

OFFICE OF GENERIC DRUGS

2017 ANNUAL REPORT

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



FDA Office of Generic Drugs 2017 at a Glance¹

- 2017 marked the highest number of combined generic drug approvals and tentative approvals in the history of the FDA's generic drug program—1,027
- Issued approvals for first generic versions of commonly used drugs including Strattera, Truvada, Coreg CR, and Vytorin
- Met and exceeded the goals and commitments of the Generic Drug User Fee Amendments of 2012 (GDUFA I)
- Negotiated the Generic Drug User Fee Amendments of 2017 (GDUFA II), which continues GDUFA for five more years
- Held four public meetings on the development of generic drugs, including complex generic drug products
- Published 178 product-specific guidances and 17 general guidances for industry related to generic drug development
- Awarded 46 new grants and contracts for generic drug development research in support of GDUFA I's regulatory science priorities that will complement FDA's research efforts
- Supported 73 ongoing external research collaborations
- Verified the validity of FDA's bioequivalence standards for certain drugs through scientific studies, confirming the proven efficacy and safety of generic drugs

¹ Regulatory Science Priorities available at: <https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm526900.pdf>

Director's Message

Welcome to the 2017 Annual Report of the Office of Generic Drugs (OGD) in the U.S. Food and Drug Administration (FDA). In 2017, FDA approved 843 abbreviated new drug applications (ANDAs) and tentatively approved 184 ANDAs. These numbers exceed the record-setting number of applications approved or tentatively approved in 2016. Making more high quality, affordable generic drugs accessible to the American people is a win for public health.

OGD marked significant milestones in 2017, including successfully completing the inaugural five years of the generic drug user fee program through the first iteration of the Generic Drug User Fee Amendments of 2012 (GDUFA I). Beginning in fiscal year 2012, user fees paid to the FDA by industry fortified the Agency with the resources necessary for it to review and approve applications for generic drugs in a timely and predictable way. Through this report, we are proud to share data that demonstrates OGD's commitment to meeting or exceeding GDUFA I goals and to continue under GDUFA II to communicate our progress toward enhancing our efficiency and expediting the review and approval of generic drug applications.

The success of the generic drug program is due in large part to the generic drug user fee program and to the dedicated staff that make up FDA's generic drug program. In 2017, OGD's 470 staff members worked with our Agency counterparts to meet and exceed the commitments of GDUFA I, while standing up and preparing to implement GDUFA II. At the end of FY 2017, Congress reauthorized the generic drug user fee program for another five years, and OGD is off to a robust start with implementing the new goals and commitments of GDUFA II.²

The FDA Commissioner, Dr. Scott Gottlieb, made generic drugs and drug pricing an agency priority by introducing the Drug Competition Action Plan³ (DCAP) and by emphasizing the critical value of generic drugs to public health. In OGD, we are energized by this enhanced focus on generic drugs and the momentum of this plan.



Kathleen Uhl, MD
Director, Office of Generic Drugs

² New goals and commitments of GDUFA II in GDUFA II Commitment letter: <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>

³ Dr. Gottlieb's introduction to the Drug Competition Action Plan (DCAP): <https://blogs.fda.gov/fdavoice/index.php/2017/06/fda-working-to-lift-barriers-to-generic-drug-competition/>

At the end of FY 2017, Congress reauthorized the generic drug user fee program for another five years, and OGD is off to a robust start implementing the new goals and commitments of GDUFA II.

A cornerstone of DCAP is its focus on generic drug competition. Medicines become more affordable through competition when multiple generic versions of brand-name drugs are available to patients. OGD approved 80 first generic drugs in 2017. Considered a public health priority, FDA prioritizes reviews of applications for first generics, which open the market to generic competition. DCAP recognizes the market value in having three generics approved and prioritizes OGD's review of applications up to the third approval.

OGD also used innovative approaches for evaluating the equivalence of drugs and tools that support generic drug development geared to make generic drugs available for all drugs. Complex dosage forms, such as some inhaled generic versions, injectables, and topical medications, are increasingly in demand and generally more difficult to develop. As always, we considered input from industry and other stakeholders in the annual list of FDA's regulatory science priorities.⁴ Through these and other efforts, OGD assisted applicants with important tools to facilitate developing generic versions of brand-name medications.

In all, 2017 was the most productive and successful year of our generic drug program to date. We look forward to continuing our critical role with industry, the research community, lawmakers, patients, health care providers, and other stakeholders in the United States and around the world to increase access to affordable, high quality generic drugs.

Kathleen Uhl, MD

Director, Office of Generic Drugs

⁴ FDA's regulatory science priorities: <https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm>

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Fortifying the U.S. Generic Drug Program

In 2017, FDA marked the final year of the first iteration of user fees for generic drugs—the Generic Drug User Fee Amendments of 2012 (GDUFA I)—and the start of the reauthorized generic drug user fee program—the Generic Drug User Fee Amendments of 2017 (GDUFA II). Under GDUFA, FDA committed to performance goals, and industry agreed to pay user fees each year it is involved in the program.

The GDUFA *performance goals* include time frames within which FDA has committed to take a first action on an abbreviated new drug application (ANDA), an amendment to an ANDA, and prior approval supplements (PASs), which are post-approval changes requiring a supplemental submission and approval. The Agency meets these time frames by 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 that identifies deficiencies in an application that will prevent FDA from granting an approval and then communicating these deficiencies to the applicant in a complete response letter, or
4. making a “refuse-to-receive” decision because the ANDA is not sufficiently complete to permit a substantive review.

The **GDUFA II Commitment Letter**⁵ explains the specifics of the GDUFA II agreement.

FDA has met or exceeded all GDUFA I commitments to date. In 2017, FDA approved 427 PASs, and communicated with industry through more than 4,500 information requests and more than 1,900 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 of more than 2,700 controlled correspondence letters (FDA's answers to product development questions) in 2017, up from 1,800 in 2016.

Table 1. Major GDUFA I 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 amendments	12 months	60%	75%	90%
Prior Approval Supplements	6 months*	60%	75%	90%
ANDA teleconference requests completed		200	250	300
Controlled correspondence+	2 months	70%^	70%	90%
ANDAs, amendments, and PASs with FDA prior to Oct 1, 2012	Act on 90% by the end of FY2017			

Note: "Performance goals" in the title of the table means that FDA should take a first action (as defined above) on a certain percent of applications, etc., within the time frames listed; it does not mean that FDA should approve applications, etc., within these time frames. For definitions of the Tier amendments, please see the GDUFA I Commitment Letter⁶.

FY means fiscal year.

+ These controlled correspondence numbers are based only on the controlled correspondence that FDA received that did not require input from an applicable clinical division.

* (or 10 months if an inspection was required)

^ (within 4 months)

~ (within 10 months)

⁵ GDUFA II Commitment Letter: <https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm>

⁶ GDUFA I Commitment Letter: <https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm>



Guidances, Policies, and Procedures

Product-Specific Guidances

In 2017, OGD issued 178 new product-specific guidances for industry. Many of these documents focused on complex dosage forms, such as auto-injectors, inhalation powders, nasal sprays, topical products, and ophthalmic products.

OGD issues product-specific guidances to facilitate the efficient premarket development, successful filing, and substantive review of generic drug products. The recommendations in these guidances describe the Agency's current thinking and expectations on the development of a specific drug and consider the unique features of the reference listed drug that should be incorporated into a generic version of that drug.

OGD develops product-specific guidances soon after brand-name drugs are approved. These guidances help to ensure that industry has clarity in the Agency's expectations as they develop generic versions, so that patients have access to a generic drug at the earliest possible opportunity. OGD also develops and issues product-specific guidances based on requests from industry and public health priorities. An OGD working group reviews requests for product-specific guidances and makes recommendations to industry to meet current and anticipated patient and industry needs. Requests related to product-specific guidances can be sent to GenericDrugs@fda.hhs.gov.⁷

OGD revises existing product-specific guidances as new information or scientific methodology becomes available. This year, OGD revised 54 product-specific guidances. These revised draft guidances

⁷ Contact information for the Generic Drug mailbox: GenericDrugs@fda.hhs.gov

incorporate an examination of emerging postmarket reports of adverse events with the reference listed drug, an analysis of new studies, a review of relevant literature, and an examination of reports of therapeutic inequivalence in approved ANDAs. As of December 2017, about 1,600 product-specific guidances are posted on FDA's website at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>.⁸

Guidances

FDA publishes regulatory guidances to share the Agency's current thinking and recommendations to industry on specific topics, including generic drug development, regulatory review, and ANDA approval processes. In 2017, OGD published 17 regulatory draft and final guidances, including several that were intended to facilitate the development of complex generic drug products, such as the draft guidances for industry: *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*^{9, 10} and *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*^{11, 12}, and the guidance for industry *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*¹³.

All guidances issued in 2017 appear in Appendix for Regulatory Guidances, page 20.

Manuals of Policies and Procedures

A Manual of Policies and Procedures (MAPP) documents internal FDA 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.

All MAPPs issued in 2017 appear in Appendix for Manual of Policies and Procedures (MAPP), page 21.

Drug Competition Action Plan

Concerned that many consumers are being priced out of the medicines they need, FDA Commissioner Scott Gottlieb introduced the Drug Competition Action Plan (DCAP) soon after he arrived at the FDA. To implement the Commissioner's plan, OGD took several steps to increase competition for prescription drugs and facilitate entry of low-cost alternatives to the market. In June, OGD published a list of off-patent, off-exclusivity branded drugs without approved generics. We maintain this list to improve transparency and encourage the development and submission of ANDAs in markets with limited competition.

We updated the list in December. In the update, we modified the methodology used to compile the first edition of the list to reflect that the list is now based on drug products, not active ingredients. OGD also implemented policies to

⁸ Product-Specific Guidances for Generic Drug Development: <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>

⁹ Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578366.pdf>

¹⁰ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹¹ ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf>

¹² When final, this guidance will represent the FDA's current thinking on this topic.

¹³ General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf>

In 2017, OGD delivered 47 product-specific guidances on the development of complex generic drug products.

expedite the review of greater numbers of generic drug applications when competition is limited. For example, we revised the generic drug review prioritization MAPP to prioritize review of generic drug applications until there are three generics approved for a brand product. DCAP's established priorities ensure we maximize our ability to balance the goals of the Hatch-Waxman Amendments¹⁴ to incentivize new drug innovation and facilitate the generic drug access that Congress intended.

One of our GDUFA II commitments is to enhance development and review of ANDAs for complex generic drug products, which can require more review cycles. Through the publication of the draft guidances for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*¹⁵ and *Submission of ANDAs for Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*,^{16, 17} and the guidance for industry *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*,¹⁸ we have provided additional information and assistance to ANDA applicants. We held three public meetings in October and issued 47 product-specific guidances on the development of complex generic drug products.

The next phases of DCAP include critically reviewing our Hatch-Waxman implementation and soliciting input on places where FDA's regulations—including the standards and procedures related to generic drug approvals—are being used in ways that may create obstacles to generic access, instead of ensuring the vigorous competition Congress intended. On July 18, 2017, OGD held a meeting titled "Administering the Hatch-Waxman Amendments: Ensuring a Balance between Innovation and Access." The Agency is considering comments submitted to the public docket that closed in November 2017.

14 Public Law 98-417.

15 Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA: <https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm578366.pdf>

16 Submission of ANDAs for Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin: <https://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm578365.pdf>

17 When final, this guidance will represent the FDA's current thinking on this topic.

18 General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: <https://www.fda.gov/downloads/Drugs/Guidance/ComplianceRegulatoryInformation/Guidances/UCM492172.pdf>



Enhancing Communication with Industry and Stakeholders

Communicating the results of regulatory science to external stakeholders and implementing these standards in ANDA review provides transparency and clarity to industry, which improves the generic drug program.

This year, CDER continued its communication with the generic drug industry and other stakeholders through public events, webinars, workshops, and meetings.

Communicating the results of regulatory science to external stakeholders and implementing standards in ANDA review provides transparency and clarity to industry.

Meetings:

- Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting¹⁹
- The annual Regulatory Education for Industry (REdI): Generic Drugs Forum²⁰, where FDA subject matter experts presented and discussed with industry the best ways to communicate with the Agency, current trends in labeling and best practices, and the regulatory science of the generic drug user fee program
- The fall technical conference of the Association for Accessible Medicines²¹, where FDA staff presented and discussed the generic drug program and GDUFA
- Generic Drug Research Public Workshop²², where FDA staff obtained input from industry and other interested stakeholders on the identification of regulatory science priorities
- FDA public workshops on the development of complex generic products including, Demonstrating Equivalence of Generic Complex Drug Substances and Formulations,²³ Topical Dermatological Generic Drug

¹⁹ Pharmaceutical Science and Clinical Pharmacology Advisory Committee Meeting: <https://www.fda.gov/AdvisoryCommittees/Calendar/ucm535513.htm>

²⁰ Regulatory Education for Industry (REdI): Generic Drugs Forum: <https://www.fda.gov/AdvisoryCommittees/Calendar/ucm535513.htm>

²¹ Fall technical conference of the Association for Accessible Medicines: <https://www.accessiblemeds.org/FallTech2017>

²² Generic Drug Research Public Workshop information available at: <https://www.fda.gov/Drugs/NewsEvents/ucm527823.htm>

²³ Demonstrating Equivalence of Generic Complex Drug Substances and Formulations: <https://www.fda.gov/drugs/newsevents/ucm552461.htm>

Products: Overcoming Barriers to Development and Improving Patient Access,²⁴ and Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review²⁵

- FDA public meeting on Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access²⁶
- The American Association of Pharmaceutical Scientists (AAPS) Annual Meeting²⁷ where Office of Bioequivalence and Office of Research and Standards staff presented oral and poster publications

Resources:

- Industry updates, such as the Center for Drug Evaluation and Research's Small Business & Industry Assistance newsletter (the SBIA Chronicles²⁸) and listserv (Small Biz Buzz²⁹), as well as two generic drug listservs (for generic drug user fee-specific updates and general generic drug updates)³⁰
- A *CDER Conversation* with OGD's Capt. Martin Shimer that explains the regulatory implications of patents and exclusivities on generic drug approvals³¹
- A video from OGD's Kimberly Witzmann that highlighted regulatory science related to generic inhalation drugs³²
- A public outreach campaign to educate patients about the benefits of generic drugs,³³ including website updates at www.fda.gov/GenericDrugs
- Enhanced monthly and quarterly activities reporting in GDUFA II,³⁴ including metrics such as the types of complete response letters issued, the number of first cycle approvals, among others
- New and updated Generic Drug User Fee Amendments (GDUFA) web pages³⁵
- Monthly updates to the Activities Report of the Generic Drugs Program Monthly Performance³⁶
- Brief videos for industry by FDA staff highlighting new features of GDUFA II.³⁷

24 Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access: <https://www.fda.gov/Drugs/NewsEvents/ucm557252.htm>

25 Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review: <https://www.fda.gov/Drugs/NewsEvents/ucm554182.htm>

26 Administering the Hatch-Waxman Amendments: Ensuring a Balance Between Innovation and Access: <https://www.fda.gov/Drugs/NewsEvents/ucm563986.htm>

27 American Association of Pharmaceutical Scientists (AAPS) Annual Meeting available at: <https://annual.aapsmeeting.org/>

28 SBIA Chronicles: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm299560.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

29 Small Biz Buzz: <https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm270887.htm>

30 Generic Drugs Listservs: <https://www.fda.gov/aboutfda/contactfda/stayinformed/getemailupdates/default.htm>

31 CDER Conversation: Patents and Exclusivities for Generic Drug Products: <https://www.fda.gov/Drugs/NewsEvents/ucm577114.htm>

32 Video from OGD's Kimberly Witzmann highlighting regulatory science related to generic inhalation drugs: <https://www.fda.gov/Drugs/ScienceResearch/ucm580348.htm>

33 A public outreach campaign to educate patients about the benefits of generic drugs, including website updates: <https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/default.htm>

34 Activities Report of the Generic Drug Program (FY 2017): <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm584749.htm>

35 New and updated generic drug user fee amendment web pages: <https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>

36 Monthly updates to the Activities Report of the Generic Drugs Program Monthly Performance: <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm584749.htm>

37 Brief videos for industry by FDA staff highlighting new features of GDUFA II: <https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm580458.htm>

Approvals and Other Regulatory Actions

FDA considers the approval of the first generic of a brand drug to be a public health priority and expedites review of these submissions. (A list of noteworthy first generic drugs approved in 2017 is provided in the resources section of the appendix, page 22.)

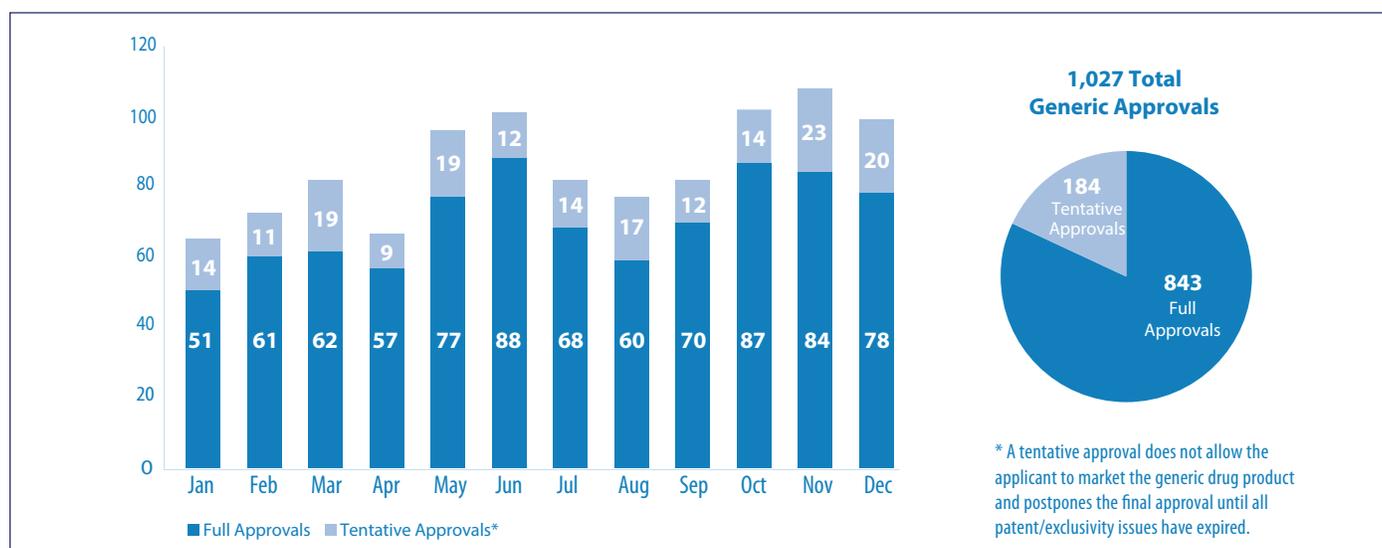
Table 2. Significant First Generic Drug Approvals in 2017

Generic	Brand-name	Indications (Abbreviated)
Atomoxetine Capsules	Strattera	Treatment of attention deficit hyperactivity disorder
Emtricitabine and Tenofovir Disoproxil Fumarate Tablets	Truvada	Treatment of HIV and for pre-exposure prophylaxis
Ezetimibe and Simvastatin Tablets	Vytorin	Management of high cholesterol
Mesalamine Delayed-release Tablets	Asacol HD	Treatment of moderately active ulcerative colitis
Prasugrel Tablets	Effient	Blood thinner
Sevelamer Carbonate Tablets	Renvela	Control of serum phosphorus levels in adults with chronic kidney disease

The Agency approved or tentatively approved 1,027 generic drugs during 2017—more than any other year in the history of the generic drug program.

OGD maintains a complete list of first generic approvals,³⁸ which can be accessed via the OGD web page.³⁹ For full indication information, please check the Drugs@FDA online database.⁴⁰

Table 3. 2017 Generic Drugs Approved



38 List of first generic approvals: <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/andagenericdrugapprovals/default.htm>

39 OGD web page: <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm119100.htm>

40 Drugs@FDA database: <https://www.accessdata.fda.gov/scripts/cder/daf/>



2017 Regulatory Science Research

The results of OGD's GDUFA regulatory science research provide tools for industry to develop new generic drug products and for FDA to evaluate the equivalence of a proposed generic drug.

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 May 2017, FDA held a public workshop on GDUFA regulatory science priorities, at which the Agency reported on the status of the GDUFA I regulatory science program and developed the FY 2018 GDUFA II regulatory science plan.⁴¹

FDA awarded funding for seven new contracts and for 39 ongoing grants and contracts to conduct regulatory science research. OGD had 73 ongoing external research collaborations at the end of 2017 because many projects that had been awarded in previous years continued into 2017.

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

- 1. Postmarket evaluation and patient perceptions of generic drugs**—FDA provides funding for research into monitoring methods, understanding patient perceptions of generic drugs,

⁴¹ FY 2018 GDUFA II regulatory science plan: <https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM582777.pdf>

and verifying the therapeutic equivalence of generic drugs via patient brand-to-generic switching studies. This research provides additional data in therapeutic areas where concerns exist about the substitutability of generic drugs and allows FDA to verify generic drug substitutability. In 2017, FDA awarded funding for continuing grants and contracts to assess the therapeutic interchangeability between brand-name and generic drug products in specific patient populations and to analyze the impact of product-level, patient-level, and provider-level factors on generic drug substitution.

- 2. Equivalence methods for complex drug products**—FDA provides funding for research into making generic versions available for all drug products, including complex drugs with unique characteristics. This research supports the development of guidance and policy that clarifies the ANDA pathway for complex products, such as drug-device combinations, transdermal systems, and products that contain complex mixtures and peptides. In 2017, FDA awarded funding for continuing grants and contracts that will compare physicochemical product quality and performance attributes of ointments, identify different types of polymers used as a mixture in long-acting drug products, and develop analytical methods to profile complex drugs in urine. In addition, FDA granted new awards in 2017 to investigate the in vitro-in vivo correlations of long-acting injectable suspensions and to develop analytical methods to characterize star-shaped polyesters.
- 3. Equivalence of locally acting products**—FDA provides funding for research into new bioequivalence (BE) methods and pathways for locally acting drug products, such as inhaled, ophthalmic, or gastrointestinal drug products. This research is needed because of a lack of sensitive BE methods for these locally acting drug products. This research priority includes evaluating in vitro alternatives to comparative clinical endpoint BE studies. Additionally, in 2017 FDA awarded funding for continuing grants and contracts to evaluate the pharmacokinetic profiles of dry powder inhalers, assess the differences in response among individuals of small airway delivery for orally inhaled drug products, and assess the dermal pharmacokinetics by microdialysis and microperfusion techniques. In addition, FDA granted new awards to investigate the microstructure of dry powder inhaler formulations, investigate orthogonal analytical approaches to demonstrate the BE of nasal suspension formulations, and develop a method to evaluate patient perceptions of dry powder inhaler airflow resistance.

In 2017, GDUFA I funded more than \$20 million in research programs.

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

FDA continues to prioritize research into abuse-deterrent formulations, narrow therapeutic index drugs, and the equivalence of modified-release solid oral dosage forms. In 2017, FDA awarded funding for continuing grants and contracts to develop a mechanism-based absorption model to predict pharmacokinetic profiles of supersaturating formulations and evaluate the formulation dependence of drug interactions with proton pump inhibitors for oral modified-release products. In addition, FDA made a new award to investigate the precipitation behavior and kinetics for water-insoluble drugs and these drugs' impact on oral absorption.

5. **Cross-cutting computational and analytical tools**—FDA provides funding for research that is 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 pharmacodynamic models or clinical trial simulation, systems biology, and quantitative risk modeling. In 2017, FDA awarded funding for continuing grants and contracts to evaluate model-based BE statistical approaches for sparse design pharmacokinetic studies and to develop an algorithm for population-based statistical analysis in physiologically based pharmacokinetic models. In addition, FDA granted a new award to develop population model-based nonlinear mixed-effects models that can be used for sparse pharmacokinetic study designs.

In 2017, GDUFA I funded more than \$20 million in regulatory science research programs. In keeping with FDA's commitment to promote quality science and clinical relevance, FDA staff or external collaborators published 25 peer-reviewed scholarly articles and book chapters, presented 76 external talks, and exhibited 52 posters at national and international scientific and medical conferences. In the five years of GDUFA I, FDA staff or external collaborators published more than 170 peer-reviewed scholarly articles and book chapters and presented more than 250 external talks and 350 posters at national and international scientific and medical conferences.

Significant 2017 Research Accomplishments

FDA staff and external collaborators from the University of Connecticut published two papers on the investigation of the physicochemical properties⁴² of and in vitro release testing methods⁴³ for ophthalmic ointment formulations that had the same composition but were made by different manufacturing processes. The results demonstrated that differences in the manufacturing process and source of petrolatum had a significant influence on both the physicochemical attributes and the in vitro drug release profiles. In addition, these results indicate that differences in manufacturing and excipient sources may impact the in vitro performance and potentially influence the in vivo performance of ophthalmic ointments. Another significant project involving FDA staff and external collaborators from the University of Florida used semi-mechanistic simulation approaches to predict the systemic pharmacokinetics of inhaled corticosteroids delivered via dry powder inhalers.⁴⁴ In one of the simulation approaches used, predictions were made from using the pulmonary absorption rate estimated from in vitro studies without the need for actual pharmacokinetic information. These simulation approaches provide better understanding of drug product performance and mechanisms of drug deposition in the lung, and therefore can be helpful during drug product development.

In addition, OGD published a draft guidance for industry titled, ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin on October 1, 2017.^{45, 46} This guidance reflects the work that OGD has conducted through research with internal FDA laboratories and external collaborators on peptide drug products. The guidance outlines information to help determine when an application for a synthetic peptide drug product that refers to a previously approved peptide drug product of recombinant origin via an ANDA should be submitted as an ANDA.

OGD published a draft guidance for industry entitled “General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products”^{47, 48} on November 22, 2017. This draft guidance provides recommendations for companies seeking to submit an ANDA for a product with abuse-deterrent labeling. The guidance recommends studies, such as comparative in vitro and pharmacokinetic studies, that ANDA applicant should conduct and submit in support of their ANDA to show that it is no less abuse deterrent than the reference listed drug for all potential routes of abuse.

42 Bao Q, Jog R, Shen J, Newman B, Wang Y, Choi S, and Burgess DJ, 2017, Physicochemical Attributes and Dissolution Testing of Ophthalmic Ointments, 523(1):310–319.

43 Bao Q, Shen J, Jog R, Zhang C, Newman B, Wang Y, Choi S, and Burgess DJ, 2017, In Vitro Release Testing Method Development for Ophthalmic Ointments, Int J Pharm, 526(1-2):145–156.

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45 ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin: <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578365.pdf>

46 When final, this guidance will represent the FDA's current thinking on this topic. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578365.pdf>

47 General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf>

48 When final, this guidance will represent the FDA's current thinking on this topic. <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM492172.pdf>

The Office of Generic Drugs (OGD)

OGD comprises an immediate office and four subordinate offices. OGD hired approximately 125 new employees in 2017, bringing the total number of OGD employees to 470.

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.

OGD comprises an immediate office and four subordinate offices. OGD hired approximately 125 new employees in 2017, bringing the total number of OGD employees to 470.

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 divisions of bioequivalence within the Office of Bioequivalence evaluate formulations for quantitative and qualitative equivalence and review 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 the 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 publication⁴⁹ (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.

⁴⁹ Approved Drug Products with Therapeutic Equivalence Evaluations: <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>

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 PASs, and amendments meet established quality standards for filing and labeling. ORO oversees the review of ANDAs across all disciplines to ensure that OGD meets the generic drug user fee program's 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 (ORS)

The Office of Research and Standards 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. This provides clarity to industry, streamlining generic drug product development and review. ORS implements the generic drug user fee regulatory science program, which supports scientific research to develop pathways for generic versions of complex reference products that lack competition. The office also evaluates the postapproval safety, product use, and BE of approved generic drugs.

Further, the Office of Research and Standards supports the creation of guidances for industry about developing generic forms of drug products without generic versions such as complex 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

In 2017, OGD issued the following regulatory guidances:

Draft Guidances:⁵⁰

- *180-Day Exclusivity: Questions and Answers*, January 2017
- *Referencing Approved Drug Products in ANDA Submissions*, January 2017
- *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, January 2017
- *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*, October 2017
- *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*, October 2017
- *ANDA Submissions—Refuse-to-Receive Standards: Questions and Answers*, October 2017
- *ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA*, October 2017
- *Requests for Reconsideration at the Division Level Under GDUFA*, October 2017
- *Determining Whether to Submit an ANDA or a 505(b)(2) Application*, October 2017

Manual of Policies and Procedures (MAPP)

In 2017, OGD issued the following MAPPs:

- MAPP 5240.3 (Rev. 3), *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*, June 2017
- MAPP 5210.4 (Rev. 2), *Review of Bioequivalence Studies with Clinical Endpoints in ANDAs*, June 2017
- MAPP 5200.14, *Filing Review of Abbreviated New Drug Applications*, September 2017
- MAPP 5220.3, *Communicating Certain Deficiencies Identified During Filing Review of*

- *Post-Complete Response Letter Meetings Between FDA and ANDA Applicants Under GDUFA*, October 2017
- *Controlled Correspondence Related to Generic Drug Development*, November 2017
- *ANDAs: Pre-Submission of Facility Information Related to Prioritized Generic Drug Applications*, (led by the Office of Pharmaceutical Quality), Revised November 2017
- *Information Requests and Discipline Review Letters Under GDUFA*, December 2017

Final Guidances:

- *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
- *ANDA Submissions—Prior Approval Supplements Under GDUFA*, October 2017
- *Completeness Assessments for Type II API DMFs Under GDUFA*, October 2017
- *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products*, November 2017

ANDAs, September 2017

- MAPP 5200.1, *Receiving and Processing a Request for Voluntary Withdrawal of an Approved ANDA*, October 2017
- MAPP 5200.12, *Communicating Abbreviated New Drug Application Review Status Updates with Industry*, October 2017
- MAPP 5240.3 (Rev.4), *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*, November 2017

⁵⁰ 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 Conversation: Patents and Exclusivities for Generic Drug Products with Capt. Martin Shimer:** <https://www.fda.gov/Drugs/NewsEvents/ucm577114.htm>
- **CDER Small Business and Industry Assistance:** <https://www.fda.gov/drugs/developmentapprovalprocess/smallbusinessassistance/ucm299560.htm>
- **FDA Voice Blog: Generic Drug User Fees Reauthorization: A Victory for Public Health: Reducing the Hurdles for Complex Generic Drug Development:** <https://blogs.fda.gov/fdavoices/index.php/2017/10/reducing-the-hurdles-for-complex-generic-drug-development/>
- **First Generic Drug Approvals:** <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/drugandbiologicapprovalreports/andagenericdrugapprovals/default.htm>
- **Generic Drugs:** <https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/default.htm>
- **Generic Drug User Fee Amendments (GDUFA):** <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>
- **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>



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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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