

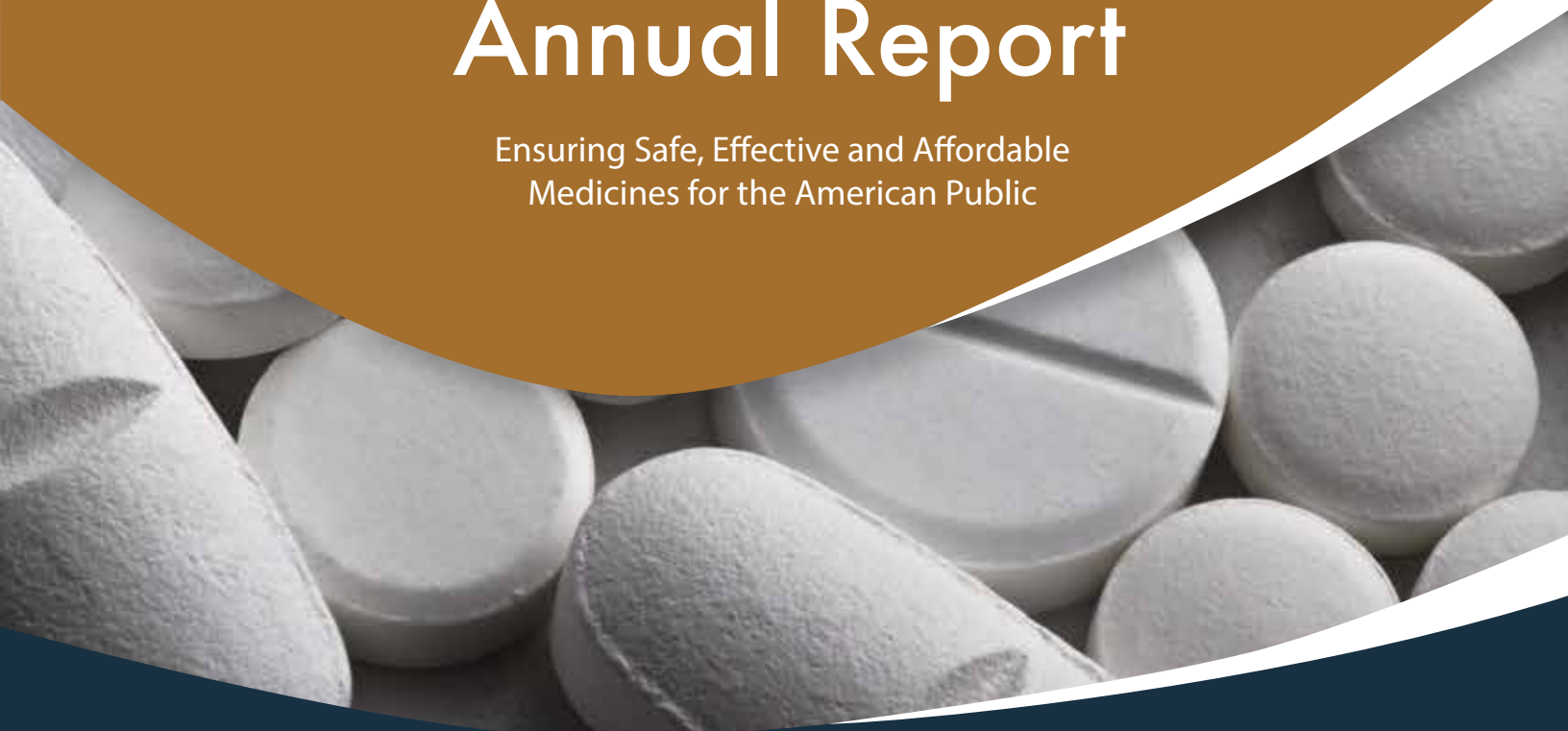
OFFICE OF GENERIC DRUGS

•2015•

OGD

Annual Report

Ensuring Safe, Effective and Affordable
Medicines for the American Public



U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs

2015 marked the highest number of generic drug approvals and tentative approvals ever—more than 700.



DIRECTOR'S MESSAGE

At FDA's Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research, 2015 was an exciting year. It marked our first full year of operation after expanding into a "Super Office" at FDA, which translates to more staffing to handle a growing workload—and greater ability to advance the quality and availability of cost saving generic drugs in the U.S.

Our reorganization and increased review capacity came at a critical time. Since 2012, a new law called the Generic Drug User Fee Amendments (GDUFA), which authorizes funding for FDA for the review and approval of generic drugs, has been challenging FDA to reach a variety of goals.

We're on track for meeting all of the goals under GDUFA and going above and beyond our obligations outlined in the GDUFA Commitment Letter. We are streamlining OGD's review processes to expedite thorough review of pending applications for generic drug products, thereby cutting the average time required to review generic drug applications. We are building a modern, 21st century generic drug program.



Kathleen Uhl, M.D.

Director, Office of Generic Drugs

GDUFA requires FDA, specifically OGD and the other offices involved in generic drug review activities, to conduct reviews of generic applications in a timely way. GDUFA metrics ramp up over time and ultimately result in a 10-month GDUFA goal for all original ANDAs. There are a variety of additional metrics related to other work done by OGD such as controls, amendments and supplements to ANDAs.

Among other accomplishments, 2015 marked the highest number of generic drug approvals and tentative approvals ever—more than 700. OGD spent 2015 continuing to increase communications with industry, putting out a record amount of formal correspondence to industry on application-specific issues, closing out controlled correspondence and providing target action dates (TADs).

Despite our progress, we have a lot more work to do, but we want to do this collaboratively. Achieving ambitious goals that work for the public health requires broad input from the public, including industry, the research community, lawmakers and other stakeholders. We encourage you to read our annual report and to participate in our stakeholder and public meetings. We welcome all to attend—but those who cannot join us in person can still contribute by sending thoughts and ideas to our public docket (FDA-2013-N-0402). With our ongoing efforts—and strong public input—we are confident that 2016 and beyond will be as successful as 2015.

We are confident in OGD's ability to meet our GDUFA goals. There is incredible momentum. We are proud of our accomplishments so far, and we in OGD and the other offices involved in generic drug review activities are enthusiastic about GDUFA Year 4. Generic drugs make up nearly 88 percent of prescriptions filled in the United States and represent affordable access to treatment for many patients and consumers. These individuals depend on FDA to ensure that generic drugs perform clinically in the same way as their brand name counterpart drugs. The success of OGD and the GDUFA program underscores our commitment to hold the generic drug industry to standards of high quality, and to maintain the public's confidence that generic drugs are safe, effective, affordable alternatives.



The Office of Generic Drugs is located in Building 75 on the FDA White Oak Campus in Silver Spring, Maryland.

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FDA'S GENERIC DRUG PROGRAM

Over the last several decades, the generic industry, the number of [abbreviated new drug applications](#), or “ANDAs,” submitted to FDA for review and the number of foreign facilities making generic drugs all grew substantially. Generic drugs now account for 88% of prescriptions dispensed in the United States¹, and saved the U.S. health system \$1.68 trillion from 2005 to 2014². As a result, FDA's generic drug program became increasingly under-resourced.

Due to the significant expansion of the generic drug industry and corresponding increase in ANDA submissions, FDA adapted its systems and processes to continue to meet its scientific, GDUFA and other program goals. As the interface for ANDA applicants to interact with the agency, OGD benefits from and relies on the efforts of many FDA offices, including:

- **Center for Biologics Evaluation and Research**
- **Center for Drug Evaluation and Research**
 - Office of Communications
 - Office of Compliance
 - Office of Management
 - Office of Medical Policy
 - Office of New Drugs
 - Office of Pharmaceutical Quality
 - Office of Strategic Programs
 - Office of Surveillance and Epidemiology
 - Office of Translational Sciences
- **Center for Devices and Radiological Health**
- **Office of Chief Counsel**
- **Office of the Commissioner**
- **Office of Regulatory Affairs**

1. IMS Institute for Healthcare Informatics

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

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THE OFFICE OF GENERIC DRUGS (OGD)

The [Office of Generic Drugs \(OGD\)](#) reports directly to the Director of the Center for Drug Evaluation and Research (CDER) and comprises an Immediate Office and four subordinate offices. OGD hired approximately 125 new employees in 2015 to achieve GDUFA mandates to hire additional staff to support the growing generic drug program. Additional GDUFA hires were distributed across the many CDER and FDA offices involved in the generic drug program.

Immediate Office (IO)

The IO provides oversight, leadership, strategic direction and support for OGD and its four sub-offices. Divisional staffs within the IO include:

Clinical Safety Surveillance Staff (CSSS)

Obtains and coordinates information regarding the safety and surveillance of generic drug products. Serves as OGD liaison to CDER's Office of Surveillance and Epidemiology (OSE) and other drug surveillance organizations within CDER.

Communications Staff (CS)

Oversees and coordinates all communications that originate from OGD. Serves as liaison to CDER's Office of Communications and FDA's Office of Media Affairs.

Generic Regulatory Affairs Team (GReAT)

Provides oversight, outreach, strategic liaison and integration of cross-OGD and cross-Center regulatory programs and initiatives.

Global International Affairs Team

Enhances OGD's ability to address complex global issues strategically and proactively as the world leader in the science and regulation of generic medicines. Coordinates and supports OGD's global engagement activities in collaboration with internal and external stakeholders.

Program Management and Analysis Staff (PMAS)

Provides leadership, guidance and support services to OGD on all aspects of budget, contracts, facilities management, human resources, personnel operations services, scientific fellowships and recruitment activities.

Office of Bioequivalence (OB)

OB consists of an Immediate Office, three Divisions of Bioequivalence and a Division of Clinical Review. This office reviews all bioequivalence studies submitted with applications, evaluates formulations for qualitative and quantitative (Q1/Q2) sameness and collaborates with other Offices to consider newer methods for demonstration of equivalence in complex dosage forms and for products that have been identified as having potential safety or therapeutic issues. OB evaluates bioequivalence (BE) studies with clinical endpoints and protocols to support generic application review, identifies potential clinical safety, product use or BE issues and provides guidance for resolution.

Office of Research and Standards (ORS)

ORS consists of an Immediate Office, a Division of Therapeutic Performance and a Division of Quantitative Methods and Modeling. ORS leads in the development of scientific standards for generic drugs, establishes predictive and physiological models of drug product performance, drug absorption, drug pharmacology and other quantitative methods for ensuring generic drug equivalence and develops new tools for analyzing in vitro pharmacokinetic, pharmacodynamic and clinical BE studies. ORS implements the GDUFA regulatory science program, a program which supports scientific research to develop pathways for generic versions of complex reference products that lack competition and also evaluates post-approval safety, product use and BE issues with approved generic drugs.

Office of Regulatory Operations (ORO)

ORO consists of an Immediate Office, the Division of Filing Review, Division of Labeling Review, Division of Project Management, and Division of Quality Management Systems. ORO provides oversight across all review disciplines to ensure that all generic drug review and decision-making activities are well-documented and follow a clearly defined, rigorous, scientific, and regulatory review process. ORO ensures that incoming [abbreviated new drug applications \(ANDAs\)](#), relevant PASs and amendments meet established standards for filing and labeling. Regulatory Project Managers within ORO oversee the review of ANDAs across all disciplines by planning, organizing, prioritizing and assigning ANDA review work and ensuring OGD meets GDUFA goal dates.

ORO monitors, analyzes and improves OGD's business processes and systems. ORO staff respond to controlled correspondences, review suitability petitions and ANDAs, and maintain internal and external FDA Paragraph IV (PIV) patent certification databases. Overall, ORO responds to more than 50,000 submissions a year.

Office of Generic Drug Policy (OGDP)

OGDP consists of an Immediate Office, the Division of Legal and Regulatory Support and the Division of Policy Development. OGDP represents OGD on policy issues, provides direction in the development and implementation of statements of policy related to generic drugs and maintains the ["Approved Drug Products with Therapeutic Equivalence Evaluations"](#) publication (also known as the "Orange Book").

GDUFA: ENABLING GENERIC DRUG PROGRAM SUCCESS

FDA and the generic industry developed a proposal for a generic drug user fee program and Congress enacted it as part of the Food and Drug Administration Safety and Innovation Act of 2012.

Under GDUFA, industry agreed to pay approximately \$300 million in fees each year of the five-year program. In exchange, FDA committed to performance goals, the specifics of which are contained in the Generic Drug User Fee Act Program Performance Goals and Procedures agreement that was negotiated with industry ([“GDUFA Commitment Letter”](#)). Because of the amount of hiring, restructuring and catch-up needed, performance goals were set to commence in the later years of the program.


The GDUFA performance goals are timeframes by which FDA is to take a “first action” on an ANDA, amendment to an ANDA, and prior approval supplements (PASs – post-approval changes requiring supplemental submission and approval prior to distribution of the product made using the change). These timeframes can be met by either granting an approval or tentative approval (in which an ANDA is ready for approval but relevant patents or exclusivities accorded to the reference listed drug remain), or, if there are deficiencies that prevent approval, identifying those deficiencies to the applicant in a complete response letter or in a refusal to receive the application. A “refuse-to-receive” decision indicates that FDA determined that an ANDA is not sufficiently complete to permit a substantive review. When deficiencies are identified, industry usually responds by correcting them through an amendment to the application.

At the end of 2015, FDA had met or exceeded all performance goals outlined in the GDUFA Commitment Letter.

Major GDUFA Performance Goals and Commitments

Goals	Review Time	FY2015	FY2016	FY2017
Original ANDA submission	15 months	60%	75%	90%~
Tier 1 first major amendment	10 months	60%	75%	90%
Tier 1 minor amendments (1st-3rd)	3 months*	60%	75%	90%
Tier 1 minor amendments (4th-5th)	6 months*	60%	75%	90%
Tier 2 amendment	12 months	60%	75%	90%
Prior Approval Supplements	6 months*	60%	75%	90%
ANDA teleconference requests	10 business days	200	250	300
Controlled correspondence+	2 months	70%^	70%	90%

ANDAs, amendments and PASs in backlog on Oct 1, 2012

Act on 90% by end of FY2017 

Note: Performance goals in the chart means FDA should take a “first action” (as defined above) on a certain percent of applications, etc. within the timeframes listed; it does not mean FDA should approve applications, etc. within such timeframes.
 +If no input required from clinical division
 *10 months if inspection required
 ^4 months
 ~10 months

Actions on Pre-GDUFA (“Backlog”) Applications

One of FDA’s major GDUFA commitments was to take a “first action” on 90% of the “backlog” applications. Backlog applications are defined as pre-GDUFA applications pending before the Agency on October 1, 2012; FDA’s first action on these applications is required by the end of Fiscal Year 2017.

As of October 1, 2012, the backlog included 2,866 ANDAs and 1,873 PASs. By December 31, 2015, FDA completed first actions on 84% of ANDAs and 88% of PASs. FDA is well ahead of schedule in achieving the GDUFA goal to significantly reduce the backlog and our ultimate goal of eliminating it.

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Percentage of Backlog Applications with First Action

First Actions 10/1/2012 to 12/31/2015

Actions	ANDAs	PASs
Number with First Action*	2,414	1,666
Percentage Complete	84%	88%
Approval	609	959
Tentative Approval	151	4
Complete Response with an Inspection**	1,384	465
Refuse to Receive	69	2
Withdrawn Application	201	236

* Numbers reflect data available at the time of report publication and may change based on refreshed counts in our tracking systems, including application status updates. These numbers are not intended for Congressional reporting purposes.

**Complete Response with an Inspection is a written FDA communication to an applicant usually describing all of the deficiencies that the agency has identified in an application that must be satisfactorily addressed before it can be approved.

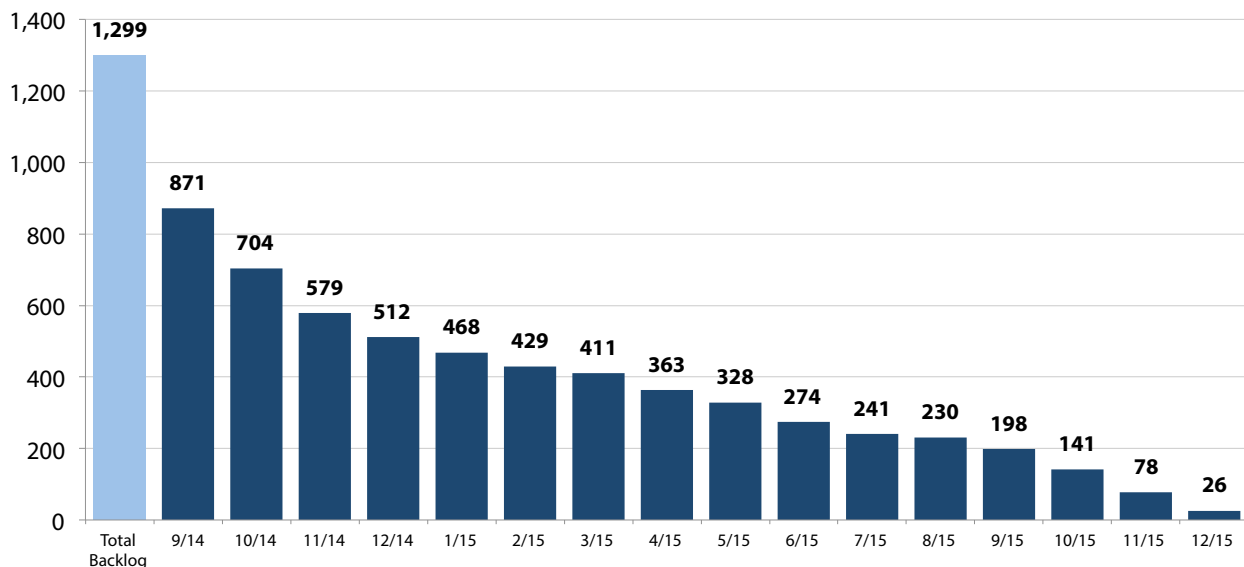
Controlled Correspondence

Controlled correspondence (commonly referred to as “controls”) are product development questions that FDA answers to help companies develop applications. FDA had a backlog of controlled correspondence submitted before October 2014, when GDUFA goal dates started. FDA has essentially eliminated that backlog.

In 2015, OGD closed out a record number of controls for industry: 2,065 controls.

Controlled Correspondence Backlog

Workload Summary Pre-FY2015 GDUFA Controls (submitted prior to 10/2014)



Improving Business Processes

As part of the strategy to achieve GDUFA goals, OGD continued to streamline existing processes to create more efficient systems, implemented written processes such as standard operating procedures and the Manuals of Policies and Procedures (MAPPs) and provided input to the Office of Business Informatics as they launched an informatics platform for review staff within CDER.

Informatics Platform

Launched October 1, 2014, the new CDER informatics regulatory review platform (often referred to as “the platform”) integrates review processes and connects CDER drug and biologic review staff in a single system. The platform supports the review, approval, and management of original ANDAs, supplemental ANDAs, controlled correspondence related to generic drug development, facility inspections and user fee checks. The platform assists with analytics and metrics reporting, goal and history tracking, process approval and task management and management of master data, reference data and product, sponsor and application data.

Important aspects of the platform include:

- Integrated data, workflow and reporting required to conduct and manage timely quality drug reviews
- Coordinated inspections and user fee checks
- Improved alignment and collaboration around priorities with goal dates, target action dates and discipline review dates
- The availability of review status information to support consistent communication with sponsors and timely reporting on approvals
- Enables prioritization process for first generics, Paragraph IV patent certifications and exclusivity issues

The platform helps FDA meet its GDUFA commitments and obligations to the public by serving as a single integrated system to better coordinate and integrate ANDA review work. OGD is the first CDER Office to function entirely on this platform, refining and improving the platform so that future regulatory work performed throughout CDER can be conducted in the platform.

Review Process

In 2014, OGD enacted a critical improvement to the ANDA review process - assigning a regulatory project manager (RPM) to each ANDA. This change provides industry with a central point of contact for each ANDA within OGD. The RPM works in collaboration with discipline project managers in OGD and regulatory business process managers in the Office of Pharmaceutical Quality (OPQ) to make sure reviews are on track to meet GDUFA goal dates.

OGD continues to communicate with our external stakeholders to provide more clarity and predictability to the application review process, including assigning precise goal dates and evaluating the use of these dates to improve the likelihood of ANDA action. In 2015, OGD completed the CDER PET drug project, in which industry and FDA worked together to ensure all positron emission topography (PET) drugs marketed in the United States are in compliance with FDA requirements.

Filing and Labeling Review

The filing backlog for ANDAs has been essentially eliminated. Filing is the process by which FDA evaluates if a drug applicant's submitted application is sufficiently complete to permit FDA's substantive review. In August 2014, there were more than 1,100 applications that had not been reviewed for an initial filing decision. Today there is no backlog, and filing is performed in real time. OGD issued filing decisions within 60 days for 99% of ANDAs submitted in FY 2015 that had GDUFA goal dates, and, on average, filing decisions are made and communicated to industry in approximately 40 days.

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Staff Training and Professional Development

ORO reconfigured employee orientation to complement discipline-based classroom training, online instruction and on-the-job activities. All OGD project managers underwent in-depth communication and customer engagement training as part of FDA's focus on increased and improved communication with industry. Information technology training for all OGD employees facilitated improved use of the CDER informatics platform. Widespread Lean Six Sigma deployment, a method that relies on a collaborative team effort to improve performance by systematically removing waste, ensured enhanced efficiency of the ANDA review process.

Guidances and Standards

Product-Specific Guidance Documents

OGD issues product-specific recommendations (or “bioequivalence guidances”) to facilitate efficient filing review, pre-market development of generic drug products, and accurate tracking of OGD’s activities in this area. These recommendations describe the Agency’s current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to specific reference-listed drugs.

OGD is able to improve generic product availability by providing information on scientifically and clinically supported methods. “Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA” (a general ANDA guidance) explains broader principles that apply to the majority of products and product-specific bioequivalence (BE) guidances are tailored to a specific drug development program and takes into account the unique features of the drug. These BE guidances clarify our expectations concerning specific products so industry can develop generic versions of branded drugs more quickly.

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OGD starts developing BE guidances soon after new drugs are approved and designated as Reference Listed Drugs in the Orange Book in order to ensure that patients have access to a generic drug at the earliest possible opportunity. OGD prioritizes guidance development based on a number of factors, including the timing of the date one year prior to expiration of marketing exclusivity (known as NCE-1). Other factors OGD considers include the complexity of the formulation, ability to accurately measure its bioavailability at the site of action, scientific methods to demonstrate bioequivalence and previous experience with and knowledge of similar drugs.

OGD also takes into consideration the level of demand for guidances, which are assessed through incoming requests for guidance development and by analyzing the list of 100 top-selling drugs and other broadly used drugs. To this end, OGD has established a working group dedicated specifically to reviewing requests for BE guidance received at GenericDrugs@fda.hhs.gov and creating recommendations to meet both current and anticipated patient and industry needs.

There are now over 1,300 product-specific guidances posted on the Internet. In 2015, OGD issued 124 new and 48 revised [individual product bioequivalence guidances](#). Many of the guidances issued in 2015 involved complex dosage forms, such as inhalational powders, nasal sprays, topical products and ophthalmic products.



OGD routinely looks at existing product-specific BE guidances and updates them as new information becomes available. The revised draft product-specific BE recommendations take into account careful examination of emerging postmarket reports of adverse events, analysis of new studies and review of relevant literature. When OGD becomes aware of new information that could impact successful generic substitution, the scientific recommendations considered necessary for approval must evolve.

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Regulatory Guidances

GDUFA is designed to speed the delivery of safe and effective generic drugs to the public and to reduce costs to industry. OGD publishes guidances to assist generic drug manufacturers in their applications, with particular attention to the development and approval processes that have the greatest potential impact on patient safety, drug efficacy and costs.

In 2015, OGD published the following guidance documents on generic drugs:

- [Guidance for Industry on ANDA Submissions—Refuse-to-Receive Standards](#), May 2015
- [Guidance for Industry on Size Shape, and Other Physical Attributes of Generic Tablets and Capsules](#), June 2015 (in collaboration with the Office of Pharmaceutical Quality)
- [Guidance for Industry on Controlled Correspondence Related to Generic Drug Development](#), September 2015
- [Guidance for Industry on Acceptability of Draft Labeling to Support ANDA Approval](#), October 2015

Manuals of Policies and Procedures (MAPPs)

[MAPPs](#) document internal FDA policies and procedures, and are made accessible to the public to provide greater transparency into our operations. OGD's MAPPs define our policy, mission and goals as they relate to generic drugs.

In 2015, OGD issued the following MAPPs:

- [MAPP 5200.3 Rev. 1: Communications with Industry with Respect to Pre-GDUFA Year Three Abbreviated New Drug Applications](#), August 2015
- [MAPP 5241.2: Consolidation of ANDAs by the Office of Generic Drugs](#), October 2015
- [MAPP 5200.7: Review of ANDA Amendments and Supplements by the Division of Filing Review](#), November 2015

ENHANCING COMMUNICATION WITH INDUSTRY AND STAKEHOLDERS

Timely and meaningful communications between FDA and industry are critical components of an efficient review process. Industry, FDA, patients and other stakeholders will benefit from effective communication practices that may lead to shortened approval times. Similarly, communicating the results of regulatory science to external stakeholders and implementing these standards in ANDA review provide transparency and clarity that can serve to improve the generic drug program.

Timely and meaningful communications between FDA and industry are critical components of an efficient review process.

In 2015, OGD communicated with the generic drug industry and other stakeholders on a variety of platforms, including:

- The [Regulatory Education for Industry \(REdI\) Generic Drugs Forum](#), held annually in collaboration with CDER's Small Business and Industry Assistance (SBIA), offered industry the opportunity to discuss the generic drug approval process with FDA subject matter experts.
- A webinar on [OGD's new communication initiatives](#) detailed what ANDA applicants can expect from OGD's new communication commitments, such as real-time responses to reviewer questions and timely updates from Regulatory Project Management staff.
- An instructional webinar on "[Guidance for Industry: Controlled Correspondence Related to Generic Drug Development](#)" provided additional insight into the process for submitting correspondence to FDA requesting information related to generic drug development.
- Information on patents and exclusivity, drug master files and other updates of interest to industry were shared through the SBIA newsletter (the SBIA Chronicles) and listserv (Small Biz Buzz).

APPROVALS AND OTHER REGULATORY ACTIONS

OGD awarded 580 approvals and 146 tentative approvals in 2015. This total includes 99 approvals and tentative approvals in December, the most approvals and tentative approvals granted in a single month since the start of the generic drug program. OGD issued 1,278 Complete Responses, or written letters to applicants identifying deficiencies that applicants need to resolve before approval of an ANDA.

FDA considers first generics to be a public health priority and prioritizes review of these submissions. For a list of

99 approvals and tentative approvals in December, the most approvals and tentative approvals granted in a single month since the start of the generic drug program.

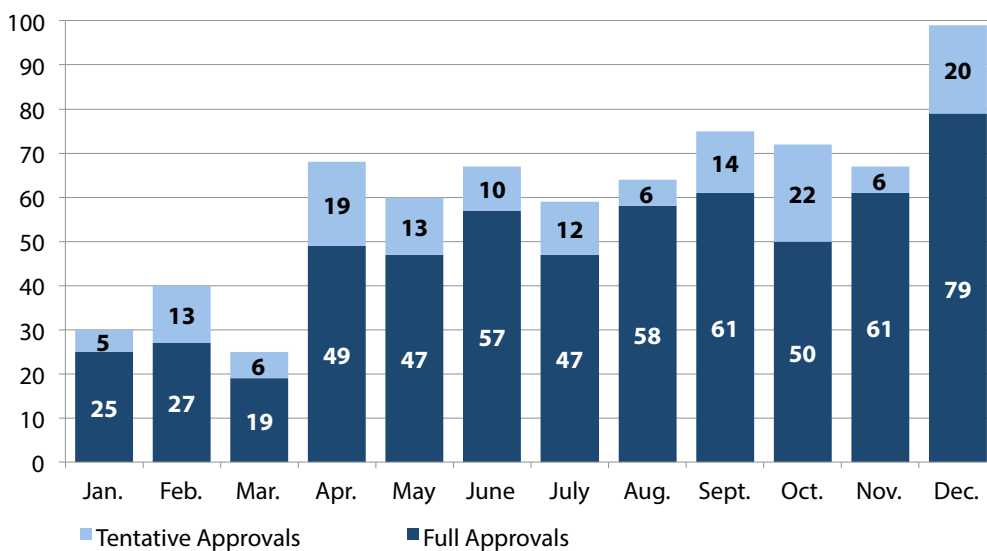
noteworthy first generic drug approvals, see the [Appendix](#) at the end of this report. These approvals may represent the first time a generic for this drug has been approved, they may serve an underserved public health need or they may address drug shortages.

Significant First Generic Drug Approvals in 2015		
Generic	Brand Name	Indications (Abbreviated)
alosetron	Lotronex	Irritable Bowel Syndrome
aripiprazole	Abilify	Schizophrenia, Bipolar Disorder
darifenacin	Enablex	Overactive bladder
eptifibatide	Integrelin	Heart attack
estradiol	Vagifem	Menopause
levoleucovorin	Fusilev	Supports cancer treatment
linezolid	Zyvox	Pneumonia, serious infections
tetrabenazine	Xenazine	Huntington’s Disease
tigecycline	Tygacil	Pneumonia, serious infections

For a list of all first generic drugs approved in 2015, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm482213.htm>.

Monthly Approvals and Tentative Approvals increased over the course of 2015, ending with December’s program high of 99.

Approvals and Tentative Approvals – CY2015



2015 GDUFA REGULATORY SCIENCE PLAN

As part of GDUFA implementation, FDA agreed to consult with the public, industry and academia to develop an annual list of regulatory science initiatives specific to research on generic drugs. So far, GDUFA has funded \$34.9 million in research programs. Other GDUFA Regulatory Science studies are developing testing mechanisms that would allow industry to efficiently develop new generics for products that currently only exist in brand-name versions.

The regulatory science results will provide new tools for FDA to evaluate generic drug equivalence and for industry to efficiently develop new generic products in all product categories, thereby providing increased access to safe and effective generic drugs.

In June 2015, OGD held the third annual public hearing on GDUFA regulatory science priorities. The meeting provided an overview of the current status of the regulatory science initiatives for generic drugs and provided an opportunity for the public input on research priorities in these topic areas. The outcome was the [FY 2015 GDUFA regulatory science plan](#). The GDUFA regulatory science plan has a large extramural component and OGD staff reviewed more than 100 proposals in 2015 to yield 23 new awards that complement internal activities. OGD had more than 90 ongoing external research collaborations at the end of 2015, as many projects awarded in previous years continued in 2015. In keeping with our commitment to promote quality science and clinical relevance, updates on our work in progress can be found in more than one hundred published scholarly articles, presentations, posters and book chapters.

The regulatory science results will provide new tools for FDA to evaluate generic drug equivalence and for industry to efficiently develop new generic products in all product categories.

GDUFA research funding for new and continuing awards was distributed across the GDUFA regulatory science priority areas:

1. **Post-market evaluation of generic drugs** - research into monitoring methods, understanding patient perceptions of generic drugs and verifying therapeutic equivalence via patient brand-to-generic switching studies.

These investigations provide additional data in therapeutic areas where concerns exist about the substitutability of generic drugs and allow FDA to verify if generic drugs are fully interchangeable, safe and effective in comparison to their RLD.

2. **Equivalence of complex drug products** - research into making generic versions available in all product categories, including complex drugs with unique characteristics.

FDA spends an increasing amount of time reviewing and developing policy for complex drug products, and future generic products will need to demonstrate equivalence to increasingly complex RLDs. This research supports the development of guidance and policy that clarifies the ANDA pathway for complex products, such as drug-device combinations, transdermal systems, implants and parenteral microspheres, nanomaterials (e.g. liposomes and iron colloids) and products that contain complex mixtures and peptides.

3. **Equivalence of locally acting products** - research into new bioequivalence methods and pathways for locally acting drugs (such as inhalation, topical dermatological, nasal, ophthalmic, gastrointestinal and otic drug products).

The lack of efficient bioequivalence pathways for locally acting drug products has limited the availability of generic drugs in this category. This research priority includes evaluating in vitro alternatives to clinical endpoint bioequivalence studies. One example of an in vitro alternative is that for a generic product that is qualitatively (Q1) and quantitatively (Q2) similar in ingredients to its reference product, an ANDA applicant could use a set of comprehensive laboratory characterization test to demonstrate that there is no significant difference between their product and the reference (Q3 equivalence).

4. **Therapeutic equivalence evaluation and standards** - support the evolution of risk-based equivalence and product quality standards to ensure therapeutic equivalence across all dosage forms and routes of delivery.

FDA continues to prioritize research for abuse-deterrent formulations, narrow therapeutic index (NTI) drugs and equivalence of modified-release solid oral dosage forms. Developing the pathway for generic versions of abuse-deterrent formulations requires tolls for evaluating antagonist/agonist combinations and technologies to deter nasal abuse. Based on the significant clinical impact of small variations in drug exposure, generic versions of NTI drugs require risk-based review that includes identifying NTI drug methods, adjusting bioequivalence standards and improving manufacturing quality through advances in process control, continuous manufacturing and quality metrics. Modified-release solid oral dosage forms have more failure modes than immediate-release (IR) products; therefore research into improving review standards for equivalence of modified-release products is critical.

5. **Cross-cutting computational and analytical tools** - essential to developing a modern ANDA review process.

Research priorities for advanced analytical methods include developing methods that characterize peptides and other complex mixtures that evaluate particle size, surface chemistry and gene expression for impurities or immunogenicity. Modeling and simulation tools that FDA will investigate include physiologically-based pharmacokinetic or absorption models, pharmacodynamic models or clinical trial simulation, systems biology and quantitative risk modeling. Investment in data warehouse infrastructure is needed to further enable computational tools for research and regulatory review.

Significant 2015 Research Accomplishments

The most significant results to come out of the GDUFA regulatory science program in 2015 were from two post-approval BE studies in patients with epilepsy. The results from BE studies in patients were completely consistent with the healthy subject BE studies used for original approval. These study results provide evidence to support successful generic substitution of anti-epileptic drugs (AED).

In one study, FDA initiated BE studies of lamotrigine IR tablets in epilepsy patients. FDA initiated these studies, and the epilepsy community provided input into the study design, to address concerns that generic AED substitution may lead to increased seizure breakthrough or adverse effects. The study results demonstrated that brand and generic lamotrigine tablets are bioequivalent with each other in epilepsy patients under clinical use conditions. In another study, two generic lamotrigine products from two different manufacturers with disparate pharmacokinetic parameters were also bioequivalent with each other in epilepsy patients.

APPENDIX: Notable First Generics Approvals



- **Ritonavir Tablets USP, 100 mg.**
Roxane Laboratories, Inc. (RLD Norvir®/Abbvie Inc.)
Treats HIV infection. Approved 1/15/15
- **Esomeprazole Magnesium DR Capsules, 20 mg Base and 40 mg Base.**
Ivax Pharmaceuticals, Inc. (RLD Nexium® DR Capsules/AstraZeneca)
Treats gastroesophageal reflux disease; lowers risk of bleeding after endoscopy in patients with ulcers. Approved 1/26/2015
- **Scopolamine Transdermal Therapeutics System, 1 mg/3 days.**
Perrigo R&D company. (RLD Transderm Scop®, 1 mg/3 days/Novartis)
Prevents nausea and vomiting associated with motion sickness and recovery from anesthesia and surgery. Approved 1/30/2015
- **Levoleucovorin Calcium Injection, 10 mg/mL.**
Sandoz, Inc. (RLD Fusilev® Injection/Spectrum Pharmaceuticals)
Prevents harmful effects of high-dose methotrexate therapy in patients with bone cancer. Approved 3/9/2015
- **Darifenacin Hydrobromide Extended-release Tablets, 7.5 mg and 15 mg.**
Anchen Pharmaceuticals, Inc. (RLD Enablex®/Actavis)
Treats overactive bladder. Approved 3/13/2015
- **Glatiramer Acetate Injection, 20 mg/mL, 1 mL prefilled syringe.**
Sandoz, Inc. (RLD Copaxone®/Teva Pharmaceuticals)
Treats relapsing forms of multiple sclerosis (MS). Approved 4/16/2015
- **Aripiprazole, multiple doses and dosage forms.**
Alembic Pharmaceuticals Ltd.; Hetero Labs Ltd.; Teva Pharmaceuticals; Torrent Pharmaceuticals Ltd.
(RLD Abilify®/Otsuka Pharmaceutical)
Treats schizophrenia and bipolar disorder. Approved 4/28/2015
- **Alosetron Hydrochloride Tablets, 0.5 mg and 1 mg Tablets.**
Roxane Laboratories Inc. (RLD Lotronex®/Prometheus)
Treats irritable bowel syndrome in women. Approved 5/4/2015
- **Risedronate Sodium Delayed-Release Tablets, 35 mg.**
Teva Pharmaceuticals USA. (RLD Atelvia®/Actavis Pharma, Inc.)
Treats and prevents osteoporosis; treats Paget's disease of the bone. Approved 5/18/2015
- **Linezolid Tablets, 600 mg.**
Teva Pharmaceuticals USA. (RLD Zyvox®/Pfizer Inc.)
Treats pneumonia and other serious infections. Approved 5/18/2015

Notable First Generics Approvals

continued

- **Tigecycline for Injection, 50 mg/vial.**
Sandoz, Inc. (Tygacil®/Wyeth Pharmaceuticals Inc.)
Treats pneumonia and other serious infections. Approved 5/27/2015
- **Moxifloxacin Ophthalmic Solution USP, 0.5%.**
Lupin Limited. (RLD Vigamox®/Alcon)
Treats bacterial conjunctivitis. Approved 5/28/2015
- **Estradiol Vaginal Inserts USP, 10 mcg.**
Amneal Pharmaceuticals. (RLD Vagifem®/Novo Nordisk)
Treats uncomfortable vaginal changes caused by menopause. Approved 5/29/2015
- **Linezolid for Oral Suspension 100 mg/5 mL.**
Roxane Laboratories, Inc. (RLD Zyvox® for Oral Suspension/Pharmacia and Upjohn Company)
Treats pneumonia and other serious infections. Approved 6/3/2015
- **Eptifibatid Injection, 7.5 mg/100 mL.**
Teva Pharmaceuticals Inc. (RLD Integrilin®/Schering Corporation)
Prevents blood clots during a heart attack or angioplasty. Approved 6/5/2015
- **Gemifloxacin Mesylate Tablets, 320 mg.**
Orchid Healthcare (RLD Factive® Tablets/LG Life Sciences, Ltd.)
Treats various bacterial infections. Approved 6/15/2015
- **Ezetimibe Tablets, 10 mg.**
Glenmark Pharmaceuticals Ltd. (RLD Zetia® Tablets/MSD International GMBH)
Lowers high cholesterol levels. Approved 6/26/2015
- **Desvenlafaxine Succinate ER Tablets, 50 mg and 100 mg.**
Lupin Pharmaceuticals. (RLD Pristiq® ER Tablets/Wyeth Pharmaceuticals)
Treats major depressive disorder. Approved 6/29/2015
- **Travoprost Ophthalmic Solution USP, 0.004% (Ionic Buffered Solution).**
Apotex Inc. (RLD Travatan Z® USP, 0.004%/Alcon)
Treats glaucoma and hypertension in the eye. Approved 7/10/2015
- **Olopatadine Hydrochloride Ophthalmic Solution USP, 0.2%.**
Barr Laboratories, Inc. (RLD Pataday® Ophthalmic Solution, 0.2%/Alcon)
Treats eye itching caused by pink eye. Approved 7/13/2015
- **Bivalirudin for Injection, 250 mg/vial (single-use vial).**
Hospira, Inc. (RLD Angiomax® Injection, for intravenous use/The Medicines Company)
Prevents blood clots during angioplasty. Approved 7/14/2015
- **Linezolid Injection, 200 mg/100 mL and 600 mg/300 mL.**
Sandoz Inc. (RLD Zyvox® Injection/Pharmacia and Upjohn Company)
Treats pneumonia and other serious infections. Approved 7/16/2015

- **Paliperidone Extended – release Tablets, 1.5 mg, 3 mg, 6 mg and 9 mg.**
Actavis Laboratories FL, Inc. (RLD Invega® ER tablets/Janssen)
Treats schizophrenia. Approved 8/3/2015
- **Rivastigmine Transdermal System, 13.3 mg/24 hr.**
Alvogen Pine Brook, Inc. (RLD Exelon® TDS/Novartis)
Treats dementia associated with Alzheimer's disease and Parkinson's disease. Approved 8/31/2015
- **Tetrabenazine Tablets, 12.5 mg and 25 mg.**
Sun Pharma Global FZE. (RLD Xenazine® Tablets/Valeant)
Treats movement disorder (chorea) caused by Huntington's disease. Approved 8/17/2015
- **Hydroxyprogesterone Caproate Injection USP, 250 mg/mL (1.25 g/5 mL vials).**
McGuff Pharmaceuticals, Inc. (RLD Delalutin® Injection/Bristol Myers)
Treats advanced adenocarcinoma of the uterine corpus (Stage III and IV); treats primary and secondary amenorrhea and abnormal uterine bleeding in the absence of organic pathology; test for endogenous estrogen production and for the production of secretory endometrium and desquamation. Approved 8/24/2015
- **Rivastigmine Transdermal System, 4.6 mg/24 hr and 9.5 mg/24 hr.**
Alvogen Pine Brook, Inc. (RLD Exelon® Transdermal System/Novartis Pharmaceuticals)
Treats dementia associated with Alzheimer's disease and Parkinson's disease. Approved 9/3/2015
- **Clozapine Orally Disintegrating Tablets, 25 mg and 100 mg.**
Mylan Pharmaceuticals Inc. (RLD Fazaclo® Orally Disintegrating Tablets/Jazz Pharmaceuticals, Inc.)
Treats schizophrenia; reduces risk of suicidal behavior in patients with schizophrenia or schizoaffective disorder. Approved 9/15/2015
- **Adapalene and Benzoyl Peroxide Gel, 0.1%/2.5%.**
Actavis Mid Atlantic LLC. (RLD Epiduo® Topical Gel/Galderma Laboratories, L.P.)
Treats acne. Approved 9/30/2015
- **Nevirapine Extended-Release Tablets, 100 mg.**
Alvogen and Mylan (RLD Viramune® XR Tablets/Boehringer Ingelheim)
Treats HIV infection. Approved 11/9/2015
- **Cefoxitin for Injection USP, 100 gm/Bag PBP Smartpak.**
Samson Medical Technologies. (RLD Mefoxin® Injection/Merck)
Treats or prevents bacterial infections. Approved 11/16/2015
- **Mesalamine Rectal Suppository 1000 mg.**
Mylan Pharmaceuticals, Inc. (RLD Canasa®/Forrest Laboratories)
Treats and prevents flare-ups of ulcerative colitis. Approved 11/24/2015
- **Clozapine Orally Disintegrating Tablets 150 mg & 200mg.**
Barr Pharmaceuticals, Inc. (RLD Fazaclo®/Jazz Pharmaceuticals)
Treats schizophrenia; reduces risk of suicidal behavior in patients with schizophrenia or schizoaffective disorder. Approved 11/25/2015

Notable First Generics Approvals

continued

- **Isradipine Extended-Release Tablets 5 mg & 10 mg.**
Mylan Pharmaceuticals, Inc. (RLD Dynacirc[®] CR Tablets/GlaxoSmithKline)
Treats hypertension. Approved 11/27/2015
- **Imatinib Mesylate Tablets, 100 mg & 400 mg.**
Sun Pharma Global FZE. (RLD Gleevec[®] Tablets/Novartis)
Treats leukemia and other kinds of cancer and related diseases. Approved 12/3/2015
- **Olopatadine Hydrochloride Ophthalmic Solution USP, 0.1%.**
USV North America; Zach System S.P.A; Novel; Apotex (RLD Patanol[®] Ophthalmic Solution/Alcon)
Treats eye itching caused by pink eye. Approved 12/7/2015
- **Amikacin Sulfate Injection USP, 250 mg/mL.**
Fresenius Kabi USA, LLC. (RLD Amikacin[®] Sulfate Injection, USP/Eurohealth International Sarl)
Treats serious infections. Approved 12/9/2015
- **Fesoterodine Fumarate Extended-Release Tablets, 4 mg & 8 mg.**
Alkem Laboratories. (RLD Toviaz[®] Extended-Release Tablets /Pfizer)
Treats overactive bladder symptoms such as loss of bladder control or frequent need to urinate. Approved 12/10/2015
- **Levetiracetam Tablets 250 mg, 750 mg, & 1000 mg.**
Secan Pharmaceuticals. (RLD Keppra[®]/UCB Inc.)
Treats seizures. Approved 12/16/2015
- **Busulfan Injection, 6 mg/mL (10 mL SDV).**
Pharmaforce. (RLD Busulfex[®] Injection/Otsuka)
Treats certain kinds of leukemia; prepares the body for a stem cell transplant. Approved 12/22/2015
- **Neostigmine Methylsulfate Injection USP, 5 mg/10 mL & 10 mg/10 mL.**
Eurohealth International SARL. (RLD Bloxiverz[®]/ Eclat Pharmaceuticals)
Reverses the effects of anesthesia after surgery. Approved 12/28/2015

For a list of all first generics approved in 2015, see

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/ANDAGenericDrugApprovals/ucm482213.htm>.

We Welcome Your Feedback

OGD welcomes feedback from stakeholders, and we will continue to communicate with industry as we implement changes to meet GDUFA goals.



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