to Approval	287	214	91
Multi-Cycle Approvals			
Average Total Time to Approval	481	333	239
Average Calendar Days Spent During Review by FDA	396	244	165
Average Calendar Days Spent by Applicant Responding to CR	85	89	74
Total Combined (First Cycle and Multi-Cycle)			
Combined Average Total Time to Approval	322	226	96

*First cycle approvals may include supplements for which ECDs and IRs were issued in order to help applicants correct difficiencies in the current review cycle. This reduces the need for additional review cycles; however, it may add to the total review time for first cycle approvals.

The table below presents data on the third and fourth FDASIA metrics (the number of original ANDAs and PASs pending with FDA for more than 10 months on September 30, 2012, and the number of these with final regulatory action). A final regulatory action is either an approval by FDA or a withdrawal by the sponsor.

Number of Pending Applications with Final Regulatory Action*

Submission Type	Applications Pending for Longer than 10 Months as of September 30, 2012	Final Regulatory Actions Taken			Number Remaining
		FY 2013	FY 2014	FY 2015	
ANDA	1,854	383	371	315	785
PAS	912	301	284	159	168
Total	2,766	684	656	474	953

*Data in this table have been adjusted as a result of ongoing data validation

Drug Safety and Inspections Performance

Many active ingredients that are used in human generic medicines that are marketed in the United States are manufactured in foreign countries. Prior to the passage of GDUFA, domestic facilities were routinely inspected about once every 2 years while their foreign counterparts were inspected about once every 7 to 13 years.[23] This regulatory disparity, combined with limited resources and the associated cost of inspecting foreign facilities, produced an increasing gap in the level of oversight that is needed to ensure the safety of the human generic drug supply. The Agency is addressing this regulatory disparity in part through a risk-adjusted inspection schedule further discussed in this section.

GDUFA Inspection Strategy

GDUFA requires FDA to leverage the information obtained through self-identification to conduct accurate and reliable surveillance of human generic drugs and to facilitate inspections.

FDA also committed to:

- Prioritize inspections of establishments not previously inspected and those that are associated with ANDAs that are otherwise approvable or eligible for tentative approval except for an outstanding inspection.

- Study foreign government regulatory inspections, report findings publicly, and develop a program to utilize foreign inspections classifications when and where appropriate.
- Make inspection classification results available to the public and industry. These can be found on the FDA website at www.accessdata.fda.gov/scripts/inspsearch/.

Risk-Adjusted Biennial cGMP Surveillance Inspection

To ensure that foreign and domestic firms are held to consistent high-quality standards, FDA agreed to conduct risk-adjusted biennial cGMP surveillance inspections of human generic API and FDF manufacturers, with the goal of achieving risk-adjusted parity of inspection frequency between foreign and domestic establishments by FY 2017. Section 705 of FDASIA amended section 510(h) of the FD&C Act to require a risk-based schedule for inspections of

[23] FDA Fact Sheet: New User Fees for Generic Drugs Will Enhance Americans' Access to Less Expensive Drugs and Generate Major Cost Savings, www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FDASIA/ucm310992.htm

establishments, whether they are located domestically or internationally.[24]

To accomplish this goal, FDA is employing a site selection surveillance inspection model that runs annually on all facilities in the FDA's inventory. The model does not distinguish – for purposes of risk ranking – if the site is foreign or domestic-based. Risk is assessed consistent with the requirements of FDASIA section 705.

The risk model drives inspection planning. By following the risk-adjusted model that does not consider foreign or domestic location, FDA is meeting its risk-adjusted parity commitment. Risk-adjusted parity between domestic and foreign drug inspection frequency is achieved by measuring FDA's compliance with the model on an annual basis.

In addition to achieving risk-adjusted parity in the frequency of inspections, FDA also committed to ensuring that domestic and foreign inspections are conducted with "comparable depth and rigor."[25] To accomplish this goal, FDA is:

- Continuing to ensure that domestic and foreign inspections are conducted according to one set of compliance programs.
- Continuing to ensure that the same trained FDA staff investigators generally conduct both domestic and foreign inspections. Under FDA's GDUFA hiring initiative, new investigators dedicated to generic facilities are expected to conduct both domestic and foreign inspections.[26]
- Conducting an increasing amount of foreign cGMP surveillance inspections that are classified as "abbreviated" pursuant to FDA Compliance Program 7356.002.[27] Prior to GDUFA, the biennial frequency for domestic inspections resulted in those inspections being classified as "abbreviated" more commonly than in the foreign setting, in which facilities were more likely to be inspected for the first time (and therefore generally

[24] Section 705 of FDASIA amends section 510(h) of the FD&C Act to require FDA to establish a risk-based schedule for drug inspections. Section 510(h)(4) specifies that the risk-based schedule is based on the following factors: "(A) The compliance history of the establishment; (B) The records, history, and nature of recalls linked to the establishment; (C) The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment; (D) The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years; (E) Whether the establishment has been inspected by a foreign government or an agency of a foreign government recognized under section 809; (F) Any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources."

[25] GDUFA Commitment Letter, p.16: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf.

[26] While the hiring initiative is intended to address the overall increase in the number of generic facility inspections needed, new investigators will not be the sole force doing these types of inspections. Investigators hired separately from the GDUFA initiative also will be conducting generic facility inspections.

[27] See FDA Compliance Program Guidance Manual - 7356.002, Drug Manufacturing Inspections, p. 8, for a description of "Abbreviated" drug CGMP surveillance inspections www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/UCM125404.pdf

subject to a “comprehensive” or “full” surveillance inspection). This may have led to some disparity in the level of depth and rigor with which domestic and foreign surveillance inspections were conducted. While this continues to generally be true as never-inspected foreign facilities are prioritized for inspection, under GDUFA, FDA has also made a concerted effort to narrow this disparity in depth and rigor by, where appropriate, conducting some foreign inspections in an “abbreviated” manner.

ANDA and DMF Review Efficiency Enhancements

FDA committed to undertake various initiatives aimed at enhancing the premarket review of human generic drugs. This section provides the status of these initiatives.

Management Initiative	Performance Area	FY 2013*	FY 2014*	FY 2015
CR Letters				
CR letters issued reflect full division-level reviews of deficiencies from relevant disciplines, including inspections and consults.	ANDA GDUFA CR letters issued	481[†]	589[‡]	816[§]
	PAS GDUFA CR letters issued	315[†]	170[‡]	164[§]
	DMF GDUFA CR letters issued	275	530	764
Inspections				
Inspection classification results, along with relevant information, are made public.	Inspections	Inspection classification results, along with relevant information, were made public and are available at: www.accessdata.fda.gov/scripts/inspsearch/	Inspection classification results, along with relevant information, were made public and are available at: www.accessdata.fda.gov/scripts/inspsearch/	
RTR Standards				
FDA to develop enhanced RTR standards for ANDAs and other related submissions	RTR Standards	Draft Guidance was published on October 1, 2012	Final Guidance was published on September 16, 2014, and is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf. Draft Guidance on Refuse to Receive for Lack of Proper Justification of Impurity Limits was published on September 16, 2014, and is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM414598	

*Data in this table have been adjusted as a result of ongoing data validation
[†]CR totals include the backlog and the FY 2013 cohort. The FY 2013 report included backlog submissions only.
[‡]CR totals include FY 2014 CRs from the backlog, the FY 2013 and the FY 2014 cohorts
[§]CR totals include FY 2015 CRs from the backlog, the FY 2013, the FY 2014 and the FY 2015 cohorts

Management Initiative	Performance Area	FY 2013	FY 2014	FY 2015
Expedited Review of Paragraph IV Applications				
Expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.	Expedited Review of Paragraph IV Applications	Expedited review was implemented consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, and also included those applications that became eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted	Expedited review was implemented consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3 Rev 1[28], Prioritization of the Review of Original ANDAs, Amendments, and Supplements, and also included those applications that became eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted.	Expedited review was implemented consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3 Rev 1, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, and also included those applications that became eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted.
Type II API DMFs Available for Reference				
FDA will deem the DMF available for reference, placing the DMF number in a publicly available list of Type II API DMFs available for reference	Type II API DMFs Available for Reference List	Published Type II DMF - Available for Reference List: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls	Continued Publication of Type II DMF - Available for Reference List: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls	Continued Publication of Type II DMF - Available for Reference List: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls
DMF Workload	DMFs found complete	1,165	1,168	637
	Total CA review cycles performed (includes multiple cycles on the same DMF):	1,700	1,779	901
	DMF GDUFA Incomplete letters issued	526	602	268
	DMF CR letters	275	530	764
	DMF no further comments letters	491	443	502

[28] MAPP updated 8/1/2014: www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf

Management Initiative	Performance Area	FY 2013**	FY 2014**	FY 2015
ANDA Teleconferences Workload				
When requested by the ANDA applicant within 10 business days of FDA issuing a first cycle CR letter, FDA will schedule a teleconference to clarify issues and answer questions.[29]	Teleconferences requested	23	64	52
	Teleconferences closed out	21	56	47
	Teleconferences denied	2	8	5
DMF Teleconferences Workload				
When requested by a DMF holder within 10 business days of FDA issuing a first cycle DMF deficiency letter, FDA will schedule a teleconference to clarify issues and answer questions. Priority for such teleconferences will be given to DMFs referenced in expedited and first major deficiency applications.	Teleconferences requested	10	9	5
	Teleconferences closed out	10	9	5
	Teleconferences denied	0	0	0

**These figures represent the final FY 2013 and FY 2014 GDUFA Teleconference data; prior years' numbers are updated annually

[29] FDA may close out a request for a first cycle complete response teleconference by: (1) holding the teleconference; or (2) responding to questions in the sponsor's teleconference request in writing in lieu of holding the teleconference.

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Research Performance

Under GDUFA, FDA committed to advance scientific efforts to develop new human generic products and novel dosage forms. Through its regulatory science initiatives, FDA continues to work on developing tools, standards, and approaches to assess the safety, efficacy, and quality of these products and facilitate the path to market approval.

FY 2015 Generic Drug Research Priorities

FDA agreed in the GDUFA Commitment Letter to immediately begin working on the FY 2013 Regulatory Science Plan and to consult with industry and the public to create an annual list of regulatory science initiatives specific to research on generic drugs for every year afterwards.

An FDA working group was convened to develop the FY 2014 and FY 2015 GDUFA regulatory research priorities. On June 21, 2013, FDA held the FY 2013 Regulatory Science Initiatives Part 15 Public Hearing to solicit input from industry and other stakeholders in developing the FY 2014 human generic drug research priorities. The hearing provided an overview of the FY 2013 research initiatives and an opportunity to listen to presentations by stakeholders. Information obtained during the public hearing and from other sources, e.g. open public docket for comment, was considered in developing the FY 2014 Regulatory Science Plan.[30]

On May 16, 2014, FDA held the FY 2014 Regulatory Science Initiatives Part 15 public hearing which provided an overview of the status of the human generic drug regulatory science program and an opportunity for public input in developing the FY 2015 research priorities. Information obtained during the public hearing, and other inputs, e.g., comments to public docket, was considered in developing the FY 2015 Regulatory Science Plan.[31]

On June 5, 2015, FDA held the FY 2015 Regulatory Science Initiatives Part 15 public hearing which provided an overview of the status of the human generic drug regulatory science program and an opportunity for public input in developing the FY 2016 research priorities. Information obtained during the public hearing, and other inputs, e.g., comments to public docket, was considered in developing the FY 2016 Regulatory Science Plan.[32]

The FY 2016 human generic drug regulatory science priorities identified were:

- Topic 1: Post-market evaluation of generic drugs

[30] The list of the FY 2013 research initiatives (in the GDUFA Commitment Letter) and FY 2014 research initiatives can be found at www.fda.gov/GDUFARegScience
[31] The list of the FY 2015 research initiatives can be found at: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM417234.pdf.
[32] The list of the FY 2016 research initiatives can be found at: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM469453.pdf.

- Topic 2: Equivalence of complex drug products
- Topic 3: Equivalence of locally-acting products
- Topic 4: Therapeutic equivalence evaluation and standards
- Topic 5: Computational and Analytical Tools

A description of these priorities is provided in Appendix B.

A complete list of FY 2013, FY 2014, and FY 2015 awarded studies can be found at www.fda.gov/GDUFARegScience. A summary is provided below:

FY 2013

In September 2013, FDA used FY 2013 GDUFA funds to award 28 new external research projects related to generic drug regulatory science.[33]

FY 2014

In September 2014, FDA awarded 34 new external research projects and continued to support 24 ongoing external research projects using FY 2014 GDUFA funds.[34]

FY 2015

In September 2015, FDA awarded 22 new external research projects and continued to support 42 ongoing external research projects using FY 2015 GDUFA funds.[35]

[33] List can be found in the GDUFA Commitment Letter at:
www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf
List of extensions or expansions of scope of work for previously awarded FY 2013 contracts and grants:
www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM420448.pdf
[34] List of FY 2014 Awarded GDUFA Regulatory Research Contracts and Grants:
www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM420446.pdf
[35] www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM469224.pdf.

Appendices

Appendix A: Definitions of Key Terms

A. Act on an Application means that FDA will either issue a complete response letter, an approval letter, a tentative approval letter, or a refuse to receive action.

B. Active pharmaceutical ingredient (API) means:
(i) a substance, or a mixture when the substance is unstable or cannot be transported on its own, intended to be used as a component of a drug and intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the human body; or
(ii) a substance intended for final crystallization, purification, or salt formation, or any combination of those activities, to become the final active pharmaceutical ingredient as defined in paragraph (i).

C. Amendments to an ANDA - Amendments are classified as either major, minor, or telephone and assigned tiers (1, 2, 3, or unsolicited).[36]

- Major amendments contain a substantial amount of new data or new information not previously submitted to or reviewed by FDA, requiring, in FDA's judgment, a substantial expenditure of FDA resources.
- Minor amendments require, in FDA's judgment, fewer FDA resources than are necessary to review a major amendment, but more than are necessary to review the information submitted in response to an ECD.
- If an amendment would otherwise be classified as minor, but the deficiencies are of a limited number or complexity, it can be classified as a telephone amendment at the discretion of the reviewer's team leader. Telephone amendments represent the reviewer's highest priority work assignments.

D. ANDA (Abbreviated New Drug Application) is an application submitted under section 505(j) of the FD&C Act. It contains data which when submitted to FDA's Center for Biologics (CBER) or Center for Drug Evaluation and Research, Office of Generic Drugs (CDER/OGD), provides for the review and, if adequate, ultimate approval of a generic drug product. Generic drug applications are called "abbreviated" because they are not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must, in most cases, scientifically demonstrate that its product is pharmaceutically equivalent and bioequivalent to an innovator product that FDA has found to be safe and effective. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, quality alternative to the American public.

E. Backlog refers to the ANDAs and ANDA prior approval supplements (PASs) that were pending review with the Agency as of October 1, 2012.

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[36]See Draft Guidance for Industry *ANDA Submissions — Amendments and Easily Correctable Deficiencies*, July 2014, available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404440.pdf.

F. Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.

G. Closing out a request for a first cycle review teleconference means:
(i) holding the teleconference; or
(ii) responding to questions in the sponsor's teleconference request in writing in lieu of holding the teleconference.

H. Cohort: The GDUFA program is structured based on five cohorts of submission dates (original ANDAs, PASs, and DMFs), corresponding to the five fiscal years to be covered by the program. The year 1 cohort refers to the dates of submissions made electronically in FY 2013 (October 1, 2012, to September 30, 2013). The year 2 cohort refers to the dates of submissions made electronically in FY 2014 (October 1, 2013, to September 30, 2014). The year 3 cohort refers to the dates of submissions made electronically in FY 2015 (October 1, 2014, to September 30, 2015). The year 4 cohort refers to submissions made electronically in FY 2016 (October 1, 2015, to September 30, 2016). The year 5 cohort refers to submissions made electronically in FY 2017 (October 1, 2016, to September 30, 2017).

I. Complete response (CR) letter refers to a written communication to an applicant or DMF holder from FDA usually describing all of the deficiencies that the agency has identified in an abbreviated application (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. CR letters will reflect a complete review and will require a complete response from industry to restart the clock. Refer to 21 CFR 314.110 and www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084138.htm for additional details.

J. Complete review refers to a full division-level review from all relevant review disciplines, including inspections, and includes other matters relating to the ANDA and associated DMFs as well as consults with other agency components

K. Controlled Correspondence (CC) is a correspondence submitted to the Agency, by or on behalf of a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development. See http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm411478.pdf . Controlled correspondence does not include Citizen Petitions, petitions for reconsideration, or requests for stay.

L. Delaying Amendment refers to an amendment to an ANDA from the ANDA sponsor to address actions by a third party that would cause delay or impede application review or approval timing and that were not or may not have been initially recognized by FDA as necessary when the application was first submitted. FDA's Office of Generic Drugs shall have broad discretion to determine what constitutes a delaying event caused by actions generally outside of the applicants control taking into account facts and information supplied by the ANDA sponsor.

M. Type II API Drug Master File (DMF) is a confidential, detailed document submitted by API manufacturers to FDA. A DMF contains the chemistry, manufacturing and controls of a drug component and is submitted to FDA by a person that intends to authorize FDA to reference the

information to support approval of a generic drug submission without the submitter having to disclose the information to the generic drug submission applicant.

N. Excipient is defined as an ingredient/component which is added to the drug product which is not the active pharmaceutical ingredient.

O. Expedited review of application: means that a submission will receive heightened review priority per MAPP 5240.3 Rev.1, Prioritization of the Review of Original ANDAs, Amendments, and Supplements.[37]

P. Facility is described as a business or other entity under one management either direct or indirect and at one geographic location or address engaged in manufacturing or processing an active pharmaceutical ingredient or a finished dosage form, but does not include a business or other entity whose only manufacturing or processing activities are one or more of the following: repackaging, relabeling, or testing. For purposes of this definition, separate buildings within close proximity are considered to be at one geographic location or address if the activities in them are closely related to the same business enterprise, under the supervision of the same local management, and are capable of being inspected by FDA during a single inspection.

Q. Finished Dosage Form (FDF) means:
(i) a drug product in the form in which it will be administered to a patient, such as a tablet, capsule, solution, or topical application;
(ii) a drug product in a form in which reconstitution is necessary prior to administration to a patient, such as oral suspensions or lyophilized powders; or
(iii) any combination of an API with another component of a drug product for purposes of production of such a drug product.

R. First major deficiency application refers to an ANDA which has been issued its first complete response letter classified as having major deficiency(ies).

S. Generic drug is a drug product that is approved by FDA based in part on FDA's finding that an innovator product has been shown to be safe and effective. Generic drugs generally have the same, conditions of use, route of administration, dosage form, strength, and labeling as the brand product they reference, and are bioequivalent to the brand product.

T. Generic Drug Program refers to all Agency activities related to the determination of approvability of an ANDA.

U. Major and minor amendments**:** All references to "major" and "minor" amendments in this document are intended to refer to the distinctions that FDA described in its Draft Guidance for Industry: *ANDA Submissions — Amendments and Easily Correctable Deficiencies Under GDUFA,* July 2014. See, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404440.pdf

[37] Available online at www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf.

V. Original ANDA - The initial submission to FDA's CDER OGD or CBER of an ANDA.

W. Parity as used in reference to parity in inspections between foreign and domestic facilities means inspection at an equal frequency plus or minus 20 percent with comparable depth and rigor of inspection.

X. Prior Approval Supplement (PAS) means a request to the Secretary to approve a change in the drug substance, drug product, production process, quality controls, equipment, or facilities covered by an approved abbreviated new drug application when that change has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.[38]

Y. Refuse to Receive (RTR) means refusal to receive an ANDA for review. See 21 CFR 314.101 and the Final Guidance for Industry *ANDA Submissions — Refuse-to-File Standards*, September 2014. www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm370352.pdf.

Z. Resubmission: A resubmitted original application is a response to a Refuse to Receive action letter addressing all identified user fee and/or technical deficiencies.

AA. Solicited amendment is an amendment to an ANDA submitted in response to a CR letter.

BB. Submission refers to an ANDA, an amendment to an ANDA, a PAS to an ANDA, or an amendment to a PAS.

CC. Submission date is the date an ANDA, ANDA amendment, ANDA supplement, or Type II active pharmaceutical drug master file arrives in the appropriate electronic portal of FDA and the fees have been paid.

DD. Tentative Approval Letter - If a generic drug product is ready for approval but cannot be approved due a patent or exclusivity related to the reference listed drug product, FDA issues a tentative approval letter to the applicant, and the tentative approval letter details the basis for the tentative approval. The FD&C Act delays final approval of the generic drug product until all patent or exclusivity issues have been resolved. A tentative approval does not allow the applicant to market the generic drug product.

EE. Tier 1 amendment refers to all solicited first major amendments and the first five minor amendments, as well as unsolicited amendments that OGD agrees, based on an indication by the applicant and taking into account information supplied by the applicant, either are the result of delaying actions by the innovator applicant or would eventually be solicited.

FF. Tier 2 amendment refers to all unsolicited amendments that are not submitted based on delaying actions as determined by the OGD, taking into account the facts and information supplied by the ANDA applicant, with the exception of those amendments that only remove information for review.

GG. Tier 3 amendment is any solicited major amendment subsequent to the first major amendment and/or any minor amendment subsequent to the fifth minor amendment.

[38] Per section 744A(10) of the FD&C Act .

HH. Unsolicited amendment is an amendment with information that is not requested by FDA and is submitted on the applicant's own initiative. Unsolicited amendments are categorized as either delaying or nondelaying. For purposes of GDUFA commitments, FDA does not classify amendments that are routine or administrative in nature and that do not require scientific review (e.g., requests for final ANDA approval, patent amendments, general correspondence, and USP monograph updates) to be unsolicited amendments.

Appendix B: FY 2016 Generic Drug Regulatory Science Priorities

Under GDUFA, FDA committed to develop an annual list of regulatory science priorities for generic drugs. FDA obtained input from industry and stakeholders in order to compile the following list of FY 2016 Generic Drug regulatory science priorities:

Topic 1: Post-market evaluation of generic drugs

Post-market evaluation of generic drugs includes research into monitoring methods, understanding patient perceptions of generic drug quality and effectiveness, and verifying therapeutic equivalence via patient brand-to-generic switching studies. These investigations provide additional data in therapeutic areas where concern exists about the substitutability of generic drugs and allow FDA to verify that generic drugs are fully interchangeable, safe, and effective in comparison to their reference listed drug (RLD). Based on public and FDA input, FY 2016 research priorities include evaluating modified release formulations, such as those for anti-epileptic drugs and identifying the role replicate design studies may add to bioequivalence determinations. New FY 2016 priorities include piloting surveillance methodologies for generic drugs within FDA's Sentinel Program.[39]

Topic 2: Equivalence of complex drug products

Equivalence of complex drug products includes research into making generic versions available in all product categories, including complex drugs with unique characteristics. FDA spends an increasing amount of time reviewing and developing policy for complex drug products, and future generic products will need to demonstrate equivalence to increasingly complex RLDs. This scientific research supports the development of guidance and policy that clarifies the Abbreviated New Drug Application (ANDA) pathway for complex products, such as drug-device combinations, transdermal systems, implants and parenteral microspheres, nanomaterials (e.g. liposomes and iron colloids), and products that contain complex mixtures and peptides. New FY 2016 priorities include transdermal irritation studies and research into human factors studies that will aid in evaluation of product substitutability and robustness for drug-device combinations.

Topic 3: Equivalence of locally-acting products

Equivalence of locally-acting products includes research into new bioequivalence methods and pathways for locally-acting drugs. To date, the lack of efficient bioequivalence pathways for locally-acting drug products has limited the availability of generic drugs in this category, which includes inhalation, topical dermatological, nasal, ophthalmic, gastrointestinal, and otic drug products. This research priority includes evaluating in vitro alternatives to clinical endpoint bioequivalence studies. Often these in vitro alternatives are based on microstructure characterization (Q3 equivalence) for products that are qualitatively (Q1) and quantitatively (Q2) similar in formulation. New

[39] FDA's Sentinel Initiative was implemented in 2008 to creat a national electronic system for monitoring FDA-regulated medical product safety. The Sentinel Program expands FDA's existing postmarket safety surveillance systems by enabling FDA to actively gather information about the safety and performance of these products once they reach the market.

FY 2016 priorities include BE approaches for non-Q1 and Q2 nasal and MDI formulations.

Topic 4: Therapeutic equivalence evaluation and standards

Therapeutic equivalence evaluation and standards research supports the evolution of risk-based equivalence and product quality standards to ensure therapeutic equivalence across all dosage forms and routes of delivery. FDA continues to prioritize research for abuse-deterrent formulations, narrow therapeutic index (NTI) drugs, and equivalence of modified release solid oral dosage forms. Developing the pathway for generic versions of abuse-deterrent formulations requires tools for evaluating antagonist/agonist combinations and technologies to deter nasal abuse. Based on the significant clinical impact of small variations in drug exposure, generic versions of NTI drugs require risk-based review that includes identifying NTI drug methods, adjusting bioequivalence standards, and improving manufacturing quality through advances in process control, continuous manufacturing and quality metrics. Modified release solid oral dosage forms have more failure modes than immediate release products; therefore, research into improving review standards for equivalence of modified release products is critical. New FY 2016 research priorities include the interpretation of fully replicate design BE studies to identify more precisely when they add value to the ANDA review of modified release products, research to support improved consistency of the manufacturing of modified release products (including analytical characterization of the release mechanism, improvement to IVIVC/dissolution methods, and use of quality metrics), and research to improve the evaluation of excipients both for safety and for their impact on BCS class III biowaivers.

Topic 5: Computational and analytical tools

Computational and analytical tools impact the other four GDUFA regulatory science priority areas and are essential to modernizing the ANDA review process. Modeling and simulation tools that FDA will investigate include physiologically-based pharmacokinetic or absorption models; pharmacodynamic models or clinical trial simulation; systems biology; and quantitative risk modeling. Research priorities for advanced analytical methods include developing methods that characterize peptides and other complex mixtures and that evaluate particle size, surface chemistry, and gene expression for impurities or immunogenicity. Investment in data warehouse infrastructure is needed to further enable computational tools for research and regulatory review. New FY 2016 research priorities include investigating the use of modeling and simulation tools to address questions of substitutability outside the range of traditional bioequivalence studies such as pediatric and geriatric populations or patients taking proton-pump inhibitors and generalization of statistical methods for evaluating in vitro equivalence.

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