

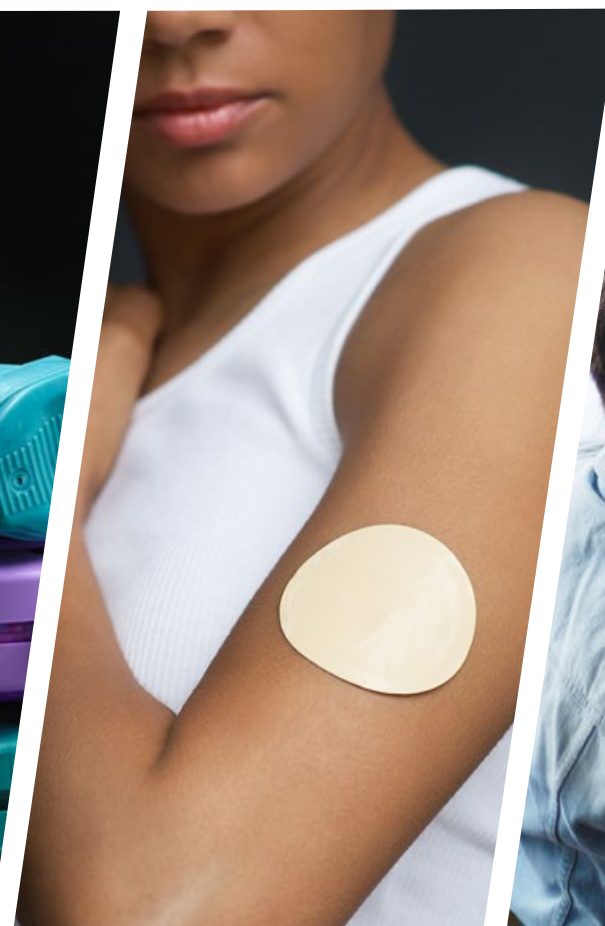
**U.S. FOOD & DRUG
ADMINISTRATION**

OFFICE OF GENERIC DRUGS

2018

ANNUAL REPORT

Ensuring Safe, Effective, and Affordable
Medicines for the American Public



February 2019
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FDA's Office of Generic Drugs 2018 at a Glance

FDA's Office of Generic Drugs celebrated numerous successes during 2018 and the first year of the Generic Drug User Fee Amendments Reauthorization (GDUFA II):

- Approved or tentatively approved 1,021 Abbreviated New Drug Applications (ANDAs).
- Published more than 250 new or revised guidances, product-specific guidances (PSGs), and manuals of policies and procedures (MAPPs) for stakeholders.
- Successfully implemented many of the new provisions in GDUFA II and the FDA Reauthorization Act of 2017 (FDARA). These included requests for pre-ANDA meetings, reconsideration requests, one-time marketing status updates to the "Orange Book," and competitive generic therapy designation and exclusivity requests, among many others.
- Continued facilitating a robust generic drug pipeline by conducting and sharing regulatory science research, issuing guidances, and providing timely responses to controlled correspondence.
- Maintained reproducibly high volume and high quality output.
- Created dynamic communication processes that allow for more transparency and predictability for industry.
- Launched a new online functionality for controlled correspondence inquiries from industry and responded to about 700 such inquiries via the Center for Drug Evaluation and Research's Direct NextGen Collaboration Portal.
- Issued 2,648 complete response letters detailing important issues to be resolved by the applicant before FDA could grant an approval.

Director's Message

Welcome to the 2018 Annual Report of the Office of Generic Drugs (OGD) in the Center for Drug Evaluation and Research (CDER) of the U.S. Food and Drug Administration (FDA).

Our 2018 accomplishments included approval or tentative approval of more than 1,000 generic drugs, with record-breaking monthly approval actions in October and November. First generics (approvals for generic drug products for branded drugs that previously had no FDA-approved generic) made up nearly 10% of 2018's approvals. Of these first generics, 18% were for complex generic drugs while about 14% of all generics approvals were for complex generic drugs. Additionally, our bridging activities for older Abbreviated New Drug Applications (ANDAs) helped us achieve this high level of productivity and resulted in the largest number of regulatory actions in a single year. Now, all generic ANDAs have review goals, regardless of when the application was originally submitted. We also implemented a new statutory pathway for designating drugs as Competitive Generic Therapies (CGTs) and five new applications for products designated as CGTs were approved and granted CGT exclusivity per FDARA ([the FDA Reauthorization Act of 2017](#)).

OGD also supported the FDA's [Drug Competition Action Plan](#). This plan focuses on improving the efficiency of generic drug development, review, and approval processes, maximizing scientific and regulatory clarity with respect to generic drugs for complex products. It also seeks to close loopholes that allow brand drug companies to "game" the Hatch-Waxman Amendments in ways that forestall the generic competition that Congress intended. As you will see in this report, OGD activities have directly supported this high-priority FDA initiative.

OGD marked significant milestones in 2018. We had approval of the first original ANDA submitted under GDUFA II and the first CGT-designated ANDA. In July 2018, we had the largest output of regulatory actions in a single month, which included 96 final approvals, 30 tentative approvals, and 357 complete responses. These results can be credited to an increased number of original ANDA submissions in September 2017, which had 10-month GDUFA goal dates in July 2018; the large number of GDUFA I pre-year 3 original ANDA submissions that, per GDUFA I, had no GDUFA goal date and therefore received GDUFA II bridging goal dates for July 2018; and other regulatory submissions that had July 2018 GDUFA goal dates.

OGD also implemented a new pre-ANDA program for complex generic drug products per GDUFA II, which resulted in 92 pre-ANDA meeting requests – double the requests for similar meetings in the previous year,



Kathleen Uhl, MD
Director, Office of Generic Drugs, 2013-2019

“The incredible dedication of our staff to the generic drugs program and to our public health mission made 2018 a phenomenally productive year.”

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demonstrating a robust generic drug pipeline for those drug products that are particularly difficult to make into generics.

On the global front, OGD worked collaboratively with colleagues across CDER to explore a new concept of harmonizing scientific and technical standards for generic drugs under the International Council for Harmonisation (ICH). The ICH Assembly endorsed FDA’s reflection paper describing the proposal in November 2018. Harmonization of these standards will help us advance a generic drug market that drives product competition, lowers drug prices, and increases patient access to high-quality medicines.

Dedication Drives Our Success

The incredible dedication of our staff to the Generic Drugs Program and to our public health mission made 2018 a phenomenally productive year. We built upon previous goal-breaking achievements and increased our capacity and productivity to create an extremely successful year. I am confident going forward that OGD Leadership at the Office and Division levels will capably and enthusiastically continue the progress of this program. Our leadership is looking forward to challenges and opportunities in the years ahead. OGD’s critical role with industry, the research community, lawmakers, patients, health care providers, and other stakeholders in the United States and around the world will continue in order to safeguard access to affordable, high-quality generic drugs.

As the end of my OGD Directorship draws near with my retirement from FDA in early 2019, I want to take this opportunity to express my sincere appreciation of and gratitude to all the staff and leadership in OGD. It has been a pleasure and my distinct honor serving and leading FDA’s Generic Drugs Program. With the close of 2018, our program is in superlative shape and historically in the best place it has ever been. The program had spectacular accomplishments in 2018 through the efforts of every staff member in OGD and many others across FDA. The incredible momentum and growth of this program is due to the efforts to realize our mission and vision and to this incredibly talented, knowledgeable, and dedicated staff.

Kathleen Uhl, MD
Director, Office of Generic Drugs, 2013-2019

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Fortifying the U.S. Generic Drug Program

FDA is in the second year of the reauthorized generic drug user fee program, the Generic Drug User Fee Amendments of 2017 (GDUFA II). Under GDUFA I, FDA committed to performance goals which continue under GDUFA II and industry continues to pay user fees each year. GDUFA performance goals include time frames within which FDA committed to take a first action on an ANDA, an amendment to an ANDA, prior approval supplements (PAS), which are post-approval changes requiring a supplemental submission and approval, and amendments to PAS.

The agency meets these time frames by accomplishing one of four actions:

1. Granting an approval
2. Granting a tentative approval (e.g., when an ANDA is ready for approval but FDA is blocked from approving it because of remaining patents or exclusivities related to the reference listed drug)
3. Issuing a complete response letter, which identifies deficiencies in an application that will prevent FDA from granting an approval and then communicating these deficiencies to the applicant
4. Making a “refuse-to-accept” decision because the ANDA is not sufficiently complete to permit a substantive review

The [GDUFA II Commitment Letter](#) explains the specifics of the GDUFA II agreement. OGD prides itself in meeting the commitments set forth in the GDUFA II agreement, as well as with implementing the new features in GDUFA II that work for FDA and industry to help meet our goals of more first-cycle approvals and more approvals of safe and effective generic drugs for patients.

In 2018, FDA approved or tentatively approved 1,021 ANDAs. Also in 2018, FDA approved or tentatively approved 894 PAS and communicated with industry through 1,180 information requests and 2,648 complete response letters that detailed important issues that needed to be resolved by the applicant before FDA could grant an approval. FDA responded to a record 2,919 controlled correspondence letters with answers to product development questions from industry.

Table 1. Major GDUFA II Performance Goals and Commitments

Submission Type	GDUFA II Goal
Standard Original ANDAs	90% within 10 months
Priority Original ANDAs	90% within 8 months with successful Pre-Submission Facility Correspondence (PFC) 90% within 10 months without successful PFC
Standard Major ANDA Amendments	90% within 8 months if preapproval inspection not required 90% within 10 months if preapproval inspection required
Priority Major ANDA Amendments	90% within 6 months if preapproval inspection not required 90% within 8 months if preapproval inspection required with successful PFC 90% within 10 months if preapproval inspection required without successful PFC
Standard Original PAS	90% within 6 months if preapproval inspection not required 90% within 10 months if preapproval inspection required
Priority Original PAS	90% within 4 months if preapproval inspection not required 90% within 8 months if preapproval inspection required with successful PFC 90% within 10 months if preapproval inspection required without successful PFC
Standard Major PAS Amendments	90% within 6 months if preapproval inspection not required 90% within 10 months if preapproval inspection required
Priority Major PAS Amendments	90% within 4 months if preapproval inspection not required 90% within 8 months if preapproval inspection required with successful PFC 90% within 10 months if preapproval inspection required without successful PFC
Standard Controlled Correspondence	90% within 60 days
Complex Controlled Correspondence*	90% within 120 days

*Complex controlled correspondence means:

1. Controlled correspondence involving evaluation of clinical content,
2. Bioequivalence protocols for Reference Listed Drugs with Risk Evaluation and Mitigation Strategy Elements to Assure Safe Use, or
3. Requested evaluations of alternative bioequivalence approaches within the same study type (e.g., pharmacokinetic, in vitro, clinical).

In 2018, OGD issued filing determinations within 60 days of submission for nearly all ANDAs submitted. Continual filing review process improvement efforts, along with enhanced communications with applicants to improve submission quality, resulted in a refuse-to-accept rate of less than 7 percent in 2018, compared to less than 13 percent in 2017.



Guidances, Policies, and Procedures

Product-Specific Guidances

FDA's efforts to improve generic drug access start with providing critical guidance and support to generic drug developers. Timely guidance from FDA allows generic drug applicants to build agency recommendations into their research and development programs, which helps applicants submit higher quality ANDAs. These recommendations are described in [product-specific guidances \(PSGs\)](#). These guidances give applicants better opportunities to efficiently develop generic drug products and to prepare more complete and accurate ANDAs. PSGs help applicants submit ANDAs to FDA with fewer deficiencies, which helps lead to more first-cycle approvals.

In 2018, OGD issued 128 new and 117 revised PSGs (revisions to existing PSGs are generated, for example, as new information or scientific methodologies become available). PSGs address uncertainties and provide the agency's current thinking on product development questions. PSGs help make industry's research and development decisions more efficient and cost-effective. PSGs also advance the opportunity for discussion of new or alternative generic drug development strategies – especially for complex generic drug products. Almost half of the PSGs FDA issued in 2018 were for complex products.

OGD develops PSGs based on public health priorities, requests from industry, and current and anticipated patient and industry needs.

OGD's [ongoing scientific research under GDUFA](#) enables the agency to make recommendations to support the identification of appropriate science-based methodologies and evidence for the development of many complex drug products. Complex drug products are drugs that are harder to develop as generic drug products using traditional bioequivalence approaches because of the nature of their formulation or delivery system.

Requests related to PSGs can be sent to GenericDrugs@fda.hhs.gov. As of December 31, 2018, 1,660 PSGs are posted on FDA's website at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.

Guidances

OGD publishes regulatory guidances that share the agency's current thinking and recommendations to industry on generic drug development. These publications provide critical guidance to drug developers. This year, FDA published four revised guidances and three final guidances for industry, not including product-specific guidances. Guidances issued in 2018 include the draft guidances *Formal Meetings between FDA and ANDA Applicants of Complex Products under GDUFA* and *Good ANDA Submission Practices*, and the final guidance for industry *ANDA Submissions – Amendments to Abbreviated New Drug Applications under GDUFA*.

Guidances issued in 2018 appear online at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064995.htm>.

Manuals of Policies and Procedures (MAPPs)

An FDA Manual of Policies and Procedures (MAPP) documents internal agency policies and procedures and is accessible to the public to make FDA's operations more transparent. OGD's MAPPs define FDA's policy, mission, and goals as they relate to FDA's generic drug program.

In 2018, OGD issued MAPP 5241.3, *Good Abbreviated New Drug Application Assessment Practices*, and revised MAPP 5240.5 Rev.1, *ANDA Suitability Petitions*.

These MAPPs appear online in the [CDER Manual of Policies and Procedures](#).

Drug Competition Action Plan

The [Drug Competition Action Plan \(DCAP\)](#) aims to promote competition and patient access and make it more efficient to bring generic drugs to market. In 2018, OGD made significant progress in the three major components of the DCAP: (1) streamlining the ANDA review process to increase efficiency, effectiveness, and output of approvals; (2) enhancing development and review of complex generic drug products; and (3) reducing the “gaming” that frustrates and delays generic drug approvals and extends brand monopolies beyond what Congress intended with the Hatch-Waxman Amendments of 1984.

Three important steps towards streamlining and providing transparency into the generic drug review process in 2018 included:

1. Publishing a draft guidance for industry, [Good ANDA Submission Practices](#), highlighting common and recurring deficiencies in generic drug applications that may lead to a delay in their approval, to help applicants avoid these common deficiencies, and reduce the number of review cycles needed for approval.
2. Issuing an accompanying [Good ANDA Assessment Practices MAPP](#) outlining ANDA assessment practices for OGD and the Office of Pharmaceutical Quality (OPQ), and formalizing several enhancements to the efficiency of our ANDA assessment practices, including improvements to operational effectiveness, clarification of staff responsibilities, and the establishment of consistent and clear communication between FDA and applicants.
3. Issuing the final guidance for industry, [Abbreviated New Drug Application Submissions--Amendments to Abbreviated New Drug Applications Under the Generic Drug User Fee Act](#), to explain how amendment submissions may affect an application’s review goal dates.

OGD took the following significant steps towards enhancing development and review of complex generic drug products:

1. Issuing 115 PSGs for complex products to increase transparency on methodologies for developing generic drugs and generating evidence needed to support generic approval.
2. Publishing a revised draft guidance for industry, [Assessing Adhesion with Transdermal and Topical Delivery Systems for ANDAs](#), updating recommendations for the design and conduct of studies evaluating the adhesive performance of transdermal or topical delivery systems (TDS) submitted in support of an ANDA.

3. Publishing a draft guidance for industry, [Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs](#), providing recommendations for the design and conduct of studies to evaluate the in vivo skin irritation and sensitization potential of a transdermal or TDS.
4. Approving the first generic epinephrine auto-injector. The approval of this life-saving product demonstrates FDA's commitment to removing barriers to the development and approval of complex products.

Our actions towards reducing the “gaming” that frustrates and delays generic drug approvals and extends brand monopolies beyond what Congress intended with the Hatch-Waxman Amendments of 1984 were substantial. To improve transparency around gaming tactics used to delay generic entry, including tactics used to prevent potential generic applicants from obtaining samples of certain brand name products necessary to support approval of a generic drug, OGD took the following actions:

1. In May, FDA published a [list of all drug products about which FDA has received inquiries related to reference listed drug access](#).
2. In June, FDA published two draft guidances for industry: (1) [Development of a Shared System REMS](#), which provides recommendations to assist generic drug makers with the development of shared system Risk Evaluation and Mitigation Strategies (REMS); and (2) [Waivers of the Single, Shared System REMS Requirement](#), which describes when and how the FDA will consider waiving the single, shared system REMS requirement and how generic applicants can request a waiver, along with the factors FDA will consider in evaluating a request for a waiver of the single, shared system REMS requirement. This guidance makes it clear that, while FDA encourages companies to work together to form a single, shared system, the agency will consider a waiver at any time (either upon request of the applicant, or on the agency's own initiative).
3. In October, we published the revised draft guidance for industry, [Citizen Petitions and Petitions for Stay of Action Subject to Section 505\(q\) of the Federal Food, Drug, and Cosmetic Act](#) that, among other things, describes some of the factors FDA will consider in determining whether a petition is submitted with the primary purpose of delaying the approval of a generic application. If the agency determines that this is the case, FDA will consider whether the petition can be denied on that basis, and may, in any case, note

In 2018, OGD made significant progress advancing the goals of the Drug Competition Action Plan.

this determination in the petition response. We believe this will provide an additional deterrent to pursuing these “gaming” tactics.

OGD updated the [List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic](#) in June and December. OGD will continue to update the list semiannually to ensure continued transparency and encourage the development and submission of ANDAs in markets with limited competition.

While there is no one solution to the many challenges of high drug costs, the agency is committed to doing all we can, within our jurisdiction, to advance the critically important public health mission of providing the American public with more affordable medicines.



Enhancing Communication with Industry and Stakeholders

Communicating the results of regulatory science to external stakeholders provides transparency and clarity to industry, which strengthens the generic drug program. In 2018, CDER connected with the generic drug industry and other stakeholders through public events, webinars, podcasts, workshops, meetings, and publications.

Meetings

FDA sponsored, co-sponsored, and/or participated in seven regulatory science meetings and workshops focusing on complex generic drug development and GDUFA:

- [New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products Public Meeting](#) (January 9) showcased outcomes from research projects initiated under the GDUFA Regulatory Science Program. FDA solicited ideas from the public about when and how analytical methods and procedures should be applied in the development and review of ANDAs for these complex products.
- Held annually, the [CDER Small Business and Industry Assistance \(SBIA\) Regulatory Education for Industry \(REdI\) Public Meeting: Generic Drug Forum 2018](#) (April 11-12) updates industry on current trends around GDUFA and FDA's Generic Drug Program. Topics are drawn from stakeholder feedback from previous meetings.

- FDA held the FY 2018 [Generic Drug Regulatory Science Initiatives Public Workshop](#) (May 24), which provided an overview of the status of the human generic drug regulatory science program and an opportunity for public input in developing the fiscal year 2019 research priorities.
- FDA staff presented on a variety of topics and led a [Generic Drug Town Hall](#) session at the Drug Information Association (DIA) [Annual Meeting](#) (June 24-28), including: Implementation, Policy and Regulatory Science updates related to GDUFA; Comparison of Safety Profile with Branded Cousin; and Challenges and Opportunities in Data Access and Methodology Development for Post-market Generic Drug Monitoring.
- New in 2018, the [SBIA and REdl Complex Generic Drug Product Development Public Workshop](#) (September 12-13). New in 2018, this FDA workshop offered stakeholders a deep dive into the development of complex generic drug products in a “boot-camp” style meeting. The workshop drew more than 3,000 registrants.
- The co-sponsored [FDA-DIA Workshop on Complex Generic Drug-Device Combination Products](#) (October 9-10). This FDA and DIA co-sponsored event brought together regulatory, industry and academic experts for a highly effective interactive workshop on [Complex Generic Drug-Device Combination Products](#).
- At the [Flight Simulator Workshop: Learning How to Develop Complex Generic Drugs](#) (November 3). FDA provided a hands-on training during the American Association of Pharmaceutical Scientists (AAPS) annual meeting.

Communication Resources Online

- [“Building Confidence in Generic Narrow Therapeutic Index Drugs”](#) live Webinar for Continuing Education Credit in FDA’s Division of Drug Information
- New Web page [Points of Contact for Questions Related to Generic Drugs](#)
- [Monthly Activities](#) reports and new [GDUFA II Quarterly Performance](#) reports, which include ANDAs waiting for FDA action, ANDAs waiting for Applicant Action, and Mean and Median times for approvals and tentative approvals, among other metrics

- Industry updates, such as CDER’s Small Business & Industry Assistance newsletter ([CDER SBIA Chronicles](#)) and listserv for industry ([Small Biz Buzz](#)), as well as two generic drug Listservs for subscribers interested in GDUFA-specific updates and general generic drug updates
- New and updated GDUFA webpage, [Generic Drug User Fee Amendments \(GDUFA II\)](#)
- FDA presentation “[Questions about the Proposed Topical Classification System \(TCS\), and What to Do with It](#),” part of a free Webinar series sponsored by Product Quality Research Institute (PQRI)
- A series of podcasts (co-sponsored with DIA) featuring FDA experts on topics including “[US Generic Drug Policy: Less Cost, Same Impact](#)” and “[Challenges in Generic Drug Safety and Surveillance](#)” as well as a series of live Webinars on [complex generic drug products](#)
- List of [regulatory science initiatives](#) on generic drugs

Communicating the results of regulatory science to external stakeholders provides transparency and clarity to industry.



Approvals and Other Regulatory Actions

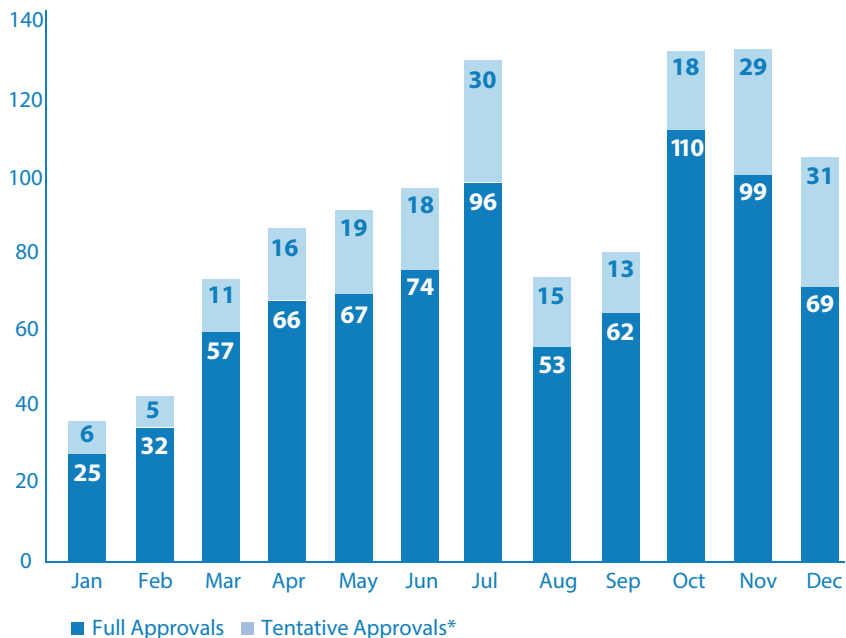
FDA considers the approval of the first generic of a brand-name drug to be a public health priority and expedites review of these submissions.

Table 2. Significant First Generic Drug Approvals in 2018*

Generic Drug Product	Brand Name	Indication of Use
Buprenorphine HCl and Naloxone Sublingual Film	Suboxone	Treatment of opioid dependence
Epinephrine Auto-injector	EpiPen	Emergency treatment of anaphylactic allergic reactions
Everolimus Tablets	Zortress	Prevention of organ rejection
Glatopa (Glatiramer Acetate) Injection Pre-Filled Syringes	Copaxone	Treatment of multiple sclerosis
Ticagrelor Tablets	Brilinta	Treatment of heart disease, stroke, diabetes

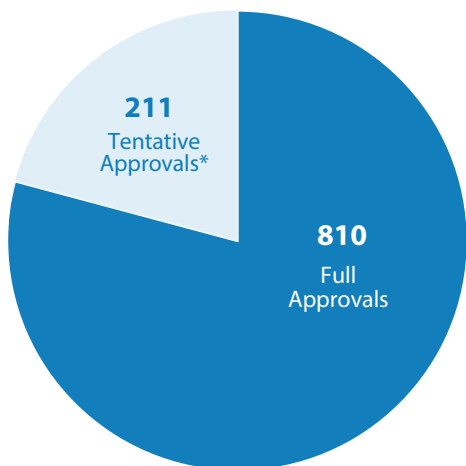
*Note: Generic Drug Products listed in alphabetical order. OGD maintains a complete [list of first generic approvals](#), which can be accessed via the [OGD web page](#). For full indication information, please check the [Drugs@FDA online database](#).

Figure 1. 2018 Generic Drugs Approved



*A tentative approval does not allow the applicant to market the generic drug product and postpones the final approval until all patent/exclusivity issues have been resolved.

Figure 2. 1,021 Total Generic Approval Actions



The agency approved or tentatively approved more than 1,000 generic drugs during 2018.

*A tentative approval does not allow the applicant to market the generic drug product and postpones the final approval until all patent/exclusivity issues have been resolved.

2018 Regulatory Science Research

The results of OGD's GDUFA regulatory science research provide needed information and tools for industry to develop new generic drug products and for FDA to evaluate the equivalence of proposed generic drugs. FDA consults with and solicits input from the public, industry, and academia to develop an annual list of GDUFA regulatory science initiatives specific to research on generic drugs.

In 2018, GDUFA II funded more than \$14 million in regulatory science research programs. FDA awarded funding for 13 new contracts and 11 new grants, as well as 9 ongoing grants and 7 contracts to conduct regulatory science research. OGD had 75 ongoing external research collaborations in 2018, with many projects that had been awarded in previous years continuing into 2018. In keeping with FDA's commitment to promote quality and clinically-relevant science, FDA staff or external collaborators published 63 peer-reviewed scholarly articles and book chapters, presented 112 external talks, and exhibited 78 posters at national and international scientific and medical conferences.

On May 24, 2018, FDA held the [FY2018 Generic Drug Regulatory Science Initiatives 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 the FY2019 regulatory science priorities. Information obtained during the public workshop, along with other input such as comments to the public docket, were considered in developing the *GDUFA Regulatory Science Priority Initiatives for Fiscal Year 2019*.

The FY2019 generic drug regulatory science priority initiatives 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

Highlighted Significant 2018 Research Accomplishments

Long-Acting Injectables

There are currently no approved generic drug products in this product category. OGD's research will help potential applicants move long-acting injectable products through the development process. In collaboration with researchers at Purdue University, FDA scientists published an article *Beyond Q1/Q2: The Impact of Manufacturing Conditions and*

*Test Methods on Drug Release From PLGA-Based Microparticle Depot Formulations*¹ that will aid potential generic drug applicants who are developing PLGA-based, long-acting injectables.

Complex Injectables and Nanomaterials

FDA scientists published a set of four papers² that describe detailed comparisons of the approved generic Sodium Ferric Gluconate Complex with the brand product. This research demonstrates the level of equivalence and sameness of complex generic drug products that have been approved by FDA's generic drug program and strengthens confidence in future complex generic drug approvals.

Quantitative Clinical Pharmacology

The 2018 report³ on the FDA public workshop, "[Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review](#)," highlighted how advanced modeling approaches can be applied to generic drug development and regulatory decision-making.

Data Analytics

FDA developed new equivalence methodologies for comparing the complex particle size distributions profiles (e.g., multiple peaks) between brand and generic products.⁴ The new approach employs a statistical distribution comparing algorithm called Earth Mover's Distance, to assess differences, and applies the population bioequivalence method to draw statistical conclusions. FDA included this approach in the product-specific guidances for barium sulfate suspension⁵ to aid generic drug developers with demonstrating that brand and generic products have the same particle size distribution.

Drug-Device Combinations

FDA research established the general utility of an in vitro permeation test methodology to compare heat effects between prospective generic and brand transdermal systems.⁶ Generic drug developers can use this work to design transdermal systems that perform the same as the brand product. FDA can use this research to compare brand and generic transdermal products without using in vivo studies. These improvements can increase the efficiency of generic drug development and review.

1. [J Pharm Sci](#). 2018 Jan;107(1):353-361.
2. [Nanomaterials \(Basel\)](#). 2017 Dec 28;8(1) [Nanomaterials \(Basel\)](#). 2018 Feb 11;8(2) [Nanomaterials \(Basel\)](#). 2018 Jan 5;8(1) [Nanomaterials \(Basel\)](#). 2017 Dec 15;7(12).
3. [Clin Pharmacol Ther](#). 2018 Jul;104(1):27-30
4. [AAPS J](#). 2018 Apr 12;20(3):62
5. FDA's Draft Guidances on Barium Sulfate posted February 2018:
<https://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM586138.pdf>
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM586142.pdf>
6. [J Control Release](#). 2018 Jan 28;270:76-88

Research studies conducted under GDUFA advance the public health by providing results that expedite access to safe and effective generic drugs.



The Office of Generic Drugs (OGD)

OGD comprises an immediate office and four subordinate offices, with approximately 500 employees total.

Immediate Office

Clinical Safety Surveillance Staff

- Obtains and coordinates information regarding the safety and surveillance of generic drug products.
- Serves as OGD's liaison to CDER's Office of Surveillance and Epidemiology and other drug surveillance units within CDER.
- Interacts with external stakeholders such as physicians, pharmacists, patients, and patient advocacy groups to investigate reports of adverse events or therapeutic inequivalence of generic drugs.

Communications Staff

- Oversees and coordinates all communications that originate from OGD.
- Collaborates with CDER's Office of Communications and FDA's Office of Media Affairs on generic drug topics.
- Engages strategically within OGD and throughout CDER to communicate accurate information on the approval and surveillance of generic drugs to staff and to external stakeholders.

Generic Regulatory Affairs Team

- Provides oversight, outreach, and strategic liaison assistance to OGD and CDER on generic drug regulatory programs and initiatives.

Global International Affairs Team

- Coordinates and supports OGD's global engagement activities in collaboration with internal and external stakeholders. Understanding generic drug manufacturing overseas is critical to ensuring the consistent quality of generic drugs sold in the United States because 80 percent of generic drugs have a global aspect to their development or production. This team enhances OGD's ability to address complex global issues strategically and proactively.
- Program Management and Analysis Staff
- Provides leadership, guidance, and support services to OGD on all aspects of budget, contracts, grants, facilities management, human resources, personnel operations services, travel, training, scientific fellowships, and recruitment activities.

Office of Bioequivalence

The Office of Bioequivalence evaluates formulations for quantitative and qualitative equivalence and reviews bioequivalence (BE) studies, including those with pharmacokinetic and pharmacodynamic endpoints. This office collaborates with other CDER and OGD offices to consider new methodologies for demonstrating BE in complex dosage forms. The Office of Bioequivalence also investigates products that have been identified as having potential safety or therapeutic inequivalence issues and shares the results of these investigations with the Clinical Safety Surveillance Staff.

The Risk Evaluation Mitigation Strategies (REMS) Team within the Office of Bioequivalence identifies generic drug applications affected by a REMS. REMS are risk management plans that use risk minimization strategies beyond professional labeling to ensure that the benefits of certain prescription drugs outweigh their risks.

The Office of Bioequivalence's Division of Clinical Review evaluates BE studies with clinical endpoints, skin adhesion and irritation/sensitization studies for transdermal delivery systems, REMS protocols, and BE studies for investigational new drugs. The division reviews suitability petitions, citizen petitions, relisting/delisting reviews, and

controlled correspondence related to clinical issues. The division also responds to consult requests related to clinical or pharmacology/toxicology issues and collaborates with OGD's Office of Research and Standards on BE recommendations and with the Clinical Safety Surveillance Staff on postmarketing surveillance investigations.

Office of Generic Drug Policy

- Develops regulatory strategies for OGD that actively promote OGD's mission of ensuring safe, effective, and affordable drugs for the American public.
- Ensures consistency in generic drug regulatory review standards and processes through development and implementation of policy documents.
- Advises CDER and OGD on Hatch-Waxman patent and exclusivity matters, as well as statutory and regulatory issues related to ANDAs.
- Maintains the [Approved Drug Products with Therapeutic Equivalence Evaluations publication](#) (also known as the "Orange Book"), which, among other things, identifies approved drug products and provides information about patents and exclusivity.
- Coordinates responses to generic drug shortage issues with CDER's Drug Shortage Staff.
- Protects, along with the FDA Office of Chief Counsel and CDER's Office of Regulatory Policy, the integrity of OGD's scientific determinations by ensuring that the administrative record for an application reflects OGD's rationale and consensus.

Office of Regulatory Operations

The Office of Regulatory Operations (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, timely, rigorous, and scientific regulatory review process. ORO ensures that incoming ANDAs, relevant PAS, and amendments meet established quality standards for filing and labeling. ORO oversees the review of ANDAs across all disciplines to ensure that OGD meets GDUFA goal dates.

ORO monitors, analyzes, and improves OGD's business processes and systems. ORO staff responds to controlled correspondence and reviews suitability petitions and ANDAs. Overall, ORO responds to more than 60,000 submissions a year.

Office of Research and Standards

The Office of Research and Standards (ORS) leads the generic drug program in the development of scientific standards and methods for generic drug equivalence. This work includes establishing predictive and physiological models of drug product performance, drug absorption, and drug pharmacology that inform the development of guidances for industry and the review of in vitro, pharmacokinetic, pharmacodynamic, and clinical BE studies. These activities provide clarity to industry, streamlining generic drug product development and review. ORS implements the GDUFA regulatory science initiatives program, which supports scientific research to develop pathways for complex generic drug products that lack competition. The office also evaluates the postapproval safety, product use, and BE of approved generic drugs.

Further, ORS supports the creation of guidances for industry about developing complex generic drug products such as drug-device combination and modified-release drug products. Interactions with potential generic drug applicants or developers may include pre-ANDA meetings and controlled correspondence regarding their individual product development.

FDA's Generic Drug Program

OGD is the primary contact for those submitting ANDAs. OGD benefits from and relies on the efforts of many FDA offices, including:

Center for Biologics Evaluation and Research

Center for Devices and Radiological Health

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 Regulatory Policy
- Office of Strategic Programs
- Office of Surveillance and Epidemiology
- Office of Translational Sciences

Office of Chief Counsel

Office of the Commissioner

Office of Regulatory Affairs

Appendix

Regulatory Guidances Issued in 2018

In 2018, FDA issued the following regulatory guidances related to generic drugs:

Draft Guidances:⁷

- [*Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*](#), January 2018
- [*Good ANDA Submission Practices*](#), January 2018
- [*Development of a Shared System REMS \(led by the Office of Regulatory Policy\)*](#), June 2018
- [*Waivers of the Single, Shared System REMS Requirement \(led by the Office of Regulatory Policy\)*](#), June 2018
- [*Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs Guidance for Industry*](#), October 2018
- [*Assessing Adhesion with Transdermal Delivery Systems and Topical Patches for ANDAs Draft Guidance for Industry*](#), October 2018
- [*Citizen Petitions and Petitions for Stay of Action Subject to Section 505\(q\) of the Federal Food, Drug, and Cosmetic Act \(led by the Office of Regulatory Policy\)*](#), October 2018

Final Guidances:

- [*Elemental Impurities in Drug Products \(led by the Office of Regulatory Policy\)*](#), August 2018
- [*ANDA Submissions – Amendments to Abbreviated New Drug Applications Under GDUFA*](#), July 2018
- [*ANDA Submissions – Content and Format of Abbreviated New Drug Applications*](#), September 2018
- [*Post-Complete Response Letter Meetings Between FDA and ANDA Applicants Under GDUFA*](#), December 2018

Manuals of Policies and Procedures (MAPPs)

In 2018, OGD issued the following MAPPs:

- MAPP 5241.3, [*Good Abbreviated New Drug Application Assessment Practices*](#), January 2018
- MAPP 5240.5 (Rev.1), [*ANDA Suitability Petitions*](#), August 2018

7. When final, these guidances will represent the FDA's current thinking on these topics.

Resources

- **Activities Report of the Generic Drug Program**
<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm584749.htm>
- **CDER Small Business and Industry Assistance**
<https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm299560.htm>
- **First Generic Drug Approvals**
<https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/andagenericdrugapprovals/default.htm>
- **Generic Drugs Web Pages**
<https://www.fda.gov/GenericDrugs>
- **Generic Drug User Fee Amendments**
<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>
- **GDUFA II Commitment Letter**
<https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/ucm525234.pdf>
- **GDUFA II Features Videos**
<https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm580458.htm>
- **GDUFA Regulatory Science**
<https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm>
- **Guidances and MAPPs Related to the Generic Drug User Fee Amendments**
<https://www.fda.gov/forindustry/userfees/genericdruguserfees/ucm316678.htm>
- **Meetings about Complex Generics:**
 - Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development:
<https://www.fda.gov/Drugs/NewsEvents/ucm554182.htm>
 - Topical Dermatological Generic Drug Products:
<https://www.fda.gov/Drugs/NewsEvents/ucm557252.htm>
 - Demonstrating Equivalence of Generic Complex Drug Substances and Formulations:
<https://www.fda.gov/Drugs/NewsEvents/ucm552461.htm>
- **Orange Book:**
<https://www.fda.gov/drugs/informationondrugs/ucm129662.htm>

We Welcome Your Feedback

OGD welcomes feedback from stakeholders and the public.
We will continue to communicate with industry as
we work to meet GDUFA II goals.

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