

FY 2014

***PERFORMANCE REPORT
TO THE
PRESIDENT AND CONGRESS***

for the

***Generic Drug User Fee
Amendments***



**Food and Drug Administration
Department of Health and Human Services**

Acting Commissioner's Report

I am pleased to present to Congress the Food and Drug Administration's (FDA or the Agency) fiscal year (FY) 2014 performance report on the Generic Drug User Fee Amendments (GDUFA) of 2012. This report details FDA's accomplishments during the period of October 1, 2013 through September 30, 2014 and outlines our goals for the future. This report marks the second 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. FDA undertook a concerted effort to ensure that all of the performance goals were achieved without compromising the safety and efficacy of human generic drug products. In the last year, FDA made significant progress toward eliminating the backlog of applications. Additionally, the GDUFA-authorized hiring initiative enabled FDA to increase its domestic and foreign staff, thus positioning the Agency to achieve its commitments under GDUFA. Database enhancements and IT infrastructure improvements are expected to strengthen FDA's capacity to ensure the continued safety and efficacy of human generic drug products.

Under GDUFA, the Agency has worked diligently to focus on the timeliness of new human generic drug application reviews. FDA has implemented plans to effectively streamline the review process. The Agency successfully launched a training program aimed at establishing consistency in the review process and ensuring that all reviewers, including new hires, are well prepared to support the GDUFA initiatives. A consistent, thorough, and timely review process will increase American consumers' access to high quality, lower cost generic drugs.

FDA will continue to strengthen its record of accomplishments while ensuring that applications for human generic drugs are reviewed in an efficient and predictable timeframe and meet the appropriate standards for approval. FDA is committed to ensuring that safe, effective, and high quality human generic drugs are accessible to the American public and we look forward to continued success in the coming years.

Stephen M. Ostroff, M.D.
Acting Commissioner of Food and Drugs

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
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
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
RTF – Refuse to File
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), which included the authorization of GDUFA. GDUFA authorizes FDA to collect user fees for the review of human generic drugs 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 biennially, with comparable rigor and frequency, using a risk-based approach. This self-identification requirement will allow FDA to create an accurate inventory of facilities and organizations involved in the manufacture of human generic drugs. This annual report presents FDA's GDUFA-related accomplishments for FY 2014.

FY 2014 GDUFA Performance

FDA has seen an increase in the volume of Abbreviated New Drug Application (ANDA) submissions, Type II API Drug Master Files (DMFs), supplements, and amendments in FY 2014. Despite the increased workload, FDA acted on more pending submissions in FY 2014 compared to the previous fiscal year.

During FY 2014, FDA accomplished the following:

- As of September 30, 2014, issued first action on approximately 65 percent of the GDUFA backlog applications since program launch (up from 34 percent in FY 2013).
- Received and reviewed 1,164 Type II API DMF Completeness Assessments (CAs).
- Continued to publish a publicly available list containing more than 2,300¹ Type II API DMFs that passed the CA and are available for reference.
- Issued more than 1,200 complete response (CR) letters reflecting full division-level review of deficiencies.
- Hired 64 percent of the anticipated GDUFA program staff, exceeding the incremental hiring goal for FY 2014.
- As of September 30, 2014, the average time to approval for the FY 2014 PAS cohort is 123 calendar days. As more PASs in each cohort receive approvals, the average number of calendar days is expected to increase. The cohort numbers for each FY will be updated and reported in future GDUFA Performance Reports.

¹ www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls

- Continued to advance scientific efforts under the regulatory research science program through a collaborative partnership with the regulated industry. FDA's efforts included a Public Hearing on regulatory science initiatives on May 16, 2014, providing stakeholders with an overview of the status of the human generic drug regulatory science program, and an opportunity for public input in developing the FY 2015 GDUFA Regulatory Science Priorities.²
- Engaged in outreach efforts to educate and inform industry participants and other stakeholders about GDUFA.
- Published multiple guidances and Manuals of Policies and Procedures (MAPPs) to clarify policies and procedures.
- Held a Public Hearing on Policy Development on September 17, 2014, providing industry and the public with a venue to express their views of the GDUFA program. FDA was particularly interested in receiving industry's input on guidances that were issued during FY 2014, issues related to generic drug exclusivity, and the category of first generics.

² The FY 2015 research priorities can be found at:
www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM417234.pdf

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Introduction

The human generic pharmaceutical drug industry has saved the American health care system over \$1.2 trillion over the 10-year period from 2003 through 2012³ under the Drug Price Competition and Patent Term Restoration, or Hatch-Waxman, Act.⁴ 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.⁵

On July 9, 2012, the President signed FDASIA into law, which included the authorization of 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 FDA'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 not only in allowing FDA to determine the universe of facilities required to pay user fees, but also in understanding the scope of the global supply chain for generic drugs. FDA will use the information obtained through the self-identification process to achieve accurate and reliable surveillance of generic drugs and to facilitate inspections and compliance. Enhanced safety of the supply chain will ultimately reduce risk.

³ Generic Pharmaceutical Association, *Generic Drug Savings in the U.S. Fifth Annual Edition: 2013*, available at: www.gphaonline.org/media/cms/2013_Savings_Study_12.19.2013_FINAL.pdf

⁴ www.gpo.gov/fdsys/pkg/STATUTE-98/pdf/STATUTE-98-Pg1585.pdf

⁵ 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.

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, 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 second year of GDUFA and presents the Agency's progress in accomplishing the program goals and enhancements detailed in the GDUFA Commitment Letter.⁶ Unless otherwise noted, all data are as of September 26, 2014.⁷

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 over the next three fiscal years. Thus, some goals are not discussed in this report, but will be discussed in subsequent years.
- 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, 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 either issue a 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 was submitted.
- Definitions of key terms used throughout this report can be found in Appendix A.

⁶ www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

⁷ The Generic Drug Review Information Technology Platform was implemented over the weekend of September 27th and 28th; data for September 29th and 30th will be included in the FY 2015 GDUFA Performance Report.

GDUFA Performance Goals and Commitments

The table below presents GDUFA performance goals and targets for FY 2013-2017. 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 Through Fifth Minor Amendment	6 months	--	--	60%	75%	90%
Tier 1 - Fourth Through 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%	**	--	--

* 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.

** FDA will strive to complete GDUFA hiring goals in FY 2015 as necessary to achieve the program's performance goals.

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 easily correctable deficiencies 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 facilitate the reduction of the number of ANDA review cycles.

The following table summarizes GDUFA workload for FY 2013 and FY 2014. 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 affords 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 has no review-time goals in FY 2014 for ANDAs, PASs, or amendments. As a result, performance is not measured against a goal in the first 2 years of the GDUFA program. However, FDA has monitored performance during the first 2 years to identify any areas where improvements are 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 have significantly exceeded that expectation.

Review Workload for Applications and Submissions

GDUFA Workload	FY 2013*	FY 2014
Original ANDAs		
Total Original ANDAs Submitted	1057	1598
ANDAs Submitted After RTR for Failure to Pay User Fees	44	36
ANDAs Submitted After RTR for Technical Reasons	75	112
ANDA Solicited Amendments		
Total Solicited ANDA Amendments Submitted	48	2
PASs		
Total PAS Submissions with Inspection Status Undetermined [†]	321	256
PAS Solicited Amendments		
Total Solicited PAS Amendments Submitted	34	6
Controlled Correspondence		
Total Controlled Correspondence Submitted	953	1087
Total Controlled Correspondence Requiring Input from Clinical Division	36	26

* These figures represent the final FY 2013 GDUFA workload data; prior years' numbers are updated annually.

[†] Inspection status is not established because there are no goals in FY 2013 and FY 2014.

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 will strive to complete GDUFA-funded human resources hiring goals as necessary to achieve the program's performance metrics and goals. The FY 2014 human resources goal was to hire 50 percent of overall GDUFA program hires. The following table presents FDA's progress towards the GDUFA human resource goals.

Fiscal Year	FTE Count as of End of Fiscal Year	Incremental Hiring Goal	Percent of Incremental Staff Hired	Goal Met
2013	291	25%	31%	Yes
2014	591	50%	64%	Yes

Generic Industry Facility Self-Identification

To increase transparency of the complex, global, human generic drug industry and enhance the safety of the supply chain, GDUFA requires facilities involved in the manufacture of finished dosage forms (FDF) or API for human generic drugs to self-identify annually. This statutory requirement enables FDA to build an accurate inventory of facilities, sites and organizations involved in the manufacture of human generic drugs; improve the Agency's ability to target compliance issues and inspections; and expedite access to human generic drug products. For FY 2014, the self-identification reporting period began on May 1, 2013 and closed on May 31, 2013. FY 2015 self-identification was completed in May 2014.

In FY 2014, more than 3,900 manufacturing and testing facilities submitted self-identification information to FDA, an increase from the more than 3,500 facilities that self-identified during the FY 2013 annual reporting period. The list is available for download on FDA's GDUFA web page.⁸

⁸ <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM330790.xls>

GDUFA Guidance and Procedural Development

FDA committed to increasing transparency in operations and enhancing communication. In FY 2014, FDA published the following guidances and MAPPs:

- DRAFT Guidance for Industry *Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules*, December 2013⁹
- FINAL Guidance for Industry *ANDAs: Stability Testing of Drug Substances and Products' Questions and Answers*, May 2014¹⁰
- DRAFT Guidance for Industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*, June 2014¹¹
- DRAFT Guidance for Industry *ANDA Submissions — Prior Approval Supplements Under GDUFA*, July 2014¹²
- DRAFT Guidance for Industry *ANDA Submissions — Amendments and Easily Correctable Deficiencies Under GDUFA*, July 2014¹³
- DRAFT Guidance for Industry *Controlled Correspondence Related to Generic Drug Development*, August 2014¹⁴
- FINAL Guidance for Industry *ANDA Submissions — Refuse to Receive Standards*, September 2014¹⁵
- DRAFT Guidance for Industry *ANDA Submissions — Refuse to Receive for Lack of Proper Justification of Impurity Limits*, September 2014¹⁶
- Manual of Policies and Procedures 5200.4: Criteria and Procedures for Managing the Review of Original ANDAs, Amendments and Supplements, August 2014¹⁷
- Manual of Policies and Procedures 5240.3 Rev 1: Prioritization of the Review of Original ANDAs, Amendments, and Supplements, August 2014¹⁸
- Maintained the “Available for Reference Type II DMFs for APIs for Generic Drug Applications” list¹⁹

⁹ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377938.pdf

¹⁰ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM366082.pdf

¹¹ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf

¹² www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404441.pdf

¹³ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404440.pdf

¹⁴ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM411478.pdf

¹⁵ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf

¹⁶ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM414598.pdf

¹⁷ www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407848.pdf

¹⁸ www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf

¹⁹ www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xlsx

Technology Enhancements

FDA employed a number of significant 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 2014 IT accomplishments are described below.

FDA has developed and piloted the first release of the CDER Informatics Platform that 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. The Platform helps FDA track GDUFA review performance goals and commitments by managing GDUFA-related work in one place. Benefits of the new platform include the following:

- Track and prioritize applications such as Paragraph IV Patent Certifications.
- Optimize resource utilization in order to meet GDUFA review goals.
- Manage inventory of facilities and sites to improve regulatory efficiency.
- Prioritize inspections based on review goals.

Facilitating Standardized Electronic Submissions

Section 1136 of FDASIA amended the Federal Food, Drug, and Cosmetic (FD&C) Act to add section 745A, which authorizes FDA to require electronic submissions for certain application types 24 months after issuance of final guidance specifying the format or formats for those electronic submissions.

- Pursuant to this authority, FDA has published the revised Draft Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, July 2014.²⁰
- In support of Data Standards implementation, FDA published Draft Guidance for Industry *Providing Regulatory Submissions in Electronic Format – Standardized Study Data* and the companion draft Data Standards Catalog pursuant to its authority under FDASIA 1136, February 2014.²¹

²⁰ www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf

²¹ www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf

- FDA has conducted an analysis of the Electronic Submission Gateway (ESG) operations in preparation for this requirement and confirmed that the ESG is stable and can meet the current and projected future submission loads.
- FDA has been working with the European Union to implement the International Standards Organization Identification of Medicinal Products standards that define, characterize, and identify each regulated Medicinal Product for human use from approval through post-marketing.

Backlog Summary

FDA is dedicated to reviewing and acting on 90 percent of the backlog of 2,866 original applications and 1,879²² PAS submissions that were pending as of October 1, 2012, by the GDUFA-defined goal of September 30, 2017. In FY 2013, FDA issued first regulatory actions on approximately 34 percent of the backlog. FDA continues to make progress toward eliminating the backlog of applications. As of this report, FDA has issued a first action on approximately 65 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
ANDA	2866	31%	60%
PAS	1879	40%	73%
Total	4745	34%	65%

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.

²² The FY 2013 GDUFA Performance Report noted there were 1,882 PAS submissions. This figure has been adjusted as a result of data validation and cleanup.

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 PASs²³ 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 responding to a CR letter(s). The figures represented under each cohort are updated annually to incorporate revised results based on ANDAs and PASs approved in the previous fiscal year. This data is presented in the following tables.

Average Calendar Days to Full Approval Action: Original ANDAs

	FY 2013	FY 2014*
First Cycle Approvals		
Average Total Time to Approval	395	---
Multi-Cycle Approvals		
Average Total Time to Approval	461	---
Average Calendar Days Spent During Review by FDA	350	---
Average Calendar Days Spent by Applicant Responding to CR	111	---
Total Combined (First Cycle and Multi-Cycle)		
Combined Average Total Time to Approval	453	---

* Given the substantial backlog, FDA continued to focus its review efforts in FY 2014 on reducing the number of pending applications that were received in previous fiscal years. No original ANDAs submitted in FY 2014 were approved. The average time to decision for the FY 2014 cohort cannot be determined until additional review data is available. Review progress on all cohort submissions will be tracked in future reports.

²³ 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.

Average Calendar Days to Full Approval Action: PASs

	FY 2013	FY 2014
First Cycle Approvals		
Average Total Time to Approval	235	120
Multi-Cycle Approvals		
Average Total Time to Approval	308	181
Average Calendar Days Spent During Review by FDA	248	125
Average Calendar Days Spent by Applicant Responding to CR	61	56
Total Combined (First Cycle and Multi-Cycle)		
Combined Average Total Time to Approval	244	123

The table below presents data on the second and third 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	
		FY 2013	FY 2014
ANDA	1,853	382	371
PAS	910	300	283
Total	2,763	682	654

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.²⁴ 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 that is 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.
- Finally, FDA committed to 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. Prior to GDUFA, FDA had the authority to inspect domestic firms on a regular basis, but no such authority existed for foreign

²⁴ 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/FederalFoodDrugandCosmeticActFDCA/SignificantAmendmentstotheFDCA/FDASIA/ucm310992.htm

firms. Section 705 of FDASIA requires a risk-based schedule for inspections of establishments, whether they are located domestically or internationally.²⁵

The table below, which was presented in the FY 2013 GDUFA Performance Report, shows estimates of the percentage of domestic and foreign facilities identified as human generic drug user fee-paying facilities that have received at least one qualifying²⁶ cGMP routine surveillance inspection in the last 2 years for FDF facilities and 3 years for API facilities. Facilities with no previous inspection record; repackager and analytical testing-only facilities; facilities that self-identified as a generic drug facility but that did not pay a GDUFA user fee; and other kinds of inspections, such as for-cause and pre-approval only, were excluded from the calculations.

Frequency of cGMP Surveillance Inspections: FDF and API Sites

cGMP Surveillance Inspection Type [†]	Location	FY 13
FDF Facilities	Domestic Facilities Inspected	82% (2-yr cycle)
	Foreign Facilities Inspected	65% (2-yr cycle)
API Facilities	Domestic Facilities Inspected	80% (3-yr cycle)
	Foreign Facilities Inspected	67% (3-yr cycle)

* A facility identified as producing both a generic FDF and generic API was counted as FDF.

While documenting a similar frequency of domestic and foreign inspection in FY 2013, the table above does not fully address the commitment to achieve *risk-adjusted* frequency parity. Rather than continuing to report percentages of domestic and foreign facility inspections for FY 2014 and future years, this report will outline the steps FDA is taking to schedule and conduct both domestic and foreign inspections according to identical risk factors.

To accomplish this goal, FDA is employing a site selection surveillance inspection model that will be run annually on all facilities in the FDA’s inventory. The model will not distinguish – for

²⁵ Sec. 705 of FDASIA amends sec. 510(h) of the FD&C Act to require FDA to establish a risk-based schedule for drug inspections. Sec. 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.”

²⁶ An inspection is considered qualifying if done by Compliance Program 7356.002 (www.fda.gov/downloads/ICECI/ComplianceManuals/ComplianceProgramManual/UCM125404.pdf) or related sub-program and that was considered a cGMP inspection for site selection model purposes.

purposes of risk ranking – if the site is foreign or domestic-based. Risk will be assessed consistent with the requirements of FDASIA section 705.

The model will drive inspection performance goals and inspection planning. By following the risk-adjusted model that does not consider foreign or domestic location, FDA’s risk-adjusted parity commitment will be met. 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.”²⁷ 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.²⁸
- Developing a new standardized inspection protocol that will be used by FDA staff investigators to inspect both foreign and domestic facilities in a more uniform manner.

²⁷ GDUFA Program Performance Goals and Procedures, p.16:

www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

²⁸ 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.

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.

Performance Area	Management Initiatives	FY 2013 Accomplishments	FY 2014 Accomplishments
CR Letters	CR letters issued reflect full division-level reviews of deficiencies from relevant disciplines, including inspections and consults.	<ul style="list-style-type: none"> • ANDA GDUFA CR letters issued: 481²⁹ • PAS GDUFA CR letters issued: 315³⁰ • DMF GDUFA CR letters issued: 275 	<ul style="list-style-type: none"> • ANDA GDUFA CR letters issued: 591³¹ • PAS GDUFA CR letters issued: 160³² • DMF GDUFA CR letters issued: 529
Inspections	Inspection classification results, along with relevant information, are made public.	<ul style="list-style-type: none"> • Inspection classification results, along with relevant information, were made public and are available at: www.accessdata.fda.gov/scripts/inspsearch/ 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Draft Guidance was published on October 1, 2012 	<ul style="list-style-type: none"> • Final Guidance was published on September 16, 2014, and is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf.
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	<ul style="list-style-type: none"> • Expedited review will be implemented consistent with existing procedure for expediting applications as set forth in CDER's Manual of Policies and Procedures (MAPP)³³ 5240.3, and will also include those applications that become 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. 	<ul style="list-style-type: none"> • Expedited review will be implemented consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3 rev 1³⁴, and will also include those applications that become 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.

²⁹ CR totals include the backlog and the FY 2013 cohort. The FY 2013 report included backlog submissions only.

³⁰ CR totals include the backlog and the FY 2013 cohort. The FY 2013 report included backlog submissions only.

³¹ CR totals include the backlog, the FY 2013 and the FY 2014 cohorts.

³² CR totals include the backlog, the FY 2013 and the FY 2014 cohorts.

³³ www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

³⁴ MAPP updated 8/1/2014:

www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf

Performance Area	Management Initiatives	FY 2013 Accomplishments	FY 2014 Accomplishments
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.	<ul style="list-style-type: none"> Published Type II DMF - Available for Reference List: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrug/UserFees/UCM332875.xls DMFs found complete: 1,165 Total CA review cycles performed (includes multiple cycles on the same DMF): 1,700 DMF GDUFA Incomplete letters issued: 526 DMF CR letters: 275 DMF no further comments letters: 491 	<ul style="list-style-type: none"> Continued Publication of Type II DMF - Available for Reference List: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrug/UserFees/UCM332875.xls DMFs found complete: 1,164 Total CA review cycles performed (includes multiple cycles on the same DMF): 1,775 DMF GDUFA Incomplete letters issued: 601 DMF CR letters: 529 DMF no further comments letters: 433
ANDA Teleconferences	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. ³⁵	<ul style="list-style-type: none"> Teleconferences requested: 23* Teleconferences closed out: 21 Teleconferences denied: 2 	<ul style="list-style-type: none"> Teleconferences requested: 64 Teleconferences closed out: 52 Teleconferences denied: 7
DMF Teleconferences	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.	<ul style="list-style-type: none"> Teleconferences requested: 10* Teleconferences closed out: 10 Teleconferences denied: 0 	<ul style="list-style-type: none"> Teleconferences requested: 10 Teleconferences closed out: 8 Teleconferences denied: 1

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

³⁵ 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. Although there are no teleconference goals with industry in the first 2 years of the program, FDA is developing procedures and tracking systems for implementation of this metric.

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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 2014 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 Meeting to solicit input from industry and other stakeholders in developing the FY 2014 human generic drug research priorities. The meeting provided an overview of the FY 2013 research initiatives³⁶ and an opportunity to listen to presentations by stakeholders. Information obtained during the public meeting and from other sources, e.g., open public docket for comment, was considered in developing the FY 2014 Regulatory Science Plan.

The five FY 2014 human generic drug regulatory science priorities identified were:

- Post-market Evaluation of Generic Drugs
- Equivalence of Complex Products
- Equivalence of Locally Acting Products
- Therapeutic Equivalence Evaluation and Standards
- Computational and Analytical Tools

A description of these priorities is provided in Appendix B.

In September 2013, FDA used FY 2013 GDUFA funds to award 28 new external research projects related to generic drug regulatory science. The complete list of these projects is found in appendix C. In September 2014, FDA awarded 34 new external research projects and continued to support 24 ongoing external research projects using FY 2014 GDUFA funds.

On May 16, 2014, FDA held the FY 2014 Regulatory Science Initiatives Part 15 public meeting 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

³⁶ The list of the FY 2013 research initiatives can be found at www.fda.gov/GDUFARegScience.

obtained during the public meeting, and other inputs, e.g., comments to public docket, was considered in developing the FY 2015 Regulatory Science Plan.³⁷

³⁷ The list of the FY 2015 research initiatives can be found at:
www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM417234.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).³⁸
- 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 Easily Correctable Deficiency (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.

³⁸See 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 submission that contains a question from the generic industry, normally asking FDA for guidance pertaining to a specific drug product. FDA's OGD provides assistance to pharmaceutical firms and related industry regarding a variety of questions posed as "controlled documents." See www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm120610.htm . Controlled correspondence does not include Citizen Petitions, petitions for reconsideration, or requests for stay.
- L. A 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.
- M. Excipient is defined as an ingredient/component which is added to the drug product which is not the active pharmaceutical ingredient.

- N. Expedited review of application: means that a submission will receive heightened review priority as determined by the CBER and CDER/OGD Regulatory Project Managers (RPMs) and management. Expedited review may be granted following a request from the applicant (including where expedited review is requested for a supplemental ANDA under 21 CFR 314.70(b)(4)), or at CBER or CDER/OGD's initiative.³⁹
- O. 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.
- P. 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.
- Q. First major deficiency application refers to an ANDA which has been issued its first complete response letter classified as having major deficiency(ies).
- R. A 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 are commonly, but not in all cases, identical to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use.
- S. Generic Drug Program refers to all Agency activities related to the determination of approvability of an ANDA.
- T. 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
- U. Original ANDA - The initial submission to FDA's CDER OGD or CBER of an ANDA.

³⁹ See MAPP 5240.3 Rev. 1, Prioritization of the Review of Original ANDAs, Amendments, and Supplements. Available online at www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf.

- V. 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.
- W. Prior Approval Supplement (PAS) is a change to an approved ANDA requiring supplemental submission and approval by the FDA prior to distribution of the product made using the change. (Source: www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#S)
- X. 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.
- Y. Resubmission: A resubmitted original application is a response to a Refuse to Receive action letter addressing all identified user fee and/or technical deficiencies.
- Z. A solicited amendment is an amendment to an ANDA submitted in response to a CR letter.
- AA. A submission refers to an ANDA, an amendment to an ANDA, a PAS to an ANDA, or an amendment to a PAS.
- BB. 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.
- CC. 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.
- DD. 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.
- EE. A 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.
- FF. 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 2014 Generic Drug Regulatory Science Priorities

Because of the market penetration of human generic drugs (84 percent of human drug prescriptions in 2012), it is important that the human generic drug program have a range of tools to assure that these products are being successfully substituted and have the same safety and efficacy profile as their reference listed drug (RLD). **Post-market Evaluation of Generic Drugs** includes research into surveillance/monitoring methods for generic drugs, and understanding of patient perceptions of generic drug quality and effectiveness. It also includes evaluation/verification of therapeutic equivalence via brand to generic switching studies in patients. These investigations provide additional data in therapeutic areas where there is concern expressed about substitutability of generic drugs.

The amount of review and policy development time spent on complex products is increasing and future generic products will need to demonstrate equivalence to increasingly complex RLDs. **Equivalence of Complex Products** includes research to make generic versions available in all product categories and for all available RLDs, including products that have unique characteristics. These scientific investigations will support guidance and policy development needed to clarify the ANDA pathway for complex products. This research will impact equivalence for drug-device combinations, transdermal systems, implants and parenteral microspheres, liposomes and iron colloids, as well as products that contain complex mixtures and peptides.

The lack of efficient bioequivalence methods for locally acting drugs has limited the availability of generic drugs in this category. **Equivalence of Locally Acting Products** includes research into new bioequivalence (BE) methods and pathways for local acting drugs. Product categories in priority order are inhalation, topical dermatological, nasal, GI acting, ophthalmic and optic products. This priority includes re-evaluation of some statistical methodologies for topical product adhesion and irritation, and investigation of alternatives to clinical endpoint BE studies.

Therapeutic Equivalence Evaluation and Standards research supports the evolution of equivalence and product quality standards to focus on ensuring therapeutic equivalence across all dosage forms and routes of delivery. Areas of research include identifying the pathway for generic versions of abuse-deterrent formulations, risk-based equivalence standards for narrow therapeutic index (NTI) drugs, methods for BE study analysis such as pAUC, product quality standards (Quality by Design or QbD) for generic drugs, patient use factors such as tablet size, and advancing IVIVC/predictive dissolution for solid oral dosage forms.

Computational and Analytical Tools impact all other priority research areas and are essential to developing a modern ANDA review process that fully utilizes available computational and analytical tools. Modeling and simulation tools that will be investigated include PBPK/absorption models, PD models/clinical trial simulation, and quantitative risk modeling. An investment in data warehouse infrastructure will be required to enable these tools for research and review. Priorities for advanced analytical methods include characterization of peptides and other complex mixtures and particle size and surface chemistry. At the interface between methods and modeling are the statistical methods for evaluation of in vitro equivalence.

Appendix C: FY 2013 GDUFA Regulatory Research Contracts and Grants Awarded

Development of In Vivo Predictive Dissolution Method for Orally Inhaled Drug Products

- Multiple Awards to: University of Bath (1 U01 FD004953-01), University of Florida (1 U01 FD004950-01), Virginia Commonwealth University (1 U01FD004941-01)
- The goal of these grants is to develop an in vitro dissolution method for orally inhaled drug products (OIDPs) which will be capable of predicting in vivo dissolution of drugs that are administered via the inhalation route. The outcome of the project will aid in development of a tool that could be used for formulation development and optimization as well as product quality control. The multiple awards allow the evaluation of alternative approaches.

Systematic Evaluation of Excipient Effects on the Efficacy of Metered Dose Inhaler Products

- Awarded to Cirrus Pharmaceuticals, Inc (1 U01 FD004943-01)
- The goal of this grant is to investigate the effect of excipient concentrations on the aerosolization performance of typical hydrofluoroalkane (HFA) - based metered dose inhaler (MDI) formulations, as well as to evaluate the sensitivity of in vitro methods in detecting excipient concentration changes. Success would support allowing differences in inactive ingredients in generic MDI products.

Investigate the Sensitivity of Pharmacokinetics in Detecting Differences in Physicochemical Properties of the Active in Suspension Nasal Products for Local Action

- Awarded to University of Florida (HHSF223201310220C)
- The contract will investigate the effect of physicochemical properties of the active in suspension nasal drug product for local action including, but not limited to, particle size, morphic form and solvation state on the pharmacokinetic behavior of the drug product. This project could lead to a new bioequivalence approach for nasal spray suspension products.

Effect of Different Protective Packaging Configurations on Stability of Fluticasone Propionate Capsules for Inhalation

- Awarded to University of Florida (HHSF223201300479A)
- This contract will comprise packaging of the fluticasone propionate capsules using different packaging materials to determine the optimum packaging that will ensure stability of this drug product during shipping and the intended period of use in a research study. This contract supports previous awarded research activities on inhalation bioequivalence.

In Vitro Release Tests for Transdermal Drug Delivery Systems

- Multiple Awards to University of Cincinnati(1 U01FD004942-01) and University of Maryland (1 U01 FD004955-01)
- These grants will investigate in vitro - in vivo correlations of transdermal systems. The goal is to identify in vitro release test conditions that best identify heat effects on transdermal system release. The University of Maryland award will include in vivo studies while the University of Cincinnati will focus on modeling of heat effects.

In Vitro Release Tests for Topical Dermatological Products

- Awarded to Joanneum Research (1U01 FD004946-01) and University of Maryland (1U01FD004947-01)

- These grants investigate in vitro - in vivo correlations of topical dermatological products. The goal is to identify in vitro release test conditions that are best correlated with in vivo performance and thus provide alternative approaches to bioequivalence for topical products. The University of Maryland award is five year award for investigation of multiple methods across a range of products. The Joanneum Research award will support a human Open Flow Microperfusion study to evaluate the potential for this type of in vivo study to support bioequivalence of topical products.

Correlation of Mesalamine Pharmacokinetics with Local Availability

- Awarded to University of Michigan (HHSF223201300460A)
- This contract is to establish quantitative correlation of plasma PK data with local GI concentration and to improve physiologically based models for colon absorption. Results could lead to new approaches to the bioequivalence of locally acting GI drugs and improved understanding of colon absorption from modified release products.

In Vitro and In Vivo Correlations of Ocular Implants

- Awarded to University of Colorado Denver (I 1U01FD004929-01) and Auritec Pharmaceuticals, Inc (1U01FD004927-01)
- The purpose of these grants is to investigate in vitro-in vivo correlations of ophthalmic intravitreal implants. In each award, an in vitro dissolution test which correlates with in vivo ocular absorption will be investigated and compared to an animal model. The two awards will study different drugs and could help develop in vitro bioequivalence methods or improved release tests for this product category.

In vitro-In vivo Correlations of Parenteral Microsphere Drug Products

- Awarded to University of Connecticut Storrs (1U01FD004931-1) and University of Michigan (1U01FD005014-1)
- The purpose of these grants is to investigate in vitro-in vivo correlations of parenteral microspheres. An in vitro dissolution test which correlates with in vivo absorption will be investigated. The two awards will study different drugs and could lead to better guidance for industry on the development of in vitro release tests for parenteral microspheres. Better in vitro release tests will also accelerate product development of generic microsphere formulations.

Prediction of In Vivo Performance for Oral Solid Dosage Forms

- Awarded to the University of Michigan (HHSF223201310144C)
- The purpose of this contract is to improve prediction of in vivo performance of oral solid dosage forms. The scope includes modeling of GI fluid hydrodynamics, sampling of GI tract fluids composition and pH, novel dissolution methods and in vivo PK studies to validate model predictions.

Collection of Dose Adjustment and Therapeutic Monitoring Data for Narrow Therapeutic Index (NTI) Drug Classification

- Awarded to Duke University (1U01FD004858-01) and Johns Hopkins University (1U01FD004859-01)
- The objective of this grant is to collect drug dose adjustment and therapeutic monitoring data in patients to aid NTI classification. The two awards will use different medical record databases.

Bioequivalence of Generic Bupropion

- Awarded to Washington University (1U01FD004899-01)

- The purpose of this multi-year grant is to (1) demonstrate bioequivalence between generic and brand name bupropion HCl modified release products with different release patterns at steady state in patients, and (2) evaluate whether patients can perceive the difference in release pattern and experience lack of efficacy or increased adverse events after they are switched between each treatment. This grant (along with the two following awards) is part of broader effort to better understand the root cause of recent problems with bioequivalence of bupropion.

Investigation of Inequivalence of Bupropion Hydrochloride Extended Release Tablets: In Vitro Metabolism Quantification

- Awarded to University of Michigan (HHSF223201310183C)
- The objective of this contract is to conduct detailed in vitro metabolism studies on bupropion that will study the enzymes involved in bupropion metabolism as well as the enzyme kinetics to provide data for further investigation on inequivalence issue of the bupropion HCl extended release product.

Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns

- Awarded to University of Michigan (HHSF223201310164C)
- The objectives of this contract are to conduct healthy subject pharmacokinetic studies of bupropion HCl modified release products with different release patterns and different doses. This will help FDA understand how the release pattern of bupropion HCl products and the genotype of metabolic enzyme may affect the bioequivalence conclusions across different dose strengths within one product line due to the saturation of intestinal metabolism.

Evaluation of Drug Product Formulation and In-Vitro Performance Characteristics Related to Abuse-Deterrence for Solid Oral Dosage Forms of Opioids

- Awarded to National Institute for Pharmaceutical Technology and Education (HHSF223201301189P)
- The contract will investigate the effect of physicochemical properties of the active and excipients and composition of the drug product, along with the drug product manufacturing technology on the manipulation of the drug product for extraction of the active ingredient for putative abuse. This investigation will employ various mechanical and chemical manipulation techniques, commonly used by abusers, to assist in extraction of the active from the drug product, coupled with in-vitro characterization techniques. The goal is to have a better understanding of how material properties of excipients impact abuse-deterrent properties. This work will inform future FDA guidance on the evaluation of abuse deterrent formulations in ANDAs.

Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns

- Awarded to Brigham and Women's Hospital (1 U01 FD004856-01) and University of Maryland Baltimore (1 U01 FD004855-01)
- The purpose of these grants are to evaluate existing tools and to develop new methods to proactively monitor the drug safety, efficacy, usage, and substitution patterns of recently approved generic drugs whose approval was controversial and to evaluate if controversy during the approval process affects their acceptance by physicians and patients. The results will help FDA develop surveillance plans for future generic drug approvals

Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus Products in High Risk Transplant Recipients

- Awarded to University of Cincinnati (HHSF223201310224C)
- The objectives of this contract are to monitor the tacrolimus trough concentration in high immunologic risk patient populations after switching of all marketed tacrolimus capsule products

and to evaluate the necessity of therapeutic monitoring following each substitution. This study will evaluate clinical and safety outcomes among higher risk transplant recipients whose tacrolimus was converted from the brand-name formulation to multiple generic formulations. Results from this project will support generic substitution in all transplant patients.

Development of Bio-Relevant In-Vitro Assay to Determine Labile Iron in the Parenteral Iron Complex Product

- Awarded to Albany College of Pharmacy (1U01FD004889-01)
- The objective of this grant is to evaluate various in-vitro methods of determining labile iron and develop a bio-relevant in-vitro method to predict the amount of non-transferrin bound iron in vivo. Results from this project will improve in vitro release tests for iron complexes and allow FDA to provide consistent guidance to ANDA sponsors on this topic.

Evaluation of Dissolution Methods for Complex Parenteral Dosage Forms

- Awarded to University of Kentucky (1U01FD004892-01) and ZoneOne Pharma, Inc (1U01FD004893-01)
- The objective of these grants is to evaluate current in vitro release methods for complex parenteral dosage forms and analyze their capability of detecting formulation differences, predicting in-vivo performance, as well as their method robustness. The two awards will study different liposomal formulations. Better in vitro release methods will accelerate product development of generic liposomal formulations.

Appendix D: FY 2013-2014 Regulatory Science Progress Report Summary

The Regulatory Science Progress Report for FY 2013 and FY 2014 has been completed in fulfillment of requirements under FDASIA section 1124. The report provides progress made with respect to:

- Advancing regulatory science to promote the development of safe and effective drug products under the Prescription Drug User Fee Act (PDUFA)
- Regulatory science to ensure access to safe and effective generic drugs under GDUFA
- Advancing and adopting regulatory science relevant to biosimilars under the Biosimilar User Fee Act (BsUFA)
- Advancing regulatory science for medical devices under the Medical Device User Fee Act (MDUFA)
- FDA's regulatory science activities during FY 2013 – FY 2014

A summary of the scientific achievement information provided in the report follows. The full report is available on the FDA website at

www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdact/significantamendments/tothefdcact/fdasia/ucm356316.htm.

Advancing Regulatory Science Priorities and Resolving Gaps

Continually guided by consultation with the drug development community at large, and often leveraging the expertise and resources of investigators in industry and academia, FDA's program of regulatory science research has grown considerably in the past decade. In the past 2 years, FDA researchers in the three medical product centers have authored or coauthored over 1,500 scientific publications in addition to the hundreds of scientific abstracts, presentations, and posters associated with scientific meetings, seminars, advisory committee meetings, workshops, and international regulatory gatherings. The research has addressed critical areas of need such as increasing the efficiency of clinical trials, improving communications with patients and prescribers, advancing vaccine development, applying *in silico* modeling to inform regulatory decision making, enhancing product quality, and developing biomarkers to guide treatment and further personalized medicine.

Collaborative interactions with external partners and the variety of mechanisms employed have increased in FY 2013 – FY 2014. New public-private partnerships have been established, including the Medical Device Innovation Consortium,⁴⁰ the Kidney Health Initiative,⁴¹ and the Critical Path to TB Drug Regimens Consortium.⁴² The medical product centers are now engaged in 20 public private partnerships that are addressing focused research areas, including data standards for specific disease areas, models of disease progression for Alzheimer's, genetic markers of the risk of drug-induced adverse events, and the safety of anesthetics in children. FDA continues to promote regulatory science education and collaboration through its Centers of Excellence in Regulatory Science and Innovation (CERSI),⁴³ and two new CERSI programs were established in 2014 at the University of California, San Francisco/Stanford and Johns Hopkins University. The Reagan-Udall Foundation,⁴⁴ in collaboration with the FDA and the

⁴⁰ www.deviceconsortium.org

⁴¹ www.asn-online.org/khi/

⁴² www.c-path.org/programs/cptr/

⁴³ www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm301667.htm

⁴⁴ www.reaganudall.org/

Alzheimer's Association⁴⁵ has established a Fellowship within FDA's Division of Neurology Products to identify opportunities for collaboration with patient groups, academic researchers, and pharmaceutical manufacturers to advance the development of treatments for Alzheimer's and other dementias, while also establishing the Innovation in Medical Evidence and Surveillance Program⁴⁶ to advance the science and tools necessary to support post-market evidence generation on regulated products and to facilitate utilization of a robust secondary electronic healthcare data platform for generating better evidence on regulated products in the post-market settings. Finally, the Sentinel Initiative,⁴⁷ through successful completion of the Mini Sentinel Program, has leveraged electronic health care records from over 150 million patients across 18 data partners to support hundreds of queries related to post-marketing surveillance of the safety of medical products.

Adopting Advances in Regulatory Science

Integration of new regulatory science into the regulatory process has also progressed through a number of mechanisms. For example, reviewers have access to dedicated course offerings, symposia dedicated to specific issues in regulatory science, intramural journal clubs and seminars, and conferences where FDA scientists present their work to the research community. The medical product centers have organized or co-sponsored over 50 workshops or public meetings, engaging stakeholders and external expertise in discussions related to advancing regulatory science and strategies for integrating the new science into the regulatory process. Similarly, through the advisory committee process, FDA seeks scientific recommendations from top experts on broad scientific questions critical to applying the best science to regulatory decision making.

Equally important for the integration of scientific advances into the regulatory setting to improve medical product development is the issuing of guidances to sponsors. These documents represent current FDA thinking on specific scientific approaches and standards to guide the development and assessment of safety, efficacy and quality of medical products. In fiscal years 2013 and 2014 the medical product centers issued over 100 draft or final guidance documents, in addition to 129 product-specific bioequivalence guidances. Topics addressed included new antimicrobial development programs, a new pathway for the development and assessment of drugs to treat breast cancer, scientific recommendations for the validation of biomarkers, integration of pharmacogenomics information into drug evaluation, enrichment strategies for clinical trials, and recommendations for increasing data standardization in medical product applications. Guidance topics in the area of medical devices included design considerations for clinical trials, the evaluation of sex-specific data, and devices which contained wireless technology.

⁴⁵ www.alz.org/

⁴⁶ www.imeds.reaganudall.org

⁴⁷ www.fda.gov/safety/fdassentinelinitiative/default.htm



**Department of Health and Human Services
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