FY 2017

PERFORMANCE REPORT
TO
CONGRESS

for the

Generic Drug User Fee Amendments

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Commissioner's Report

I am pleased to present to Congress the Food and Drug Administration's (FDA) annual performance report on the Generic Drug User Fee Amendments of 2012 (GDUFA). This report details FDA's preliminary accomplishments in fiscal year (FY) 2017 (October 1, 2016, through September 30, 2017) and updates FDA's performance for the previous years of GDUFA. This report marks the final year of GDUFA I.

GDUFA has produced tangible results for the American public. In the last 2 years of GDUFA, FDA approved more generic drugs each year than in any other year in the history of the generic drug program. FDA took a number of actions under GDUFA that underpinned these productive years. For example, throughout GDUFA, FDA has met or exceeded all the GDUFA goals, including those to hasten the review of generic drug applications; expanded communications with industry; enhanced information technology systems and databases; issued guidances to assist generic drug manufacturers in their applications; implemented inspection efficiency enhancements; and met the backlog goal 15 months ahead of schedule. The passage of GDUFA has played an important role in facilitating FDA's efforts to expand access to affordable generic drugs while continuing to ensure the quality and safety of generic drugs.

FDA's early investments in the generic drug program and commitment to excellence have produced a robust foundation that will benefit the American consumer. FDA is positioned to ensure consistent quality oversight through the strengthening and integration of the regulatory review of generic drug applications, facility compliance inspections, quality surveillance, and risk-based policies and standards.

I am excited about FDA's significant progress in meeting the challenges and responsibilities of the generic drug program. I look forward to continued engagement with the generic drug industry, Congress, and other stakeholders.

Scott Gottlieb, M.D.
Commissioner of Food and Drugs

Acronyms

ANDA – Abbreviated New Drug Application

API – Active Pharmaceutical Ingredient

BE – Bioequivalence

Bio-IND – Investigative New Drug Applications submitted for bioavailability or BE studies under 21 CFR 320.31

BITS-PTS – Biologics Information Tracking System – Pre-Application Tracking System

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

DRL – Discipline Review Letter

ECD – Easily Correctable Deficiency

eCTD – Electronic Common Technical Document

FDA – Food and Drug Administration

FDASIA – Food and Drug Administration Safety and Innovation Act

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

FDF – Finished Dosage Form

FTE – Full-Time Equivalent

FY – Fiscal Year (October 1 – September 30)

GDUFA – Generic Drug User Fee Amendments of 2012

IR – Information Request

IT – Information Technology

IQA – Integrated Quality Assessment

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

PFC – Pre-Submission Facility Correspondence

RLD – Reference Listed Drug

RMS-BLA – Regulatory Management System – Biologics Licensing Application

RPM – Regulatory Project Manager

RTR – Refuse to Receive

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Executive Summary

On July 9, 2012, the President signed into law the Food and Drug Administration Safety and Innovation Act (FDASIA),[1] which included the authorization of the Generic Drug User Fee Act (GDUFA). GDUFA authorizes the Food and Drug Administration (FDA or the Agency) to collect user fees for human generic drug activities and enables FDA to advance a safer, more efficient, and more affordable human generic drug review program. Furthermore, GDUFA enhances FDA's ability to protect Americans in the complex global supply environment by requiring the self-identification of facilities involved in the manufacture of generic drugs and associated active pharmaceutical ingredients (API). GDUFA also allows FDA to ensure that foreign and domestic industry participants in the U.S. generic drug system are held to consistent, high-quality standards and are inspected with comparable rigor and frequency, using a risk-based approach. This self-identification requirement allows FDA to create an accurate inventory of facilities and organizations involved in the manufacture of human generic drugs.

FDA has made noteworthy advancements in the implementation of GDUFA. This annual report presents preliminary data on FDA's success in meeting fiscal year (FY) 2017 review performance goals and commitments, and updates the review goals performance for FYs 2013 through 2016.

FY 2017 GDUFA Performance

FDA's efforts to lay the foundation for a modern generic drug program have positioned the Agency to meet the FY 2017 goals, which were agreed upon in the GDUFA Commitment Letter.[2]

During FY 2017, FDA accomplished the following:

- FDA approved 763 abbreviated new drug applications (ANDAs) and tentatively approved 174 ANDAs, the highest number of combined generic drug approvals and tentative approvals in the history of the generic drug program.
- Under GDUFA, FDA committed to review and act on 90 percent of all ANDAs, prior approval supplements (PASs), and amendments that were pending on October 1, 2012, (i.e., backlog) by the end of FY 2017 (i.e., September 30, 2017). As of September 30, 2017, FDA has taken action on 98 percent of the backlog. FDA met the backlog goal in June 2016, 15 months ahead of schedule.
- FDA responded to 99 percent or more of controlled correspondence (CC) within 2 months of submission (2 months is the goal for most CC; if the CC requires input from the clinical division, 1 additional month is added to the goal, making the response due within 3 months of the submission) for those submitted through September 2017. FDA is on track to exceed the commitment to respond to 90 percent of GDUFA Year 5 CC.

[1] www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf
[2] www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf

- FDA committed to review and act on 90 percent of Year 5 PASs requiring inspection within 10 months of submission. The Agency has not missed a goal date for FY 2017 PAS submissions and, as of the end of Year 5, FDA is 100 percent on time.
- As of September 30, 2017, the average time to approval for the FY 2017 PAS cohort is 110 calendar days. As more PASs in each cohort are approved, the average number of calendar days to approval is expected to increase. The cohort numbers for each fiscal year will be updated and reported in future GDUFA Performance Reports.
- FDA has successfully coordinated the integration of the FDA Facility Evaluation and Inspection Program.
- FDA effectively implemented the Integrated Quality Assessment (IQA), which provides aligned, patient-focused, and risk-based drug product quality recommendations.
- FDA issued 138 complete responses (CR) to ANDAs received in FY 2017.
- FDA completed 802 Type II API drug master file (DMF) completeness assessments (CA).
- FDA continued to maintain the "Available for Reference Type II DMFs for APIs for Generic Drug Applications" list, containing more than 4,000 Type II API DMFs that passed the CA and are available for reference. This list is publicly available.[3]
- FDA continued to advance scientific efforts under the regulatory research science program through a collaborative partnership with the regulated industry. Some of FDA's FY 2017 efforts included hosting an advisory committee meeting on modeling and simulation in March 2017, awarding research grants and contracts, and hosting a May 2017 public workshop to obtain public input on regulatory science initiatives.

- During FY 2017, FDA engaged in outreach efforts to educate and inform industry participants and other stakeholders about GDUFA and the generic drug program. For example:

    - In October 2016, FDA speakers, along with industry, addressed key regulatory and technical issues impacting the generic drug industry and FDA at the Association for Accessible Medicines' (AAM, formerly GPhA) Fall Technical Conference.

    - In January 2017, FDA published a draft guidance entitled "Referencing Approved Drug Products in ANDA Submissions"[4] and recorded a corresponding webinar[5] for the Center for Drug Evaluation and Research's (CDER) Small Business and Industry Assistance Webinar series.

    - In April 2017, FDA staff discussed strategies for industry to provide high-quality submissions to FDA, and GDUFA regulatory science research with the generic drug

[3] www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls
[4] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536962.pdf
[5] www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm537410.htm

industry and other stakeholders at the Regulatory Education for Industry (REdI) Generic Drugs Forum.

- In July 2017, FDA held a public meeting on "Administering the Hatch-Waxman Amendments: Ensuring a Balance between Innovation and Access."

- FDA published multiple guidances and Manuals of Policies and Procedures (MAPPs), including MAPP 5240.3 Rev 3 – "Prioritization of the Review of Original ANDAs, Amendments, and Supplements"[6] and MAPP 5210.5 Rev 2 – "Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs."[7]

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

7 www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm079593.pdf

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Introduction

Millions of Americans use generic drugs to treat a wide variety of medical conditions.[8] The Food and Drug Administration (FDA) helps ensure that human generic drug products are thoroughly tested and shown to meet the statutory standards for approval, generally with evidence that they contain the same active ingredients, route of administration, labeling, 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.[9]

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 human generic drug activities.

GDUFA provides FDA with supplemental funds to hire and train additional reviewers, investigators, and support staff, and to upgrade its information technology (IT) systems. GDUFA 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 in understanding the scope of the global supply chain for human generic drugs and in allowing FDA to determine the universe of facilities required to pay user fees. FDA uses the information obtained through the self-identification process to facilitate inspections and compliance. Enhanced safety of the supply chain ultimately reduces risk.

[8] According to a report compiled by the QuintilesIMS Institute on behalf of AAM, generic drugs saved the American health care system $1.67 trillion over the 10-year period from 2007 through 2016—with over $253 billion saved in 2016 alone. The report is available at www.accessiblemeds.org/sites/default/files/2017-07/2017-AAM-Access-Savings-Report-2017-web2.pdf.

[9] 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, & Cosmetic Act (FD&C Act).

Performance Presented in This Report

GDUFA performance goals cover a wide range of improvements including: enhancing the efficiency of the review process; increasing and expediting hiring and training; decreasing the backlog of applications that were pending FDA decisions as of October 1, 2012; ensuring consistency and frequency of inspections for domestic and foreign sites; improving transparency; establishing databases and IT systems; and advancing regulatory science initiatives. This report details FDA's performance in the fifth year of GDUFA and presents the Agency's progress in accomplishing the program goals and enhancements detailed in the GDUFA Commitment Letter. Unless otherwise noted, all data are as of September 30, 2017.

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.

- Data in this report is organized by original ANDA receipt cohort.
- Several of the GDUFA I performance goals were scheduled to be implemented incrementally from FY 2015 through FY 2017. Therefore, this report includes information on goals not discussed in previous reports.
- FDA will report GDUFA performance data annually 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 the GDUFA Preliminary and Updated Performance Summary tables, we note that data on amendments has not fully matured. FDA may receive amendments to an application in fiscal years following the year of receipt; for example, FDA is still receiving amendments in FY 2018 for original ANDAs received in FY 2016. Because the information in this report is organized by receipt cohort, FDA may not have complete information on amendments for 1 or more years after the year of the receipt cohort. The FY 2016 table is limited to original ANDAs submitted in FY 2016 but is not limited to amendments that were submitted in FY 2016.
- For a performance goal to be met, FDA must review the specified percentage of submissions within the review-time goal. For example, in FY 2016, to meet the goal for original ANDAs, FDA needed to review and act on 75 percent of original ANDAs within 15 months.
- To "act on an application" means that FDA will 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 that was designated as RTR was submitted.

- Submission types with shorter review-time goals (e.g., PASs with 6-month goal dates in FY 2016, CC with 2-month goal dates in FY 2016) tend to have a larger percentage of reviews completed by the end of the fiscal year, and their preliminary performance is a more reliable indicator of their final performance. However, submission types (e.g., original ANDA submissions) with longer review-time goals (e.g., 15-month goal date in FY 2016) tend to have a smaller percentage of reviews completed, and their preliminary performance is a less reliable indicator of their final performance.

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

GDUFA Performance Goals and Commitments

This table reflects the percentage of submissions that FDA must act on to meet the goal for that fiscal year. Goals were 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%	25%	--	--

* Ten-month review cycle for 90 percent of applications submitted in year 5.
[†] Amendments may be submitted to either original ANDAs or PASs.
[§] One teleconference per DMF holder per month, with the number of teleconferences not to exceed the number of teleconferences for ANDAs.

GDUFA Preliminary and Updated Performance Summary

The following tables show the progress of the FY 2015, 2016, and 2017 cohorts respectively. FDA continues to meet all the review goals. Despite shorter timeframes in FY 2017 and approximately 40 percent more original submissions and resubmissions than originally anticipated, FDA is exceeding the review goals. FDA will be able to report final performance for FY 2017 as goal dates for each category occur. However, final performance will depend on the outcome of pending submissions and is presented as a potential range.

GDUFA FY 2015 Updated Performance	Review-Time Goal	Goal	Actions* Completed	Percent on Time†	Potential Range‡
I. Original ANDA Review-Time Goals					
Original ANDA Applications	15 months	60%	497 of 502	97%	97% to 97%
II. Amendment Review-Time Goals§					
Tier 1 - First Major Amendment	10 months	60%	28 of 93	100%	30% to 100%
Tier 1 - First through Third Minor Amendment	3 months	60%	197 of 226	98%	85% to 98%
Tier 1 - First through Third Minor Amendment Requiring an Inspection	10 months	60%	14 of 28	100%	50% to 100%
Tier 1 - Fourth through Fifth Minor Amendment	6 months	60%	--	--	--
Tier 1 - Fourth through Fifth Minor Amendments Requiring an Inspection	10 months	60%	--	--	--
Tier 1 - Unsolicited Delaying Amendment	3 month	60%	29 of 29	93%	93% to 93%
Tier 2 Amendments	12 months	60%	135 of 137	96%	94% to 96%
Tier 3 Amendments	--	--	2 Amend	--	--
III. PAS Review-Time Goals					
PASs Not Requiring Inspections	6 months	60%	343 of 343	98%	98% to 98%
PASs Requiring Inspections	10 months	60%	69 of 69	96%	96% to 96%
IV. PAS Amendment Review-Time Goals§					
Tier 1 - First Major Amendment	10 months	60%	8 of 11	100%	73% to 100%
Tier 1 - First through Third Minor Amendment	3 months	60%	91 of 92	99%	98% to 99%
Tier 1 - First through Third Minor Amendment requiring an Inspection	10 months	60%	3 of 4	100%	75% to 100%
Tier 1 - Fourth through Fifth Minor Amendment	6 months	60%	3 of 3	100%	100% to 100%
Tier 1 - Fourth through Fifth Minor Amendments Requiring an Inspection	10 months	60%	--	--	--
Tier 1 - Unsolicited Delaying Amendment	3 month	60%	6 of 6	100%	100% to 100%
Tier 2 Amendments	12 months	60%	16 of 16	100%	100% to 100%
Tier 3 Amendments	--	--	--	--	--
V. Controlled Correspondence					
Controlled Correspondence	4 months	70%	1,189 of 1,197	98%	97% to 98%
Controlled Correspondence Requiring Input from Clinical Division	5 months	70%	322 of 322	100%	100% to 100%

* Actions completed include any action taken regardless of whether it met the review-time goal.
† Percent on time represents the current percentage of actions FDA completed within the review-time goal.
‡ Range represents the minimum (all pending become late) and maximum (all pending reviewed on time) performance.
§ Amendments data has not fully matured to the point where values can be displayed for each of the metrics. Amendments to original ANDAs submitted in a fiscal year may be received in that fiscal year or in subsequent fiscal years. Therefore, FDA will not have complete data for amendments submitted to original ANDAs that were received in a given fiscal year at the end of that fiscal year

As indicated in the table below, FDA continues to meet all the review goals for the FY 2016 cohort. To date, FDA has met goals for original ANDA review, PAS review and CC; and has the potential to meet the original ANDA and PAS amendment goals.

GDUFA FY 2016 Updated Performance	Review-Time Goal	Goal	Actions* Completed	Percent on Time†	Potential Range‡
I. Original ANDA Review-Time Goals					
Original ANDA Applications	15 months	75%	680 of 833	100%	81% to 100%
II. Amendment Review-Time Goals§					
Tier 1 - First Major Amendment	10 months	75%	1 of 37	100%	3% to 100%
Tier 1 - First through Third Minor Amendment	3 months	75%	59 of 118	97%	49% to 98%
Tier 1 - First through Third Minor Amendment Requiring an Inspection	10 months	75%	0 of 2	--	0% to 100%
Tier 1 - Fourth through Fifth Minor Amendment	6 months	75%	--	--	--
Tier 1 - Fourth through Fifth Minor Amendments Requiring an Inspection	10 months	75%	--	--	--
Tier 1 - Unsolicited Delaying Amendment	3 month	75%	31 of 49	100%	63% to 100%
Tier 2 Amendments	12 months	75%	13 of 34	100%	38% to 100%
Tier 3 Amendments	--	--	--	--	--
III. PAS Review-Time Goals					
PASs Not Requiring Inspections	6 months	75%	424 of 424	99%	99% to 99%
PASs Requiring Inspections	10 months	75%	30 of 30	100%	100% to 100%
IV. PAS Amendment Review-Time Goals§					
Tier 1 - First Major Amendment	10 months	75%	3 of 6	100%	50% to 100%
Tier 1 - First through Third Minor Amendment	3 months	75%	75 of 85	97%	86% to 98%
Tier 1 - First through Third Minor Amendment Requiring an Inspection	10 months	75%	2 of 3	100%	67% to 100%
Tier 1 - Fourth through Fifth Minor Amendment	6 months	75%	1 of 1	100%	100% of 100%
Tier 1 - Fourth through Fifth Minor Amendments Requiring an Inspection	10 months	75%	--	--	--
Tier 1 - Unsolicited Delaying Amendment	3 months	75%	7 of 8	100%	88% to 100%
Tier 2 Amendments	12 months	75%	8 of 8	100%	100% to 100%
Tier 3 Amendments	--	--	--	--	--
V. Controlled Correspondence					
Controlled Correspondence	2 months	70%	1,799 of 1,804	97%	97% to 97%
Controlled Correspondence Requiring Input from Clinical Division	3 months	70%	79 of 80	99%	98% to 99%

* Actions completed include any action taken regardless of whether it met the review-time goal.
† Percent on time represents the current percentage of actions FDA completed within the review-time goal.
‡ Range represents the minimum (all pending become late) and maximum (all pending reviewed on time) performance.
§ Amendments data has not fully matured to the point where values can be displayed for each of the metrics. Amendments to original ANDAs submitted in a fiscal year may be received in that fiscal year or in subsequent fiscal years. Therefore, FDA will not have complete data for amendments submitted to original ANDAs that were received in a given fiscal year at the end of that fiscal year.

This table presents GDUFA preliminary performance data for FY 2017. Based on preliminary performance for FY 2017, FDA has not missed a goal and has the potential to meet all goals. The percentage on time to date is 99 percent or higher for both ANDAs and CCs. Also, there have already been approvals of FY 2017 original ANDAs.

GDUFA FY 2017 Preliminary Performance	Review-Time Goal	Goal	Actions* Completed	Percent on Time†	Potential Range‡
I. Original ANDA Review-Time Goals					
Original ANDA Applications	10 months	90%	324 of 1310	99%	25% to 100%
II. Amendment Review-Time Goals§					
Tier 1 - First Major Amendment	10 months	90%	0 of 2	--	0% to 100%
Tier 1 - First through Third Minor Amendment	3 months	90%	1 of 20	100%	5% to 100%
Tier 1 - First through Third Minor Amendment Requiring an Inspection	10 months	90%	--	--	--
Tier 1 - Fourth through Fifth Minor Amendment	6 months	90%	--	--	--
Tier 1 - Fourth through Fifth Minor Amendments Requiring an Inspection	10 months	90%	--	--	--
Tier 1 - Unsolicited Delaying Amendment	3 month	90%	6 of 32	100%	19% to 100%
Tier 2 Amendments	12 months	90%	0 of 8	--	0% to 100%
Tier 3 Amendments	--	--	--	--	--
III. PAS Review-Time Goals					
PASs Not Requiring Inspections	6 months	90%	292 of 388	99%	75% to 99%
PASs Requiring Inspections	10 months	90%	10 of 24	100%	42% to 100%
IV. PAS Amendment Review-Time Goals§					
Tier 1 - First Major Amendment	10 months	90%	1 of 3	100%	33% to 100%
Tier 1 - First through Third Minor Amendment	3 months	90%	10 of 21	100%	48% to 100%
Tier 1 - First through Third Minor Amendment Requiring an Inspection	10 months	90%	--	--	--
Tier 1 - Fourth through Fifth Minor Amendment	6 months	90%	--	--	--
Tier 1 - Fourth through Fifth Minor Amendments Requiring an Inspection	10 months	90%	--	--	--
Tier 1 - Unsolicited Delaying Amendment	3 months	90%	0 of 3	--	0% to 100%
Tier 2 Amendments	12 months	90%	1 of 2	100%	50% to 100%
Tier 3 Amendments	--	--	--	--	--
V. Controlled Correspondence					
Controlled Correspondence	2 months	90%	2,250 of 2,637	99%	84% to 99%
Controlled Correspondence Requiring Input from Clinical Division	3 months	90%	22 of 29	100%	76% to 100%

* Actions completed include any action taken regardless of whether it met the review-time goal.
† Percent on time represents the current percentage of actions FDA completed within the review-time goal.
‡ Range represents the minimum (all pending become late) and maximum (all pending reviewed on time) performance.
§ Amendments data have not fully matured to the point where values can be displayed for each of the metrics. Amendments to original ANDAs submitted in a fiscal year may be received in that fiscal year or in subsequent fiscal years. Therefore, FDA will not have complete data for amendments submitted to original ANDAs that were received in a given fiscal year at the end of that fiscal year.

For the receipts in FY 2013 and FY 2014, the GDUFA Commitment Letter does not require FDA to report on any performance goals. The table below presents FDA's performance in terms of completed actions for cohort years of receipt FY 2013, FY 2014, FY 2015, and FY 2016 as well as preliminary FY 2017 performance. Note that approvals of FY 2017 applications are already occurring. In general, there are a higher number of actions for submissions from earlier fiscal years because such submissions have had more time for an action to be taken.

GDUFA Performance	FY 13*	FY 14*	FY 15*	FY 16*	FY 17
ANDA Review Efficiency – Completed Actions					
Refuse to Receive for Failure to Pay Fees	62	37	7	16	13
Refuse to Receive for Technical Reasons	146	153	92	210	124
Number of CR Letters with Inspection Recommendations	858	1115	491	395	124
Number of CR Letters without Inspection Recommendations	144	78	12	13	15
Number of Tentative Approvals	112	102	56	15	5
Number of Approvals	288	441	75	79	15
PAS Review Efficiency – Completed Actions					
Number of PAS CR Letters	114	67	156	142	57
Number of PAS Approvals	258	202	349	367	228

* These figures represent the updated FY 2013, 2014, 2015, and 2016 GDUFA performance data, as well as preliminary FY 2017 GDUFA performance data.

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 (ECDs) found in ANDAs and PASs, and to clarify issues and answer questions on deficiencies used in the first cycle CR letter. FDA's communications are further discussed in the ANDA and DMF Review Efficiency Enhancements section of this report. These commitments are intended to help reduce the number of ANDA review cycles.

The following table summarizes GDUFA workload for FY 2013 through FY 2017. The GDUFA application figures represent submissions that are subject to the review metrics. Submissions to FDA are tracked according to the fiscal year in which they are submitted. Since GDUFA afforded FDA a 2-year implementation period (i.e., FY 2013 and FY 2014) to hire and train new staff and establish the necessary infrastructure, there were no review-time goals for ANDAs, PASs, or amendments in FY 2013 or FY 2014. The performance of the GDUFA review time is measured against a goal for the first time in FY 2015; however, FDA did monitor the performance during the first 2 years to identify areas where improvements were needed.

GDUFA I was negotiated based on an assumption of 750 ANDA submissions per year. As is reflected below, receipts for ANDAs significantly exceeded that expectation. Also, it is important to note that the table below shows a significant increase in PAS and CC receipts.

GDUFA Workload	FY 2013*	FY 2014*	FY 2015*	FY 2016*	FY 2017
Original ANDAs					
Total Original ANDAs Submitted	1,055	1,583	502	833	1,310
ANDAs Submitted after RTR for Failure to Pay User Fees	44	36	19	12	12
ANDAs Submitted after RTR for Technical Reasons	75	99	94	186	152
ANDA Solicited Amendments					
Total Solicited ANDA Amendments Submitted	527	317	349	157	22
PASs					
Total PAS Submissions with Inspection Status Undetermined	323†	256†	412	454	412
PAS Solicited Amendments					
Total Solicited PAS Amendments Submitted	87	40	110	95	24
CC					
Total CC Submitted	953	1,087	1,197	1,804	2,637
Total CC Requiring Input from Clinical Division	36	26	322	80	29

* Numbers for prior fiscal years are updated annually.
† Inspection status for PASs submitted in FYs 2013 and 2014 was not established because there were no PAS review goals in those fiscal years.

Management Priorities and Accomplishments

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

Human Resources

FDA committed to hiring and training the staff necessary to achieve GDUFA program goals with incremental hiring goals established for FY 2013 and FY 2014. In FY 2015, FDA met the mandated human resources goal by hiring the final 25 percent of overall GDUFA program hires nearly 11 months ahead of schedule. FDA has continued to add resources to the GDUFA program with a total of 1,192 hires by the end of FY 2015.

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

Fiscal Year	New Full-Time Equivalent Count as of End of Fiscal Year	Incremental Hiring Goal	Percent of Incremental Staff Hired*	Cumulative Percent Hired	Goal Met
2013	291	25%	31%	25%	Yes
2014	591	50%	64%	96%	Yes
2015	310	25%	34%	129%	Yes
2016	There are no additional hiring goals for GDUFA				

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

Generic Industry Facility Self-Identification

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

The table below displays the number of facilities, sites, and organizations that submitted their self-identification information to FDA during the open periods for FYs 2013 through 2017. A detailed list of all GDUFA self-identified facilities, sites, and organizations is available on FDA's GDUFA website.[10] Across the 5-year initial reporting period, an average of 3,500 GDUFA facilities, sites, and organizations self-identified each fiscal year. On average, there were 290 domestic FDF and 423 foreign FDF versus 112 domestic API and 728 foreign API.

Fiscal Year	Number of Facilities, Sites, and Organization	Self-Identification Open Period per FY	Business Operations Reported for User Fees			
			Domestic FDF	Foreign FDF	Domestic API	Foreign API
2013	3,334	Oct 02, 2012 - Dec 03, 2012*	325	433	122	763
2014	3,604	May 01, 2013 - Jun 01, 2013	315	433	128	775
2015	3,335	May 01, 2014 - Jun 01, 2014	271	410	103	692
2016	3,641	May 01, 2015 - Jun 01, 2015	283	422	105	721
2017	3,605	May 01, 2016 - Jun 01 2016	255	420	101	688

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

GDUFA Guidance and Procedural Development

FDA committed to increasing transparency in operations and enhancing communication on critical information for ANDA applicants and manufacturers. While not required by the GDUFA Commitment Letter, in FY 2017 FDA published many guidances and MAPPs, including:

- Final Guidance for Industry: ANDA Submissions – Prior Approval Supplements Under GDUFA, October 2016[11]
- Final Guidance for Industry: Generic Drug User Fee Amendments of 2012: Questions and Answers Related to Use Fee Assessments, November 2016[12]
- Final Guidance for Industry: ANDA Submissions Refuse-to-Receive Standards Rev 2, December 2016[13]
- Draft Guidance for Industry: 180-Day Exclusivity: Questions and Answers, January 2017[14]
- Draft Guidance for Industry: Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA, January 2017[15]

[10] www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm
[11] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404441.pdf
[12] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM316671.pdf
[13] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf
[14] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536725.pdf
[15] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

- Draft Guidance for Industry: Referencing Approved Drug Products in ANDA Submissions, January 2017[16]
- Final Guidance for Industry: Generic Drug User Fee Amendments of 2012: Questions and Answers Related to Self-Identification of Facilities, Review of Generic Drug Submissions, and Inspections and Compliance, July 2017[17]
- MAPP 5210.5 Rev 2: Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs, October 2016[18]
- MAPP 5240.3 Rev.3, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, June 2017[19]
- MAPP 5210.4 Rev. 2, Review of Bioequivalence Studies with Clinical Endpoints in ANDAs, June 2017[20]
- MAPP 5200.14, Filing Review of Abbreviated New Drug Applications, September 2017[21]
- MAPP 5220.3, Communicating Certain Deficiencies Identified During Filing Review of ANDAs, September 2017[22]
- FDA posted 108 new draft guidances and 86 revised draft guidances with product-specific recommendations in FY 2017. These draft guidances describe the Agency's current thinking and draft recommendations on how to develop generic drug products therapeutically equivalent to specific reference-listed drugs.

	Total # of Guidances	New Draft Guidance	Revised Draft Guidance
Oct 2016 Batch Posting	67	34	33
Dec 2016 batch posting	48	31	17
May 2017 batch posting	37	21	16
July 2017 batch posting	34	21	13
Stand-alone postings	8	1	7
Total	**194**	**108**	**86**

[16] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536962.pdf
[17] www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM530476.pdf
[18] www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM079593.pdf
[19] www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf
[20] www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm079585.pdf
[21] www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM574493.pdf
[22] www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM578093.pdf

Technology Enhancements

In FY 2017, FDA made significant technology improvements aimed at promoting the efficiency of the human generic drug review process, effectively tracking the global drug supply chain, improving the timeliness and effectiveness of facility surveillance and inspections, and managing user fee collections. FDA continues to devote resources to IT improvements that integrate human generic drug information across a next-generation enterprise-wide informatics system. FY 2017 IT accomplishments are described below.

FDA has continued to modernize the CDER Informatics Platform (Platform) for review of generic drug applications while consolidating legacy systems and increasing operational efficiency. The Platform has enabled FDA to take significant steps in furthering integration of drug review processes, managing the global inventory of manufacturing facilities and testing sites, enabling a more efficient inspection process, and supporting a more transparent team-based approach to the overall assessment of drug applications. In addition, it continues to support FDA's ability to track GDUFA review performance goals and commitments to the public by managing the review process in an integrated enterprise system designed to enhance collaboration and visibility across the application lifecycle. This year's technological accomplishments include:

- On October 15, 2016, FDA implemented enhancements to its master data management by establishing a best-practice party model designed to more fully leverage Dun & Bradstreet as well as Office of Regulatory Affairs (ORA) databases to validate and enrich facility information obtained from both pre-market submissions and registration and listing. This has significantly improved FDA's capacity to track the inventory of pharmaceutical manufacturing facilities and testing sites to support pre-application approval and surveillance inspections.
- On November 22, 2016, FDA implemented the DMF review in the Platform. The integration with other elements of the generic drug application review in a single system has resulted in a streamlined DMF review process and increased visibility across multiple ANDAs referencing the same DMF. This has improved the timeliness and efficiency of DMF reviews.
- On July 1, 2017, in accordance with commitments anticipated under GDUFA II legislation, FDA Implemented review of Pre-submission Facility Correspondence (PFC) in the Platform. This involved establishing a system-managed process for receiving manufacturing facility and bioequivalence testing site information, as well as bioequivalence site information, from applicants in an expedited manner for high priority applications. This capability allows priority ANDAs with public health priorities to receive a 20 percent shorter goal date than standard ANDA applications.
- Additionally, on September 6, 2017, in accordance with commitments anticipated under GDUFA II legislation, FDA enhanced the following systems to continue to support and track GDUFA review performance goals and commitments:
    - Regulatory Management System – Biologics Licensing Application (RMS-BLA) was enhanced to accommodate the revised user fee requirement and review schedules associated with original ANDAs, PASs, and related amendments.
    - Biologics Information Tracking System – Pre-Application Tracking System (BITS-PTS) was enhanced to accommodate various presubmission meeting and correspondence requirements.

Backlog Summary

FDA committed to reviewing and acting on 90 percent of the backlog of 2,866 original applications and 1,876[23] PAS submissions that were pending as of October 1, 2012, by the GDUFA-defined goal of September 30, 2017. FDA met the backlog goal in June 2016, 15 months ahead of schedule. As of October 2017, FDA had issued a first action on approximately 98 percent of the GDUFA backlog applications since program launch. The table below shows FDA's progress toward meeting the backlog goal.

Cumulative Percent of Backlog Issued First Action

Submission Type	Backlog as of October 1, 2012	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
ANDA	2,866	31%	60%	80%	94%	98%
PAS	1,876	40%	73%	86%	93%	98%
Total	4,742	34%	65%	82%	93%	98%

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 required FDA to report the following three metrics starting in FY 2013:

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

The first metric requires FDA to report the average total time to full approval action for ANDAs and PASs[24] 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 revised annually to incorporate updated results based on ANDAs and PASs approved in the previous fiscal year. The data are presented in the following two tables. (Note that the time-to-approval is dropping for the newer applications.)

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

[24] 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: Original ANDAs

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
First Cycle Approvals*					
Average Total Time to Approval	1,089	912	467	450	301
Multi-Cycle Approvals					
Average Total Time to Approval	1,213	1,020	690	569	--†
Average Calendar Days Spent During Review by FDA	993	881	572	536	--†
Average Calendar Days Spent by Applicant Responding to CR	220	139	118	33	--†
Total Combined (First Cycle and Multi-Cycle)					
Combined Average Total Time to Approval	1,189	968	624	492	301

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

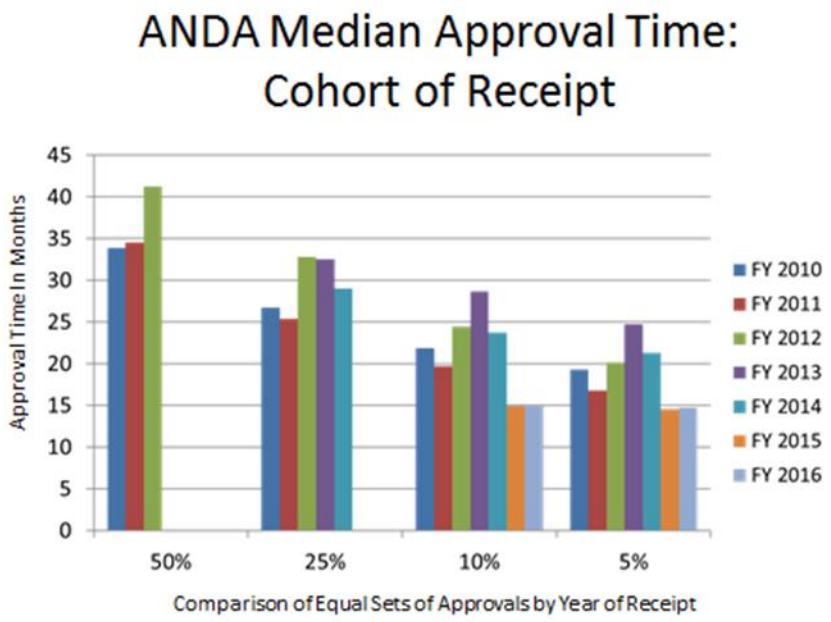
† There are no multi-cycle approvals to report yet for FY 2017.

Average Calendar Days to Full Approval Action: PASs

	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
First Cycle Approvals*					
Average Total Time to Approval	347	296	111	112	107
Multi-Cycle Approvals					
Average Total Time to Approval	721	533	445	369	276
Average Calendar Days Spent During Review by FDA	571	375	280	237	225
Average Calendar Days Spent by Applicant Responding to CR	150	157	165	131	51
Total Combined (First Cycle and Multi-Cycle)					
Combined Average Total Time to Approval	439	328	174	147	110

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

The following chart shows that applications submitted in FYs 2015 and 2016 are being approved faster than at the beginning of GDUFA. For example, the first 10 percent of applications approved out of the entire cohort of applications received in FYs 2015 and 2016 were approved faster than the first 10 percent for cohorts in the other fiscal years.



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

Number of Pending Applications with Final Regulatory Action*

Submission Type	Applications Pending for Longer Than 10 Months as of September 30, 2012	Final Regulatory Actions Taken					Number Remaining
		FY 2013	FY 2014	FY 2015	FY 2016	FY 2017	
ANDA	1,854	383 (21%)	371 (41%)	315 (58%)	239 (71%)	130 (78%)	416 (22%)
PAS	942	301 (32%)	284 (62%)	159 (79%)	87 (88%)	54 (94%)	57 (6%)
Total	**2,796**	**684 (24%)**	**655 (48%)**	**474 (65%)**	**326 (77%)**	**184 (83%)**	**473 (17%)**

* Data in this table have been adjusted as a result of ongoing data validation. The percentages in parenthesis are cumulative—for example, the 41 percent in the ANDA row under FY 2014 means that FDA took a final regulatory action on 41 percent of the 1,854 ANDAs as of the end of FY 2014. The 41 percent result was derived from dividing the total number of ANDAs (1,854) by the sum of ANDAs with a final regulatory action as of the date specified in the table column. For FY 2014, this number is 754 (383 in FY 2013 plus 371 in FY 2014).

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.[25] This regulatory disparity, combined with limited resources and the associated cost of inspecting foreign facilities, produced an increasing gap in the level of oversight that is needed to ensure the safety of the human generic drug supply. The Agency is addressing this regulatory disparity in part through a risk-adjusted inspection schedule further discussed in this section.

GDUFA Inspection Strategy

To implement its commitments in connection with GDUFA, FDA leverages 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 where appropriate.

- Make inspection classification results available to the public and industry. These can be found on the FDA website at www.accessdata.fda.gov/scripts/inspsearch/.

Risk-Adjusted Biennial Current Good Manufacturing Practices (CGMP) Surveillance Inspection

To ensure that foreign and domestic firms are held to consistent high-quality standards, FDA agreed to conduct risk-adjusted CGMP surveillance inspections of human generic API and FDF manufacturers, with the goal of achieving risk-adjusted parity of inspection frequency between foreign and domestic establishments by FY 2017. Section 705 of FDASIA amended section

[25] 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/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/FDASIA/ucm310992.htm

510(h) of the FD&C Act to require a risk-based schedule for inspections of establishments, whether they are located domestically or internationally.[26]
To accomplish this goal, FDA is employing a site selection surveillance inspection model that runs annually on all facilities in FDA's inventory. The model does not distinguish—for purposes of risk ranking—if the site is foreign or domestic-based. Risk is assessed consistent with the requirements of FDASIA section 705.

Risk-adjusted parity between domestic and foreign drug inspection frequency is achieved by inspecting the highest-ranking facilities as determined by the site selection model each year.

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 the pharmaceutical program are expected to conduct both domestic and foreign generic drug inspections.[28]
- Prioritizing in the risk-based approach foreign establishments that have never been inspected. This will allow FDA to conduct more CGMP inspections of these establishments in future years that are classified as "abbreviated" pursuant to FDA Compliance Program 7356.002.[29]

FDA has also taken discrete steps to conduct more stand-alone pre-approval inspections. These are pre-approval inspections not linked to surveillance inspections. In 2015, FDA modified its pre-approval inspection compliance program guidance manual to foster more stand-alone pre-approval inspections. Specifically, FDA changed inspection triggers to remove "time since last surveillance inspection" as a factor. This ensured that pre-approval inspection decisions and requests were based solely on the assessment of a facility's capability to manufacture the product of the application under consideration. The change was enabled due to parallel enhancements in the surveillance inspection program.

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[26] Section 705 of FDASIA amends section 510(h) of the FD&C Act to require FDA to establish a risk-based schedule for drug inspections. Section 510(h)(4) specifies that the risk-based schedule is based on the following factors: "(A) The compliance history of the establishment; (B) The records, history, and nature of recalls linked to the establishment; (C) The inherent risk of the drug manufactured, prepared, propagated, compounded, or processed at the establishment; (D) The inspection frequency and history of the establishment, including whether the establishment has been inspected pursuant to section 704 within the last 4 years; (E) Whether the establishment has been inspected by a foreign government or an agency of a foreign government recognized under section 809; (F) Any other criteria deemed necessary and appropriate by the Secretary for purposes of allocating inspection resources."
[27] GDUFA Commitment Letter, 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, investigators hired separately from the GDUFA initiative also will be conducting generic facility inspections.
[29] See FDA Compliance Program Guidance Manual - 7356.002, Drug Manufacturing Inspections, p. 8, for a description of "Abbreviated" drug CGMP surveillance inspections www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/UCM125404.pdf

The following table shows numbers of inspections of generic drug establishments conducted by fiscal year. Overall, the number of domestic inspections has remained essentially stable, while the number of foreign inspections has generally increased. In all years, there have been somewhat more foreign inspections.

Location/Firm Type	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Domestic Inspections*					
Generics Only†	198	213	187	201	268
Generic & Non-Generic	156	137	139	136	120
Total	**354**	**350**	**326**	**337**	**388**
Foreign Inspections*					
Generics Only†	291	379	440	377	446
Generic & Non-Generic	76	114	113	104	101
Total	**367**	**493**	**553**	**481**	**547**
Total Domestic and Foreign					
Generics Only†	489	592	627	578	714
Generic & Non-Generic	232	251	252	240	221
Total	**721**	**843**	**879**	**818**	**935**

*An inspection was characterized as "Generic" and GMP if the firm inspected registered with the CDER User Fee Facility Data Management (UFFDM) Self-Identification system in the appropriate fiscal year and the appropriate Program Assignment Code (PAC) (e.g., 56002) was reported in the Field Accomplishments and Compliance Tracking System (FACTS).
†A firm was characterized as "Generics Only" if it was not identified in the CDER Self-Identification system as "Manufactures Non-Generics."

Inspection Efficiency Enhancements

In an effort to transform product quality oversight from a qualitative to a quantitative and expertise-based assessment, FDA employed the following strategies:

1. Integrated Quality Assessment (IQA) - The team-based IQA provides aligned, patient-focused, and risk-based drug product quality recommendations. The unifying hallmark of IQA is the integration of review and inspection in the application assessment process. ORA investigators are fully apprised of any issue uncovered by CDER reviewers, and vice versa. IQA was initiated in 2013 and fully implemented in 2015.

2. Integration of the FDA Facility Evaluation and Inspection Program - FDA designed a new concept of operations for the integration of FDA facility evaluation and inspection that was formally signed in 2017. CDER and ORA outlined the responsibilities and the workflow for inspections at domestic and international facilities. This new operating model enables FDA to better handle the growing complexity of the pharmaceutical landscape and to meet new challenges by:

    a) Ensuring consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision-making for marketing applications across FDA;

b) Advancing strategic alignment across CDER and ORA functional units by creating clear roles and responsibilities;
c) Improving FDA's operational capacity by enhancing collaboration between various CDER and ORA offices;
d) Enhancing the quality and increasing access to facility and regulatory decisional information across FDA; and
e) Meeting user fee commitments and improving the timelines for regulatory, advisory, and enforcement actions to protect public health and promote drug quality, safety, and effectiveness.

Mutual Recognition Agreement (MRA) between FDA and the European Union (EU)

In FDASIA, Congress gave FDA the authority to enter into arrangements or agreements with a foreign government or an agency of a foreign government to recognize foreign inspections, after making a determination that the foreign government has the capability to conduct inspections in accordance with the FD&C Act. A capability determination is based upon "reviews and audits of drug safety programs, systems, and standards" of the foreign government and the results of the inspections may be used as "evidence of compliance with section 501(a)(2)(B) or section 801(r)" or for any other purposes as deemed appropriate.

In May 2014, the United States and the European Commission (EC) began negotiating to amend the 1998 Agreement on Mutual Recognition between the EU and the United States (U.S.-EU MRA), which included a Pharmaceutical Annex providing for recognition of each other's GMP inspections.

In March 2017, the U.S. and the EU successfully amended the Sectoral Annex to the 1998 U.S.-EU MRA. Under the amended annex, FDA and the EU will recognize pharmaceutical inspections conducted within each other's borders. Because each country in the EU has its own inspectorate, FDA must conduct a capability assessment of each EU country. Once a country is found capable, FDA will recognize that country's inspections.

In June 2017, the EU determined that FDA has the "capability, capacity, and procedures in place to carry out GMP inspections at the level equivalent to the EU."

ANDA and DMF Review Efficiency Enhancements

FDA committed to enhancing the premarket review of human generic drugs through various initiatives. This section provides the status of these initiatives. The following chart shows substantial increases in the number of CR letters issued for ANDAs and DMFs.

Management Initiative	Performance Area	FY 2013	FY 2014	FY 2015*	FY 2016	FY 2017
CR Letters						
CR letters issued reflect full division-level reviews of deficiencies from relevant disciplines, including inspections and consults.	ANDA GDUFA CR letters issued	481†	589‡	816§	1,356**	1,336***
	PAS GDUFA CR letters issued	315†	170‡	157§	186**	188***
	DMF GDUFA CR letters issued	275	530	763	856	744
Inspections						
Inspection classification results, along with relevant information, are made public.	Inspections	Inspection classification results, along with relevant information, were made public and are available at: www.accessdata.fda.gov/scripts/inspsearch/				

* Data in this table have been adjusted as a result of ongoing data validation.
† CR totals include the backlog and the FY 2013 cohort. The FY 2013 report included backlog submissions only.
‡ CR totals include FY 2014 CRs from the backlog and the FYs 2013 and 2014 cohorts.
§ CR totals include FY 2015 CRs from the backlog and the FY 2013, 2014, and 2015 cohorts.
** CR totals include FY 2016 CRs from the backlog and the FY 2013, 2014, 2015, and 2016 cohorts.
*** CR totals include FY 2017 CRs from the backlog and the FY 2013, 2014, 2015, 2016, and 2017 cohorts

Management Initiative	Performance Area	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
RTR Standards						
FDA to develop enhanced RTR standards for ANDAs and other related submissions	RTR Standards	Draft guidance was published on October 1, 2012	Final guidance was published on September 16, 2014, and is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf. Draft Guidance on Refuse to Receive for Lack of Proper Justification of Impurity Limits was published on September 16, 2014, and is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM414598	Revised Final Guidance on Refuse-to-Receive Standards was published on May 26, 2015, and is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf.	Final Guidance on Refuse to Receive for Lack of Justification of Impurity Limits was published on August 24, 2016, and is available at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM414598.pdf	Final Guidance for Industry: ANDA Submissions Refuse-to-Receive Standards Rev 2 was published in December 2016 and is available at: www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm370352.pdf

Management Initiative	Performance Area	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Expedited Review of Paragraph IV Applications						
Expedite review of Paragraph IV applications that are submitted on the first day that any valid Paragraph IV application for the drug in question is submitted.	Expedited review of Paragraph IV applications	Expedited review was implemented consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, and also included those applications that became eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted.	Continued expedited review implemented in FY 2013 consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3 Rev 1, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, and also included those applications that became eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted.	Continued expedited review implemented in FY 2013 consistent with existing procedure for expediting applications as set forth in CDER's MAPP 5240.3 Rev 1, Prioritization of the Review of Original ANDAs, Amendments, and Supplements, and also included those applications that became eligible for approval during the review period as a result of no blocking exclusivities, patent(s) and/or applicable stays based on appropriate documentation submitted.	Updated CDER's MAPP 5240.3 Rev 2,[30] Prioritization of the Review of Original ANDAs, Amendments, and Supplements, to include sole-source products category for expediting applications.	Updated CDER's MAPP 5240.3 Rev 3,[31] Prioritization of the Review of Original ANDAs, Amendments, and Supplements, to include generic products for which there are fewer than three ANDAs approved for the reference listed drug (RLD) and for which there are no blocking patents or exclusivities on the RLD.

[30] MAPP updated March 11, 2016: www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf.
[31] MAPP updated June 27, 2017: www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf.

Management Initiative	Performance Area	FY 2013	FY 2014	FY 2015	FY 2016	FY 2017
Type II API DMFs Available for Reference						
FDA will deem the DMF available for reference, placing the DMF number in a publicly available list of Type II API DMFs available for reference.	Type II API DMFs available for reference list	Published Type II DMF - Available for Reference List: www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM332875.xls				
FDA will conduct a completeness assessment of Type II API DMFs.	Type II API DMF CA	Final Guidance on Completeness Assessments for Type II API DMFs Under GDUFA published February 12, 2016, and is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM321884.pdf				

Management Initiative	Performance Area	FY 2013††	FY 2014††	FY 2015††	FY 2016††	FY 2017
Type II API DMFs Available for Reference						
DMF workload	DMFs found complete	1,171	1,170	637	629	593
	Total CA review cycles performed (includes multiple cycles on the same DMF):	1,700	1,779	901	890	802
	DMF GDUFA incomplete letters issued	526	602	268	262	184
	DMF CR letters	275	530	763	857	744
	DMF no further comments letters	491	443	502	1,045	1,078
ANDA Teleconferences Workload						
When requested by the ANDA applicant within 10 business days of FDA issuing a first cycle CR letter, FDA will schedule a teleconference to clarify issues and answer questions.[32]	Teleconferences requested	23	64	52	36	33
	Teleconferences closed out	21	56	47	33	27
	Teleconferences denied	2	8	5	3	6
DMF Teleconferences Workload						
When requested by a DMF holder within 10 business days of FDA issuing a first cycle DMF deficiency letter, FDA will schedule a teleconference to clarify issues and answer questions. Priority for such teleconferences will be given to DMFs referenced in expedited and first major deficiency applications.	Teleconferences requested	10	9	5	5	17
	Teleconferences closed out	10	9	5	4	14
	Teleconferences denied	0	0	0	1	3

†† These figures represent the final FY 2013, 2014, 2015, and 2016 GDUFA teleconference data; prior years' numbers are updated annually.

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

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Research Performance

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

One example of FDA's commitment to this program has been through development of product-specific guidances and recommendations for regulatory submissions (e.g., ANDAs, pre-ANDA meeting requests, CCs). FDA developed and published 194 new and revised product-specific guidances in FY 2017. The table below shows the product-specific guidance breakdown for complex and non-complex drug products.

	Complex Drug Products	Non-complex Drug Products
Number of new product-specific guidances	48	60
Number of revised product-specific guidances	42	44
Total	**90**	**104**

These product-specific guidances have provided industry with draft recommendations on the design of bioequivalence studies and scientific advice pertaining to complex dosage forms, drug substances, and drug products that can be used in the development of generic drugs.

Since FY 2013, FDA has awarded 36 research contracts and 69 grants. A complete list of FY 2013 through FY 2017 awarded studies can be found at www.fda.gov/GDUFARegScience, and the number of new and ongoing projects by fiscal year is provided in the table below.

Fiscal Year	Number of External Research Projects Awarded Using GDUFA Funds	
	New Projects	Ongoing Projects
2017	7	39
2016	16	38
2015	22	41
2014	35	16
2013	29	--

Significant FY 2017 Research Accomplishments

In addition to serving as the scientific basis to the development of product-specific guidances and specific pre-ANDA communications, research outcomes are published in the scientific literature and contribute to general guidance development. Highlighted below are 3 recent publications (out of 23 GDUFA-supported publications in FY 2017):

- Two papers were published on the investigation of physicochemical properties[33] and in vitro release testing methods[34] for ophthalmic ointment formulations which had the same composition but were made by different manufacturing processes. The study results demonstrated that differences in the manufacturing process and source of petrolatum had a significant influence on the physicochemical attributes and the in vitro drug release profiles. These findings indicate that differences in manufacturing and excipient sources may impact in vitro performance and potentially influence in vivo performance of ophthalmic ointments. These results support the use of in vitro methods of ophthalmic product bioequivalence.

- Another publication focused on using semi-mechanistic simulation approaches to predict the systemic pharmacokinetics of inhaled corticosteroids delivered via DPIs.[35] In one of the approaches used, good predictions were made from using the pulmonary absorption rate estimated from in vitro studies, without need for data obtained from clinical studies in humans. Such simulation approaches can be helpful during drug product development and provide a better understanding of product performance and mechanisms of drug deposition in the lung and support more efficient approaches to demonstrate bioequivalence of inhalation drug products.

FY 2018 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.

On June 5, 2015, FDA held the FY 2015 Regulatory Science Initiatives Part 15 public hearing, which provided an overview of the status of the human generic drug regulatory science program and an opportunity for public input in developing FY 2016 research priorities. Information obtained during the public hearing and other input (e.g., comments to the public docket) were considered in developing the FY 2016 Regulatory Science Plan.[36,37]

On May 20, 2016, FDA held the FY 2016 Regulatory Science Initiatives Part 15 public hearing, which provided an overview of the status of the human generic drug regulatory science program and an opportunity for public input in developing FY 2017 research priorities. Information obtained during the public hearing and other input (e.g., comments to the public docket) were considered in developing the FY 2017 Regulatory Science Plan.[38]

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[33] Bao Q, Jog R, Shen J, Newman B, Wang Y, Choi S, Burgess DJ. Physicochemical attributes and dissolution testing of ophthalmic ointments. Int J Pharm. 2017 May 15;523(1):310-319.
[34] Bao Q, Shen J, Jog R, Zhang C, Newman B, Wang Y, Choi S, Burgess DJ.
In vitro release testing method development for ophthalmic ointments. Int J Pharm. 2017 Jun 30;526(1-2):145-156.
[35] Bhagwat S, Schilling U, Chen MJ, Wei X, Delvadia R, Absar M, Saluja B, Hochhaus G.
Predicting Pulmonary Pharmacokinetics from In Vitro Properties of Dry Powder Inhalers. Pharm Res. 2017 Aug 10. doi: 10.1007/s11095-017-2235-y.
[36] Similar activities were held to determine research priorities for FY 2014 and FY 2015.
[37] The list of the FY 2016 research initiatives can be found at:
www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM469453.pdf.
[38] The list of the FY 2017 research initiatives can be found at:
www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM526900.pdf.

On May 3, 2017, FDA held the FY 2017 Generic Drug Research Public Workshop, which provided an overview of the status of the human generic drug regulatory science program and an opportunity for public input in developing FY 2018 research priorities. Information obtained during the public workshop and other input (e.g., comments to the public docket) were considered in developing the FY 2018 Regulatory Science Plan.[39]

The FY 2018 human generic drug regulatory science priorities identified were grouped into the following four topic areas:

- Topic 1: Complex active ingredients, formulations, or dosage forms
- Topic 2: Complex routes of delivery
- Topic 3: Complex drug-device combinations
- Topic 4: Tools and methodologies for bioequivalence and substitutability evaluation

A description of these topic areas and priorities is provided in Appendix B.

[39] The list of the FY 2018 research initiatives can be found at: www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM582777.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).[40]

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

D. ANDA (Abbreviated New Drug Application) is an application submitted under section 505(j) of the FD&C Act. It contains data which when submitted to FDA's CBER or 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 PASs that were pending as of October 1, 2012.

[40] See the 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 the deficiencies that the agency has identified in an abbreviated application (including pending amendments) or a DMF that must be satisfactorily addressed before the ANDA can be approved. CR letters will reflect a complete review and will require a complete response from industry to restart the clock. Refer to 21 CFR 314.110 and www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084138.htm for additional details.

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

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

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

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

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

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

O. Expedited review of application: means that a submission will receive heightened review priority per MAPP 5240.3 Rev.1 – "Prioritization of the Review of Original ANDAs, Amendments, and Supplements."[41]

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

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

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

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

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

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

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

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

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

X. Prior Approval Supplement (PAS) means a request to the Secretary to approve a change in the drug substance, drug product, production process, quality controls, equipment, or facilities covered by an approved abbreviated new drug application when that change has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the drug product as these factors may relate to the safety or effectiveness of the drug product.[42]

Y. Refuse to Receive (RTR) means refusal to receive an ANDA for review. See 21 CFR 314.101 and the December 2016 final guidance for industry entitled "ANDA Submissions - Refuse-to-Receive Standards": www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm370352.pdf.

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

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

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

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

DD. Tentative Approval Letter - If a generic drug product is ready for approval but cannot be approved due to a patent or exclusivity related to the reference listed drug product, FDA issues a tentative approval letter to the applicant, and the tentative approval letter details the basis for the tentative approval. FDA will not issue final approval of the generic drug product until all patent or exclusivity issues have been resolved or, in some cases, until a 30-month stay associated with patent litigation has expired. A tentative approval does not allow the applicant to market the generic drug product.

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

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

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

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. 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 non-delaying. 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 2018 Generic Drug Regulatory Science Priorities Topic Areas

Under GDUFA, FDA committed to develop an annual list of regulatory science priorities for generic drugs. FDA organized its FY 2018 priorities into the following topic areas:

Complex active ingredients, formulations, or dosage forms

- Improve advanced analytics for characterization of chemical compositions, molecular structures, and distributions in complex active ingredients
- Improve particle size, shape, and surface characterization to support demonstration of therapeutic equivalence of suspended and colloidal drug products
- Establish predictive in silico, in vitro, and animal studies to evaluate immunogenicity risk of formulation or impurity differences in generic products
- Develop predictive in vitro bioequivalence (BE) methods for long-acting injectables
- Develop better methods for evaluating abuse deterrence of generic solid oral opioid products, including in vitro alternatives to in vivo nasal studies

Complex routes of delivery

- Improve physiologically based pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery (e.g., nasal, inhalation, dermal, ophthalmic)
- Expand characterization-based BE methods across all topical dermatological products
- Expand characterization-based BE methods across all ophthalmic products
- Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids
- Develop alternatives to clinical endpoint BE studies for locally-acting nasal products

Complex drug-device combinations

- Evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products

Tools and methodologies for BE and substitutability evaluation

- Improve quantitative pharmacology and bioequivalence trial simulation to optimize design of BE studies for complex generic drug products
- Integrate predictive dissolution, PBPK, and PK/Pharmacodynamic (PD) models for decision making about generic drug bioequivalence standards
- Expand the scientific understanding of the role of excipients in generic drug products to support the expansion of the Biopharmaceutics Classification System of Class 3 bio-waivers to non-Q2 (quantitatively inequivalent) formulations
- Develop methods that will allow FDA to leverage large data sets (such as BE study submissions, electronic health records, substitution and utilization patterns, and drug

safety and quality data) for decisions related to generic drug approval and post-market surveillance of generic drug substitution

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Food and Drug Administration

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