

# **FY 2013**

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

*for the*

***Generic Drug User Fee  
Amendments***



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



## ***Commissioner's Report***

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I am pleased to present to the President and Congress the Food and Drug Administration's (FDA) fiscal year (FY) 2013 Generic Drug User Fee Amendments of 2012 (GDUFA) Performance Report. This performance report covers the period of October 1, 2012, through September 30, 2013, and presents FDA's accomplishments for the first year of GDUFA and expectations for the future.

GDUFA enables FDA to administer critical and measurable enhancements to the performance of the human generic drugs program and bring greater predictability and timeliness to the review of human generic drug applications. It also establishes equivalency between domestic and foreign manufacturers providing human generic products to American consumers by ensuring that all facilities, located anywhere in the world, are inspected with comparable depth and rigor using risk-based approaches.

GDUFA challenges FDA to transform its efforts to regulate the global human generic drug industry to ensure the safety and efficacy of products for American consumers. Its goals are formidable and progress towards achieving them is measured incrementally. Early investments in building infrastructure, hiring and training staff, and designing process improvements will lay the foundation for future program success.

I am proud to report that FDA has met all GDUFA program commitments for FY 2013 and laid the foundation for future success. We are committed to meeting all GDUFA performance goals while, as always, maintaining a focus on ensuring that safe, effective, and affordable human generic drugs are reviewed in an efficient and predictable time frame.

Margaret A. Hamburg, M.D.  
Commissioner of Food and Drugs

## **Acronyms**

**ANDA** – Abbreviated New Drug Application  
**API** – Active Pharmaceutical Ingredient  
**BE** – Bioequivalence  
**CA** – Completeness Assessments  
**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  
**FDA** – Food and Drug Administration  
**FDASIA** – Food and Drug Administration Safety and Innovation 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  
**RTF** – Refusal to File  
**RTR** – Refuse to Receive

## ***Executive Summary***

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For almost 30 years, the human generic drug industry has significantly contributed to public health by delivering lower-cost, bioequivalent versions of brand name drugs to a large and growing share of the public. This unprecedented growth has, however, posed significant challenges to FDA's human generic drugs program because the volume of new human generic drug applications requiring scientific review has increased significantly, resulting in an increase in workload for FDA reviewers. In addition, the industry's rapid global expansion has challenged regulatory efforts to monitor and inspect manufacturing facilities and enforce compliance within the generic drug industry. These factors have resulted in a large backlog of pending applications requiring scientific review and an increasing number of manufacturing facilities in need of inspection.

GDUFA was enacted into law on July 9, 2012, as part of the Food and Drug Administration Safety and Innovation Act (FDASIA). GDUFA is based on an agreement between FDA and the human generic drug industry, codified by Congress, to accelerate the delivery of high-quality, lower-cost human generic drugs. FDASIA authorizes GDUFA for a 5-year period from October 1, 2012, through September 30, 2017.

GDUFA will benefit the American public in numerous ways. First, it will reduce the time required to review human generic drug applications and enable FDA to make significant progress in clearing a substantial backlog of human generic applications requiring scientific review. This will make new human generic drugs accessible more quickly. Second, it will enable FDA to hold all human generic drug manufacturers to the same high-quality standards regardless of location. Prior to GDUFA, FDA was required to inspect domestic human generic drug manufacturers every 2 years, but no such requirement existed for foreign manufacturers. This disparity between domestic and foreign manufacturing facilities, combined with insufficient resources, created significant vulnerabilities in the global prescription drug supply chain. Approximately 80 percent of active ingredients used in human generic medicines and marketed in the United States are manufactured in foreign countries, and more than half of finished products are manufactured overseas. GDUFA promotes inspection parity between foreign and domestic establishments by ensuring that FDA has the necessary resources to maintain the same high quality oversight standards.

This report presents FDA accomplishments for GDUFA in FY 2013, the program's inaugural year. FDA has:

- Hired 31 percent of the anticipated GDUFA program staff, exceeding the FY 2013 performance goal.
- Implemented a number of improvements designed to enhance the efficiency of the review process and improve the quality of human generic drug submissions:

- Published criteria for Type II active pharmaceutical ingredient (API) drug master file (DMF) completeness assessments (CA) and enhanced refuse-to-accept (RTR) standards to clarify FDA requirements for complete applications.
- Received and reviewed more than 1,500 Type II API DMF CAs, more than twice the projected number.
- Launched a public list containing more than 1,000 Type II API DMFs that passed the CA and are available for reference.<sup>1</sup>
- Issued more than 1,500 complete response (CR) letters reflecting full division-level review of deficiencies.
- Instituted routine policy on communicating easily-correctable deficiencies.
- Made significant progress towards meeting the backlog requirement for pre-GDUFA applications pending on October 1, 2012. Of the 2,866 abbreviated new drug applications (ANDAs) and 1,882 prior approval supplements (PASs) pending on October 1, 2012, 868 and 752, respectively, received a first action (approval, tentative approval, CR, refusal to file (RTF), or withdrawal) as of September 30, 2013.
- Facilitated industry self-identification efforts, enabling fee calculation and improving the quality of generic industry supply chain information.
- Engaged in outreach efforts to educate and inform industry participants and other stakeholders about GDUFA.
- Awarded \$17 million in grants to advance FY 2013 regulatory science priorities, and developed FY 2014 regulatory science priorities based on significant input from stakeholders.
- Built new information technology systems and expanded on existing systems and technology investments to promote efficiency, monitor human generic drug safety and efficacy, and streamline the human generic drug approval process.

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<sup>1</sup> [www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls](http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls)

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## **Introduction**

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The human generic drug industry delivers lower-cost, bioequivalent versions of brand name drugs to a large and growing share of the public. In calendar year 2012, 84 percent of the more than three billion outpatient prescriptions dispensed in the United States were filled with generics.<sup>2</sup>

Generics play a key role in making health care more affordable to the American public. They typically cost 50 to 70 percent less than their brand-name counterparts. In the last decade alone, generic drugs have provided more than \$931 billion in savings to the nation's health care system.<sup>3</sup>

With advancements in medical technology and prescription drug therapies, FDA's responsibility to safeguard the nation's drug supply has increased significantly in both complexity and magnitude. The rapid evolution and globalization of the human generic drug industry has delivered tremendous benefits and increasing regulatory challenges. GDUFA offers a valuable opportunity for FDA to advance public health, promote transparency between FDA and generic drug sponsors, and enhance access to high-quality, lower cost generic drugs.

### **FDA's Human Generic Drug Review Program**

In 1984, the Hatch-Waxman Act<sup>4</sup> was enacted to expedite the availability of lower cost generic drugs to the public. Hatch-Waxman permitted FDA to approve, after a period of exclusivity, applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials.

Under Hatch-Waxman, an industry applicant is required to submit an ANDA containing data demonstrating that a generic drug product is comparable to a brand-name product. Approved generic drugs must meet rigorous standards established by FDA with respect to identity, strength, quality, purity, and potency. With some exceptions, a generic drug must:

- Contain the same active ingredients and the same labeled strength as the brand-name product (inactive ingredients may vary).
- Be identical in strength, dosage form, and route of administration.
- Have the same use indications.
- Be bioequivalent to the brand-name drug, which means the generic version delivers the

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<sup>2</sup> [www.drugstorenews.com/sites/drugstorenews.com/files/US%20Medicines%202012.pdf](http://www.drugstorenews.com/sites/drugstorenews.com/files/US%20Medicines%202012.pdf)

<sup>3</sup> [www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments/totheFDCA/FDASIA/ucm310992.htm](http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/SignificantAmendments/totheFDCA/FDASIA/ucm310992.htm)

<sup>4</sup> The Hatch-Waxman Act is officially titled "The Drug Price Competition and Patent Term Restoration Act of 1984" available at: [thomas.loc.gov/cgi-bin/bdquery/z?d098:SN01538:@@D&summ2=m&%7CTOM:/bss/d098query.html](http://thomas.loc.gov/cgi-bin/bdquery/z?d098:SN01538:@@D&summ2=m&%7CTOM:/bss/d098query.html)

same amount of active ingredients in the same amount of time as the brand-name drug.<sup>5</sup>

- Meet the same batch requirements for identity, strength, purity, and quality.
- Be manufactured under the same strict standards of FDA's good manufacturing practice regulations required for brand-name products.

If approved by FDA, the applicant may manufacture and market the generic drug to provide a safe, effective, and lower-cost alternative to the American public. Since 1984, FDA has approved more than 8,000 generic equivalents of brand-name drugs.<sup>6</sup>

## **GDUFA: Re-Invigorating Generic Drug Review**

The human generic drug industry's success has posed significant regulatory challenges. Over the past 13 years, the volume of new human generic drug applications requiring scientific review nearly tripled while agency resources grew at a much slower pace. At the same time, the industry's rapid global expansion challenged regulatory efforts to monitor and inspect manufacturing facilities and enforce compliance within the generic drug industry.

Furthermore, reviewer workload increased dramatically over this period of time, and the predictability and timeliness of scientific review and inspections suffered. As the backlog of applications increased to the equivalent of approximately 3 years of average application volume, the median review time of a new human generic drug application grew to 31 months.

GDUFA was enacted as part of FDASIA with the expectation that GDUFA would have a similar impact as the Prescription Drug User Fee Act (PDUFA) program, which over the past 20 years has ensured a more predictable, consistent, and efficient premarket review program and helped speed access to new, safe, and effective brand name prescription drugs. Although modeled on PDUFA, GDUFA reflects the unique needs and challenges of generic drug regulation.

GDUFA was authorized for a 5-year period from October 1, 2012, through September 30, 2017. It requires FDA to meet established performance goals that cover a wide range of activities to enhance efficiency in the review process, hire personnel, decrease the backlog of applications, ensure consistency and frequency of inspections for domestic and foreign sites, improve communication, establish databases and IT systems, and advance regulatory science initiatives.

Achieving GDUFA's goals demands a concerted management effort to invest in resources, build excellence into FDA processes, and empower FDA's work force to solve challenging problems.

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<sup>5</sup> Pharmaceutical equivalence implies the same amount of the same active substance(s), in the same dosage form, for the same route of administration, and meeting the same or comparable standards

<sup>6</sup>[www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAct/SignificantAmendments/totheFDCAct/FDASIA/ucm310992.htm](http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAct/SignificantAmendments/totheFDCAct/FDASIA/ucm310992.htm)

## Performance Included in This Report

This annual report tracks FDA's performance in the first fiscal year of GDUFA. Unless otherwise noted, all performance data are as of September 30, 2013. Definitions of key terms used throughout this report can be found in Appendix A.

The following information refers to FDA performance presented in this report:

- FDA will annually report GDUFA performance data for each fiscal year receipt cohort (defined as submissions received from October 1 to September 30 of the following year). In each fiscal year, FDA receives submissions that will have associated goals requiring completion in the following fiscal year. In these cases, FDA's performance will be reported in subsequent fiscal years either after FDA takes an action or when the goal becomes overdue, whichever comes first.
- Submission types (e.g., Tier 1 Minor Amendments) with shorter (e.g., 90 day) review-time goals 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 (e.g., 10 month) review-time goals tend to have a smaller percentage of reviews completed, and their preliminary performance is a less reliable indicator of their final performance.
- Several of the GDUFA performance goals are scheduled to be implemented incrementally over the next 5 years. Thus, some goals are not reported in this report but will be in subsequent years.

## GDUFA Performance Goals and Commitments

The table below presents GDUFA performance goals and targets for FY 2013-2017. Performance goals are met when the specified percentage of submissions are reviewed within the review-time goal shown. Goals are phased in incrementally over the 5-year authorization with most beginning in FY 2015. Definitions of application types are included in Appendix A.

GDUFA Goals/Commitment Types	Review-Time Goals	FY 13	FY 14	FY 15	FY 16	FY 17
<b>Original ANDA Review</b>						
Original ANDA Submissions	15 months	--	--	60%	75%	--
Original ANDA Submissions	10 months	--	--	--	--	90%
<b>Amendment Review*</b>						
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%
<b>PAS Review</b>						
PASs not requiring inspections	6 months	--	--	60%	75%	90%
PASs requiring inspections	10 months	--	--	60%	75%	90%
<b>Controlled Correspondence</b>						
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%
<b>ANDA Review Efficiency</b>						
30 Minute Teleconference	10 business days	--†	--†	200	250	300
<b>Drug Master File (DMF) Review Efficiency</b>						
30 Minute Teleconference	10 business days	--	--	‡	‡	‡
<b>Backlog</b>						
Review and Act on ANDAs, ANDA amendments, and ANDA PASs that are pending on Oct 1, 2012	60 months	--	--	--	--	90%
<b>Human Resources</b>						
Incremental Staffing§	Staff/Train	25%	50%	100%	--	--

\* 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. Total number of teleconferences should not exceed the number of teleconferences for ANDAs.

§ Incremental Staffing goals are shown as a percentage of the final program hiring goal. FDA will strive to complete human resources hiring goals in FY 2015 as necessary to achieve the program's performance goals.

## ***Management Priorities and Accomplishments***

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The authors of GDUFA recognized that its success would require significant start-up resources, time, and energy as FDA began implementation and industry adjusted to its new requirements. Hiring and training new review staff alone places additional demands on current FDA reviewers, inspectors, and support staff. Recognizing this, the majority of GDUFA performance goals do not begin until FY 2015.

In FY 2013, GDUFA includes one performance goal and a number of statutory requirements and associated activities that are described in the sections that follow. All of these activities are vital to lay the foundation for future program success.

### **Human Resources**

The FY 2013 human resources goal target was to hire 25 percent of overall GDUFA program hires. To achieve this goal, FDA supplemented traditional federal hiring sources by leveraging social media platforms such as LinkedIn, Facebook, and Twitter. Additionally, FDA implemented streamlined hiring authority, a corporate recruiting strategy, and detailed onboarding processes. New position descriptions were created to support GDUFA activities. Challenges were overcome through cross-center collaboration between the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Office of the Commissioner (OC), the Office of Regulatory Affairs (ORA), and the Office of International Programs (OIP).

As of September 30, 2013, FDA had hired 291 employees for the GDUFA hiring initiative.<sup>7</sup> This comprises 31 percent of planned GDUFA program hires and exceeds the FY 2013 hiring goal of 25 percent. These employees receive orientation and training specifically focused on GDUFA. Additional position-specific training is provided and tracked internally through FDA's Learning Management System.

### **Generic Industry Identification**

GDUFA requires identification of facilities involved in the manufacture of human generic drugs and associated APIs to increase transparency of the complex, global, human generic drug industry. Industry self-identification is an important component of efforts to expedite product access and facilitate inspections and compliance.

Identification information must be submitted to FDA by each person that owns a facility identified in at least one human generic drug submission that is pending or approved to produce one or more finished dosage forms (FDF) of a human generic drug or API contained in a human

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<sup>7</sup> CDER, OC, ORA, and OIP have hired 242, 20, 18, and 11 people respectively.

generic drug. Sites or organizations in which a bioanalytical study is conducted, clinical research organizations, contract analytical testing sites, and contract repackager sites must also self-identify.

FDA created a self-identification database that was fully operational at GDUFA's program launch on October 1, 2012. FDA engaged in industry outreach and education efforts to alert human generic drug industry participants of the requirement and other provisions of FDASIA. Outreach efforts included:

- Hosting a GDUFA small business conference, a public meeting, educational sessions, and webinars.
- Disseminating materials regularly to over 150,000 industry participants and stakeholders.
- Creating a GDUFA web page and posting regular updates.
- Directly contacting all generic drug industry facilities identified in FDA records.
- Reaching out to generic industry trade associations and other industry stakeholders.
- Publishing draft guidance for industry in advance of program launch to advise industry of preparatory steps.
- Publishing *Federal Register* notices at program launch as required by FDASIA.
- Participating in numerous industry-sponsored events.

More than 3,500 unique manufacturing and testing facilities submitted self-identification information to FDA during the FY 2013 annual reporting period. The list is available to download on FDA's GDUFA web page.<sup>8</sup>

## **GDUFA Statutory Requirements**

FDA completed all statutory requirements for FY 2013. They include publishing:

- *Federal Register* Notice of Requirement: "Self-Identification of Generic Drug Facilities, Sites and Organizations"<sup>9</sup>
- FY 2013 and FY 2014 GDUFA fee notices<sup>10,11</sup>

FDA published two guidances in the window between GDUFA enactment and program launch to answer anticipated questions from industry and prepare generic facilities, sites, and organizations to meet the self-identification requirement. These were:

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<sup>8</sup> [www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm352238.htm](http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm352238.htm)

<sup>9</sup> [www.gpo.gov/fdsys/pkg/FR-2012-10-02/pdf/2012-24326.pdf](http://www.gpo.gov/fdsys/pkg/FR-2012-10-02/pdf/2012-24326.pdf)

<sup>10</sup> [www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm313983.htm](http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm313983.htm)

<sup>11</sup> [www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm319566.htm](http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm319566.htm)

- “Generic Drug User Fee Amendments of 2012: Questions and Answers”<sup>12</sup>
- “Self-Identification of Generic Drug Facilities, Sites, and Organizations”<sup>13</sup>

## **New Systems and Enhanced Technology**

GDUFA requires important information technology (IT) improvements to enhance the efficiency of human generic drug review and inspections and to facilitate user fee collection and tracking. FDA continues to devote resources to IT improvements that integrate human generic drug information across relevant agency systems. FY 2013 IT accomplishments are described in the sections that follow.

### **Chemistry, Manufacturing, and Controls Records Database to Aid the Efficiency of Review and Inspections**

- By August 2013, FDA implemented an integrated data warehouse with best-in-class analytics capabilities for managing human generic drug regulatory data, and completed a pilot study to demonstrate the system’s advanced risk analytics that utilizes various sources of quality indicators including pre-market chemistry, manufacturing, and controls data.
- FDA established a multi-year initiative to incrementally modernize the analytics infrastructure and to create a marketplace of data for all regulatory reporting and analytical needs across CDER. This approach provides FDA with the foundation to improve regulatory and scientific decision making, assess organizational performance, and ensure the quality and consistency of data.
- By September 2013, FDA implemented a state-of-the-art master data management solution to manage pre- and post-market regulatory data and established a full inventory of product and ingredient master data, providing the necessary data platform to aid in FDA’s regulatory activities such as application review, reporting, publishing, and risk-based decision support and analysis.

### **Collection System to Accept GDUFA User Fee Payments**

- The GDUFA user fee collection system and processes were fully modified, tested, implemented, and functional at program launch on October 1, 2012.

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<sup>12</sup> [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM316671.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM316671.pdf).

<sup>13</sup> [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm316721.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm316721.htm)

## **Systems and Databases to Implement Program Requirements**

- FDA established an integrated work management platform to support tracking of regulatory review processes and manage resource allocation. The expansion to the human generic drug review process is in progress.
- FDA modified an existing system to support tracking, regulatory review processes, and user fee payments for Type II Master Files.
- FDA migrated all ANDA marketing applications to an existing, more robust system to support tracking, regulatory review processes, and user fee payments of these and future applications.
- CDER replaced a legacy time reporting system with a state-of-the-art time reporting solution to support GDUFA performance analysis.
- FDA has also leveraged existing technology investments to advance the development and implementation of current program requirements.

## **Electronic Data Submission Standards**

- FDA published draft guidance, “Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the Electronic Common Technical Document (eCTD) Specifications,”(draft revision)<sup>14</sup> to describe the electronic submissions process and requirements. The phase-in period for ANDA electronic applications is 24 months after publication of final guidance.
- FDA is enhancing the standard eCTD format to provide additional capabilities such as enhanced validation standards through two initiatives: the update of the U.S. regional Module 1 and development of the eCTD version 4.0.

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<sup>14</sup> [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf).

## ***Preliminary Review Performance***

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### **Generic Drug Review Performance**

Increasing access to high-quality, lower-cost, human generic drugs is GDUFA's central goal. Achieving this goal requires bringing greater predictability and timeliness to human generic drug review. As part of GDUFA, FDA committed to reducing the scientific review time of generic drug applications by more than half of its pre-GDUFA pace. This will reduce the overall time to bring a human generic drug product to market; delivering safe, effective, and affordable generic drugs to the public sooner.

During FY 2013-2017, GDUFA challenges FDA to clear a backlog equivalent to approximately 3 years of normal application receipts while, at the same time, readying processes to accelerate the review of new submissions. While progress in substantially reducing review times and eliminating the backlog will occur incrementally, FDA committed to implement immediate review program enhancements.

Among these provisions are providing timely and complete information to applicants by issuing CR letters to all ANDA sponsors. CR letters are designed to reduce the number of review cycles by reflecting full division-level reviews of deficiencies noted by relevant review disciplines. Once scientific review is completed, FDA does not hold or delay CR letters if inspection information is still pending. In these cases, however, review of the application is not counted toward meeting the GDUFA performance goal unless a fatal flaw<sup>15</sup> has been identified. FDA is also making every reasonable effort to communicate promptly with applicants to facilitate the timely revision of easily correctable deficiencies found in ANDAs and to clarify issues and answer questions during first cycle meetings.

Another major review efficiency implemented in FY 2013 is conducting CAs for Type II API DMFs and creating a publicly-available reference list of Type II API DMFs that passed the CA. Many human generic drug sponsors do not manufacture the API used in the production of their FDF products. Instead, sponsors often purchase API from another manufacturer, or manufacturers, and reference the API manufacturer(s) DMF(s) in their FDF submission. Such sponsors are vulnerable to deficiencies identified in their API partners' DMF(s). Although they may have limited control over the correction of these deficiencies, FDF manufacturers are held accountable. In the past, their applications have been delayed until the API deficiencies were corrected. The creation of the Type II API DMF Available for Reference List<sup>16</sup> provides FDF sponsors with assurance that their API partners have passed an initial review in the form of successful completion of the CA.

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<sup>15</sup> See Appendix A: Definitions of Key Terms for fatal flaw definition.

<sup>16</sup> [www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm319567.htm](http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm319567.htm)

In FY 2013, FDA received over 1,500 DMFs requiring CAs; more than double the expected volume of 700. Significant resources were directed to review these submissions for completeness.

Easily avoidable but costly errors can be minimized with clear guidance. Over the past year, FDA has sought to lay out in greater detail its requirements for complete ANDA and DMF submissions. In FY 2013, it published the following draft guidances:

- “ANDA Submissions -- Refuse-to-Receive Standards”<sup>17</sup>
- “Initial Completeness Assessments for Type II API DMFs Under GDUFA”<sup>18</sup>

Both of these guidances are designed to help sponsors increase the quality of their submissions, reduce delays, and speed review. Additional efficiency enhancements and goals will be phased in over the next 4 years.

The following table presents FDA’s human generic drug workload and summarizes actions taken in FY 2013. Application numbers represent receipts subject to the review metrics. Submissions to FDA are tracked according to the fiscal year in which they are received.

**Review Workload for Applications and Submissions**

<b>GDUFA Workload</b>	<b>FY 13</b>	<b>FY 14</b>	<b>FY 15</b>	<b>FY 16</b>	<b>FY 17</b>
<b>Original ANDA</b>					
Total Original ANDA Applications Received	992	--	--	--	--
RTR	71				
<b>PAS</b>					
PASs with Inspection status undetermined	265	--	--	--	--
<b>Controlled Correspondence</b>					
Total Controlled Correspondence	953				
Total Controlled Correspondence requiring input from clinical division	26	--	--	--	--
<b>ANDA Review Efficiency</b>					
Number of CR Letters with inspection recommendations	7	--	--	--	--
Number of CR Letters without inspection recommendations	5	--	--	--	--
Number of PAS CR Letters	19	--	--	--	--
<b>Backlog Applications</b>					
Original ANDAs	2,867	--	--	--	--
PASs	1,883	--	--	--	--

<sup>17</sup> [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf)

<sup>18</sup> [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321884.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321884.pdf)

## Backlog Summary

GDUFA commits FDA to review and act on 90 percent of generic drug submissions pending at program launch on October 1, 2012, commonly referred to as GDUFA backlog applications, by the end of FY 2017. At the time of program launch, the GDUFA backlog was approximately three times the average number of generic drug submissions FDA receives in an entire year.

During FY 2013, FDA made significant progress towards reducing the GDUFA backlog. Thirty percent of ANDAs and 40 percent of PASs pending on October 1, 2012, received a first action.

In total, over 1,200 CR letters were sent to generic application sponsors. More than half of the letters contained recommendations based on inspections. The remaining letters were sent with inspection information pending to provide earlier notification to sponsors and facilitate prompt correction of identified deficiencies. As noted previously, CR letters issued without inspection information are not counted toward meeting the GDUFA performance goal unless a fatal flaw has been identified.

## Review Time

Congress, FDA, and industry recognized that implementing GDUFA would require significant resources, and therefore chose not to include specific early program review-time goals. Instead they included a goal for FDA to maintain levels of productivity similar to pre-GDUFA levels in the first 2 years of the program.

FDASIA requires FDA to report three generic drug metrics in FY 2013:

- The average total time to decision for ANDAs and PASs received in FY 2013.
- The number of ANDAs and PASs pending with FDA for more than 10 months on September 30, 2012.
- Of these pending ANDAs and PASs, the number FDA took final action on during FY 2013.

The first metric listed above requires FDA to report the average total time to decision for ANDAs and PASs filed in FY 2013, including the number of calendar days spent during the review by FDA and the number of calendar days spent by the sponsor responding to a CR letter(s).

Given the substantial backlog, FDA focused its review efforts in FY 2013 on reducing the number of pending applications that were received in previous fiscal years. No original ANDAs submitted in FY 2013 were approved. Of the PASs submitted in FY 2013, 53 have been approved. The average time to decision for the FY 2013 cohort cannot be determined until

additional review data is available. Review progress on FY 2013 cohort submissions will be tracked in future reports.

The table below shows data on the second and third metrics: the number of ANDAs and PASs pending with FDA for more than 10 months on September 30, 2012, and the numbers of these with a final action in FY 2013.

<b>Submission Type</b>	<b>Number Pending for Longer Than 10 Months</b>	<b>Number with Final Regulatory Action</b>
ANDA	1,854	336
PAS	919	260
<b>Total</b>	<b>2,773</b>	<b>596</b>

## ***Drug Safety and Inspections Performance***

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FDA's authority to ensure safe, high-quality generic drugs requires inspecting manufacturing facilities for compliance with current good manufacturing processes (cGMP). Less than half of human generic FDF products produced for American consumers are manufactured in the United States, and a far larger share of API is manufactured abroad.

Before GDUFA was enacted, FDA was required to inspect domestic human generic product manufacturing facilities every 2 years. No such requirement existed for foreign facilities. This regulatory disparity, combined with the greater challenge and cost associated with inspecting foreign facilities, created a gap in manufacturing safety oversight. While FDA inspected domestic facilities about once every 2 years, it only had resources to conduct inspections of human foreign drug manufacturers about once every 7 to 13 years. GDUFA will help increase the safety and quality of the drugs Americans receive by ensuring that foreign and domestic human generic drug manufacturing facilities are held to the same consistent, high-quality standards.

Under GDUFA, all facilities involved in the manufacture of human generic drugs and their ingredients, both domestic and foreign, must be identified. This identification system is critical for enhancing transparency and helping FDA protect Americans in today's complex global supply environment by knowing who is involved in human generic drug manufacturing, in what role, and where they are located.

### **Risk-Adjusted Biennial cGMP Surveillance Inspection**

GDUFA commits FDA to conduct risk-adjusted biennial cGMP surveillance inspections of human generic API and generic FDF manufacturers, with the goal of achieving parity of inspection frequency between foreign and domestic firms in FY 2017. Parity is defined as an equal frequency of inspections with comparable depth and rigor, plus or minus 20 percent.

FDA has developed a dynamic risk model to help plan surveillance inspections of drug manufacturing facilities and make adjustments as public health risks change over time. As the number of inspections increases, the information gained from these inspections can better inform the risk model. FDA will have more information about facilities, and fewer facilities will be unknown. FDA also intends to obtain and use more information from foreign regulatory counterparts. These changes should allow FDA to increase the targeting and quality of facility inspections and help achieve parity in foreign and domestic surveillance.

FDA has also increased its capacity to conduct foreign drug inspections. The additional hiring authority and funding that GDUFA provides allows FDA to increase the size of the inspectorate. Hiring and training staff to increase inspections is underway. FDA has increased staff in

international offices with a significant share of generic manufacturing facilities to minimize travel costs associated with inspections.

The table below shows current estimates of the percentage of domestic and foreign facilities identified as human generic user fee-paying facilities that have received at least one qualifying<sup>19</sup> cGMP routine surveillance inspection in the last 2 years for FDF and 3 years for API facilities. Excluded are facilities with no previous inspection record; repacker and analytical testing only facilities; facilities that self-identified as a generic facility but that did not pay a user fee; and other kinds of inspections, such as for-cause and pre-approval only.

**Frequency of cGMP Surveillance Inspections: FDF and API Sites**

cGMP Surveillance Inspection Type*	Location	FY 13	FY 14	FY 15	FY 16	FY 17
<b>FDF Facilities</b>	Domestic Facilities Inspected	82% (2-yr cycle)	--	--	--	--
	Foreign Facilities Inspected	65% (2-yr cycle)	--	--	--	--
<b>API Facilities</b>	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.

As human generic user fees allow FDA to increase inspection capacity in subsequent years, the gap between domestic and foreign inspection frequencies should narrow.

Data are now being collected to evaluate inspection rigor in accordance with the current routine surveillance inspection program instructions (i.e., abbreviated inspection vs. full inspection). Comparison data addressing the parity of inspection rigor will be presented in the FY 2014 GDUFA Performance Report.

## Inspection Classification Results

At the end of an inspection, determination of whether any condition or practice violates regulations is an FDA decision that is made considering all inspectional and compliance input. An inspection classification is issued and entered in the Inspection Classification Database. Generic drug manufacturer inspection classification results are available to the public and industry on the FDA website at: [www.accessdata.fda.gov/scripts/inspsearch/](http://www.accessdata.fda.gov/scripts/inspsearch/).

<sup>19</sup> An inspection is considered qualifying if done by Compliance Program 7356.002 (<http://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.

## Quality and Transparency Focused Initiatives

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

Performance Area	Management Initiatives	FY 2013 Accomplishments
CR Letters	CR letters are being issued reflecting full division-level reviews of deficiencies from relevant disciplines, including inspections and consults.	<ul style="list-style-type: none"> <li>• ANDA GDUFA CR letters issued: 474<sup>20</sup></li> <li>• PAS GDUFA CR letters issued: 297<sup>21</sup></li> <li>• DMF GDUFA CR letters issued: 264</li> </ul>
Inspections	Inspection classification results, along with relevant information, are made public.	<ul style="list-style-type: none"> <li>• Inspection classification results, along with relevant information, were made public and are available at: <a href="http://www.accessdata.fda.gov/scripts/inspsearch/">www.accessdata.fda.gov/scripts/inspsearch/</a></li> </ul>
RTR Standards	FDA to develop enhanced RTR standards for ANDAs and other related submissions <sup>22</sup>	<ul style="list-style-type: none"> <li>• Standards were published on October 1, 2012, and are available at: <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf">www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf</a></li> </ul>
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"> <li>• Expedited review will be implemented consistent with existing procedure for expediting applications as set forth in CDER's Manual of Policies and Procedures (MAPP)<sup>23</sup> 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.</li> </ul>

<sup>20</sup> The ANDA CR letters issued data represent backlog submissions only.

<sup>21</sup> The PAS CR letters issued data represent backlog submissions only.

<sup>22</sup> Federal Register Notice available at: [www.federalregister.gov/articles/2013/10/01/2013-23793/draft-guidance-for-industry-on-abbreviated-new-drug-application-submissions-refuse-to-receive](http://www.federalregister.gov/articles/2013/10/01/2013-23793/draft-guidance-for-industry-on-abbreviated-new-drug-application-submissions-refuse-to-receive)

<sup>23</sup> <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>

Performance Area	Management Initiatives	FY 2013 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"> <li>• Published Type II DMF - Available for Reference List: <a href="http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls">www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls</a></li> <li>• DMFs paid (through 9/18/2013): 1587 (projected number for FY2013 was 700)</li> <li>• DMFs found complete as of 9/19/2013: 1,075</li> <li>• Total CA review cycles performed (includes multiple cycles on the same DMF): 1,557</li> <li>• DMF GDUFA Incomplete letters issued: 501</li> <li>• DMF CR letters: 264</li> <li>• DMF no further comments letters: 493</li> <li>• Number of letters identifying deficiencies issued: 765</li> </ul>
ANDA Teleconferences	When requested by the ANDA sponsor within 10 business days of FDA issuing a first cycle CR letter, FDA will schedule a 30 minute teleconference to clarify issues and answer questions. <sup>24</sup> Priority for such teleconferences will be given to expedited and first major amendment applications.	<ul style="list-style-type: none"> <li>• Teleconferences requested: 22</li> <li>• Teleconferences closed out: 10</li> <li>• Teleconferences denied: 1</li> </ul>
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 30 minute teleconference with a limit of one teleconference per DMF holder per month, with the total number of teleconferences not to exceed the number of teleconferences for ANDAs, 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"> <li>• Teleconferences requested: 9</li> <li>• Teleconferences closed out: 7</li> <li>• Teleconferences denied: 0</li> </ul>

<sup>24</sup> 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.

## **Research Performance**

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While many human prescription drugs are now available in brand name and generic form, others lack human generic counterparts. A portion of GDUFA revenues finance research to expand human generic drug development in important and challenging product areas, such as inhalation drugs, and to enhance postmarket safety.

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

### **FY 2013 Generic Drug Research Priorities**

Annually, FDA develops a list of regulatory science priorities based on input from industry and other stakeholders. The FY 2013 annual list was included in the commitment letter<sup>25</sup> that accompanied GDUFA. Research topics are:

1. Bioequivalence of local-acting, orally-inhaled drug products
2. Bioequivalence of local-acting, topical dermatological drug products
3. Bioequivalence of local-acting, gastro-intestinal drug products
4. Quality by design of generic drug products
5. Modeling and simulation
6. Pharmacokinetic studies and evaluation of anti-epileptic drugs
7. Excipient effects on permeability and absorption of Biopharmaceutics Classification System Class 3 Drugs
8. Product- and patient-related factors affecting switchability of drug-device combination products
9. Postmarketing surveillance of generic drug usage patterns and adverse events
10. Evaluation of drug product physical attributes on patient acceptability
11. Postmarketing assessment of generic drugs and their brand-name counterparts
12. Physicochemical characterization of complex drug substances
13. Developing a risk-based understanding of changes in API manufacturing and controls

In FY 2013, FDA's Office of Generic Drugs (OGD) awarded \$17 million in external contracts and grants to initiate new research in identified program areas. Four million dollars was

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<sup>25</sup> <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>

allocated for internal research enabling purchase of equipment for FDA labs and support for research fellows at FDA.

To date, this investment has yielded draft guidance recommending new bioequivalence methods for products without generic competition, including Albuterol Sulfate Metered Dose Inhaler, Fluticasone Propionate, Salmeterol Xinafoate Dry Power Inhaler, Acyclovir Topical Ointment and Cyclosporine Ophthalmic Emulsion.<sup>26</sup>

## **FY 2014 Generic Drug Research Priorities**

An FDA Working Group was convened to develop FY 2014 GDUFA regulatory research priorities. On June 21, 2013, FDA held a Part 15 public hearing to solicit input from stakeholders on FY 2014 human generic drug research priorities and review the status of FY 2013 initiatives. Information obtained during the public meeting, and other inputs, was considered in developing the FY 2014 Regulatory Science Plan<sup>27</sup>.

The five FY 2014 human generic drug regulatory science priorities are:

- 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.

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<sup>26</sup> [www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm)

<sup>27</sup> <http://www.fda.gov/Drugs/NewsEvents/ucm367997.htm>

# Appendices

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## Appendix A: Definitions of Key Terms

- A. To Act on an Application means that FDA will either issue a CR letter, an approval letter, a tentative approval letter for an ANDA, 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. An Amendment is a report of a change, deletion or addition of technical or administrative information.
- D. Amendment to an ANDA - Amendment requests are classified as either major, minor, or telephone and assigned tiers (1, 2, 3, or unsolicited).
- Major amendments have the same review priority as original, unreviewed ANDAs and are reviewed in accordance with OGD's first in-first reviewed procedure.
  - Minor amendments often address deficiencies that are outside the control of the applicant or deficiencies that are more easily addressed than those in a major amendment. Minor amendments have a higher priority than major amendments because they often mean an application is close to approval and should, therefore, be given priority.
  - 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.
- E. An Abbreviated New Drug Application (ANDA) is an application submitted under section 505(j). It contains data which when submitted to 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.
- F. Backlog refers to the queue of original ANDAs, ANDA amendments, and ANDA supplements pending as of October 1, 2012.
- G. 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.

- H. Biopharmaceutics Classification System is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability.
- I. Closing out a request for a first cycle review teleconference means:
- 1) Holding the teleconference; or
  - 2) Responding to questions in the sponsor's teleconference request in writing in lieu of holding the teleconference.
- J. Cohort - The GDUFA program is structured based on 5 cohorts of submission dates (original ANDAs, PASs, and DMFs), corresponding to the 5 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).
- K. 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. Complete response 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](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084138.htm) for additional details.
- L. Complete Review refers to a full division-level review from all relevant review disciplines, including inspections.
- M. Controlled Correspondence is a submission that contains a question from the generic industry, normally asking FDA for guidance pertaining to a specific drug product. 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](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm120610.htm) . Controlled correspondence does not include Citizen Petitions, petitions for reconsideration, or requests for stay.
- N. A 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. Type II API DMF refers to a submission of information to the Secretary 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. A Type II DMF is the most common form of DMF and can cover dosage form drugs manufactured under contract for another company which would file an ANDA.
- O. Electronic refers to submissions in an all-electronic common technical document format in effect at the date of submission.

- P. Excipient is defined as an inactive ingredient/component that is not the active pharmaceutical ingredient and serves as the vehicle or medium for the active ingredient.
- Q. Expedited Review of Application - While generally original ANDAs, ANDA amendments, and ANDA supplements are reviewed in the order received (first-in, first-reviewed), certain applications may be identified at the date of submission for expedited review of the original submission and amendment(s) associated with the qualifying application, as described in CDER's MAPP 5240.3. (See [www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079787.pdf](http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079787.pdf).) Products to respond to current and anticipated public health emergencies; products under special review programs, such as the President's Emergency Plan for AIDS Relief; products for which a nationwide shortage has been identified; and first generic products for which there are no blocking patents or exclusivities on the reference listed drug currently may qualify for expedited review. For ANDAs in the year 1 and 2 cohorts, FDA will 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.
- R. A Facility is 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.
- S. A Fatal Flaw is a serious and rare occurrence that requires an ANDA applicant to manufacture a new demonstration batch of its product or to conduct a new bioequivalence or clinical study. If a fatal flaw is identified, all review activities including compliance inspections will be stopped.
- T. Finished Dosage Form (FDF)
- (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.
- U. First Major Deficiency application refers to an ANDA which has been issued its first complete response letter classified as having major deficiency(ies).
- V. 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.
- W. Generic Drug Program refers to all agency activities related to the determination of approvability of an ANDA.
- X. Generic Drug Submission - includes an ANDA, an amendment to an ANDA, a PAS, or an amendment to a PAS. A generic drug submission or Type II API DMF will not be considered submitted until either (a) the transmission has been designated as completed through an electronic

gateway to FDA, except for a weekend, holiday or any other day the agency is not open for business; then it shall be deemed submitted on the next day FDA is open for business or (b) received in physical media form and documented as received in the designated document room of FDA.

- Y. Major and Minor Amendments: All references to major and minor amendments are intended to refer to the distinctions that FDA described in its Guidance for Industry: Major, Minor, Telephone Amendments to Abbreviated New Drug Applications. See [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm072888.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance/ucm072888.pdf)
- Z. Parity is used in reference to parity in inspections, between foreign and domestic facilities, meaning inspection at an equal frequency plus or minus 20 percent with comparable depth and rigor of inspection.
- AA. 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.
- BB. Refuse to Receive pertains to refusal to accept an ANDA for further review. See 21 CFR 314.101 and [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080561.pdf%201993](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080561.pdf%201993)
- CC. A Solicited Amendment is an amendment submitted in response to a Complete Response letter.
- DD. The Submission Date is the date an ANDA, ANDA amendment, ANDA supplement, or Type II API DMF arrives in the appropriate electronic portal of FDA and the fees have been paid.
- 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 sponsor and taking into account information supplied by the sponsor, 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 sponsor, 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.
- HH. An Unsolicited Amendment is an amendment with information not requested by FDA. 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) as unsolicited amendments.

## Appendix B: FY2014 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 OGD 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, gastrointestinal 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 drugs, methods for BE study analysis such as partial area under the drug concentration-time curve, product quality standards for generic drugs, patient use factors such as tablet size, and advancing in-vitro in-vivo correlation/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 physiologically based pharmacokinetic/absorption models, pharmacodynamic 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.



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



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