

OFFICE OF GENERIC DRUGS

2019 ANNUAL REPORT

Ensuring Access to Safe, Affordable, and
Effective Generic Drugs



Director's Message

Welcome to the 2019 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). I am happy to present OGD's fifth annual report and my first since joining OGD in early 2019.

Safe, effective, high-quality generic drugs play a vital role in the U.S. health care system. Affordable access to medicines is a public health priority, and competition from generic drugs can help reduce prices and improve access that benefits patients, consumers, and health care practitioners prescribing medicines.

As in past years, we're encouraged to see a strong pipeline of generic drug applications and continued interest in the development of complex generics and drugs with inadequate generic competition.

Our 2019 accomplishments include a total of more than 1,000 generic drug final and tentative approvals and our continued engagement efforts with industry helped ensure the generic drug program remained vibrant. But while these numbers indicate another accomplished year for the program, we know what truly matters is that our work results in more treatment choices and greater access to affordable medicines for patients.

This year, our approvals included 110 complex generic drugs — which are harder to develop and traditionally have lacked competition — and 107 applications for first generics of medicines that had no generic competition, including drugs to treat pulmonary arterial hypertension, breast cancer, seizures, depression, and various infections.

OGD also continued efforts under FDA's Drug Competition Action Plan (DCAP) and the Generic Drug User Fee Amendments (GDUFA) program to improve upon efficiencies in generic drug development, increase timeliness in assessment processes, provide more clarity in the science and regulation of complex generic drugs, and close loopholes that may allow delays in generic drug competition.

When FDA does the scientific work to identify the evidence needed to support approval in advance of abbreviated new drug application (ANDA) submissions, we provide ANDA applicants a clearer regulatory path to potential approval. In 2019, OGD continued proactively addressing scientific and regulatory challenges that can block competition for generic drugs.



Sally Choe, Ph.D.
Director, Office of Generic Drugs

Every approved generic drug potentially means more affordable treatment options for patients.

FDA's GDUFA regulatory science program also helps guide OGD recommendations and reflects our current scientific knowledge on how to ensure the development, assessment, and manufacture of high-quality generic drug products is based on modern scientific standards. GDUFA-funded research clears the path for new technologies and methodologies to help streamline complex generic drug development. GDUFA research informs our product-specific guidances and supports our advice and feedback to generic drug developers. We issued 274 draft and final guidances in 2019 including 269 product-specific guidances, to provide more regulatory clarity for generic drug development by giving companies clear scientific advice on how to generate the evidence needed to support approval. A key component of both DCAP and GDUFA is the resolution of scientific and regulatory obstacles that may make it difficult to obtain approval of generic drugs.

OGD worked with colleagues across CDER to educate and inform industry and other stakeholders about GDUFA and the generic drug program. We held public meetings and workshops on complex generic drug development, regulatory science initiatives, and regulatory guidances and processes. We also continued to leverage our international efforts, driving global harmonization on scientific and technical standards for generic drugs under the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). OGD's activities on the ICH Generic Drug Discussion Group resulted in ICH endorsement of the development of the first ever ICH guideline (M13) focusing on generic drugs.

In the coming year, we'll continue to take important steps to assist generic drug applicants with developing high-quality applications. We will also conduct more conferences and workshops on generic drug development to further engage with stakeholders and generic drug developers. In 2020, we will continue to do all that we can to increase access to generic medicines.

Sally Choe, Ph.D.
Director, Office of Generic Drugs

Table of Contents

Director’s Message.....	iii
Generic Drugs by the Numbers.....	2
Generic Drug Approvals	
<i>Table: 2019 Generic Drugs Approved and Tentatively Approved</i>	
First Generics	
<i>Chart: Significant First Generic Drug Approvals in 2019</i>	
Generic Drug User Fee Amendments	6
Creating Predictability and Timeliness in the Assessment of Generic Drugs	
GDUFA II: How We Did in 2019	
Approvals	
Communicating with Industry	
Supporting Complex Product Development	
Selected Accomplishments	8
What Our Commitment to Scientific Assessment of Complex Generics Means for the American Public	
The Importance of Our International Efforts	
<i>Spotlight: 35th Anniversary of the Hatch-Waxman Amendments</i>	
Monitoring and Evaluating to Ensure Generic Drugs are Safe, Effective, and High-Quality	9
Highlighted Postmarketing Safety Activities	
Communicating Our Safety Surveillance Results	
Policies that Support the Efficient Development of Safe, High-Quality, and Affordable Generic Drugs.....	10
Regulatory Guidance	
Manuals of Policies and Procedures (MAPPs)	
Generic Drugs: Competition Can Help Lower Prices	
Regulatory Science Research at OGD	14
How the Generic Drug Program’s Scientific Research Makes a Difference	
The Importance of Scientific Research for Complex Generic Drug Development	
Guidances and Recommendations Based on Scientific Research and Health Priorities	
How OGD-Funded Research Plays a Role in Ensuring Quality and Safety of Generic Drugs	
Selected Significant Research Accomplishments in 2019	
Communicating Regulatory Science Research Outcomes to Industry and Stakeholders	
Online Resources for Science and Research	
Thank You to Our Collaborators	20
Appendix.....	21
Regulatory Guidances	
Manual of Policies and Procedures	
Meetings and Workshops	
Webinars, Articles, Activities Reports	
Resources	23

Generic Drugs by the Numbers

FDA's Office of Generic Drugs (OGD) hailed many successes during calendar year 2019 (CY2019), the second year of FDA's implementation of reauthorization of the Generic Drug User Fee Amendments (GDUFA II), including:

1,014

Approved or tentatively approved Abbreviated New Drug Applications (ANDAs).

107

First generic drugs were approved, which provided access to needed therapies that treat a wide range of medical conditions where little or no competition has previously existed.

110

Complex generic drugs were approved totaling 11% of the generic drug product approvals in 2019.

269

Product-specific guidances (PSGs) were published along with 4 new or revised guidances for industry and 1 manual of policies and procedures (MAPP) for stakeholders.

2,311

Complete response letters were issued detailing important items that applicants needed to resolve before FDA could grant an approval.

3,274

Controlled correspondence inquiries, an important tool used to communicate with prospective generic drug applicants, were submitted by industry in 2019.

105

Pre-ANDA meeting requests to discuss product development and/or pre-submission issues were received in 2019.

2,311

Complete response letters were issued detailing important items that applicants needed to resolve before FDA could grant an approval.

More than 10,000

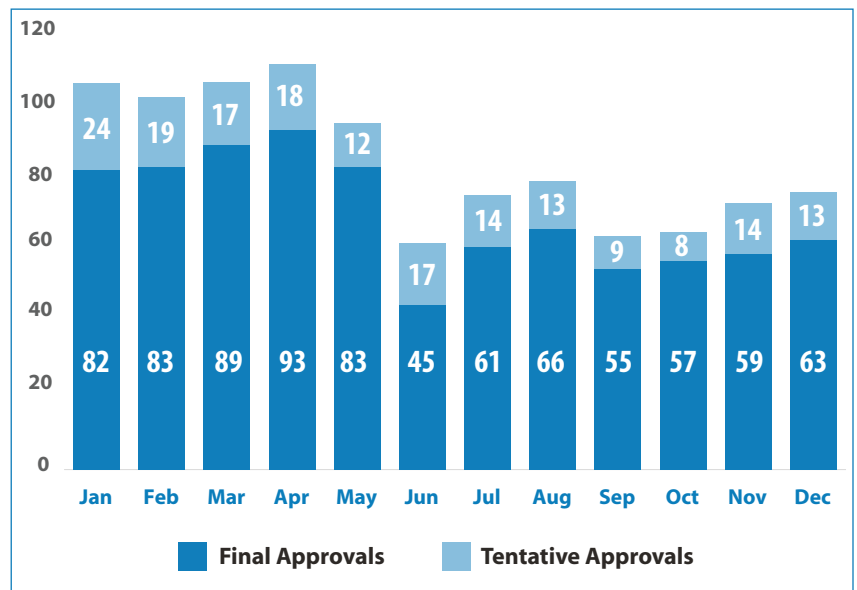
External stakeholders participated in six meetings and workshops held to educate and inform about GDUFA and the generic drug program. OGD worked collaboratively across the Center for Drug Evaluation and Research (CDER) on these meetings and workshops.



Generic Drug Approvals

As reported in an updated FDA study in December, greater competition among generic drug makers is associated with lower generic drug prices.¹ The impact of generic medicines to the consumer pocketbook is enormous — saving consumers more than a trillion dollars over the last decade.² In 2019, the generic drug program approved or tentatively approved 1,014 generic drug applications, known as Abbreviated New Drug Applications (ANDAs).

2019 Generic Drugs Approved and Tentatively* 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.

¹ <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/generic-competition-and-drug-prices>

² <https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers#q4>

First Generics

First generics provide access to needed therapies that treat a wide range of medical conditions and where little or no competition has previously existed. First generic approvals are particularly important to public health, and OGD prioritizes the review of these submissions.

Significant First Generic Drug Approvals in 2019*

Generic Drug Product	Brand Name	Indication of Use
Apixaban Tablets	Eliquis	Prevention of stroke and systemic embolism
Fingolimod Capsules	Gilenya	Treatment of relapsing forms of multiple sclerosis
Fluticasone and Salmeterol Inhalation Powder	Advair	Treatment of asthma, chronic obstructive pulmonary disease
Lurasidone Tablets	Latuda	Treatment of schizophrenia, bipolar disorder
Mesalamine Capsules	Delzicol	Treatment of ulcerative colitis
Micafungin Injection	Mycamine	Treatment of certain <i>Candida</i> infections
Naloxone Nasal Spray	Narcan	Emergency treatment of known or suspected opioid overdose
Nitisinone Capsules	Orfadin	Treatment of hereditary tyrosinemia type 1
Pregabalin Capsules	Lyrica	Treatment of neuropathic pain, fibromyalgia, seizures, postherpetic neuralgia
Vigabatrin Tablets	Sabril	Treatment of refractory complex partial seizures
Vilazodone Tablets	Viiibryd	Treatment of major depressive disorder

*Due to space limitations, abbreviated indications are listed. For full indication information, please check Drugs@FDA.



Generic Drug User Fee Amendments

CREATING PREDICTABILITY AND TIMELINESS IN THE ASSESSMENT OF GENERIC DRUGS

In 2012, following negotiations between FDA and industry, with input from public stakeholders, Congress enacted the Generic Drug User Fee Amendments (GDUFA). GDUFA enables FDA to assess industry user fees and to bring greater predictability and timeliness to the assessment of generic drug applications, with the goal of ensuring timely patient access to safe, effective, and high-quality generic drugs.

In 2019, FDA and the pharmaceutical industry entered their second year of the reauthorized generic drug user fee program, the Generic Drug User Fee Amendments of 2017 (GDUFA II). The GDUFA II performance goals include time frames within which FDA will take first action on an ANDA, an amendment to an ANDA, prior approval supplements (PASs) for post-approval changes requiring a supplemental submission and approval, and amendments to PASs. The [GDUFA II Commitment Letter](#)³ outlines the performance goals and program enhancements specified in the GDUFA II agreement.

The generic drug program has strengthened and diversified the pipeline of generic drug applications by building a robust development pathway that includes support to developers of complex generic drug products. While the pipeline numbers ebb and flow from year to year based on the generic drug applications submitted to the agency, Americans can be sure that we are ready to meet the challenges that come our way. The result is a thriving generics market that makes a difference in medicine availability and affordability for many patients.

GDUFA II: How We Did in 2019

Overall, OGD made significant progress toward its goals of improving the first-cycle approval rate and increasing access to generic drugs for patients. OGD continued to meet or exceed almost all the many required time frames it committed to accomplish.

³ The GDUFA II Commitment Letter can be found online at: <https://www.fda.gov/media/101052/download>

Approvals

In addition to our 1,014 approvals and tentative approvals, we approved or tentatively approved 786 prior approval supplements submissions.

Communicating with Industry

We extensively communicated with industry through 3,969 information requests (IRs), 2,890 Discipline Review Letters (DRLs), and 2,311 complete response letters (CRLs). These requests and letters detail important issues that need to be addressed by applicants before FDA can approve an application.

An important tool used to communicate with prospective generic drug applicants is controlled correspondence. A controlled correspondence inquiry is submitted to the agency by (or on behalf of) a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development. The staff that responds to controlled correspondence is the same review staff that is part of the assessment process. The opportunity for industry to submit controlled correspondence supports the development and submission of higher quality generic drug applications. In 2019, the Office of Generic Drugs responded to 3,274 controlled correspondence inquiries submitted by industry.

SUPPORTING COMPLEX PRODUCT DEVELOPMENT

GDUFA II includes important features that further modernize the generic drug program. For example, under GDUFA II, certain applications may be eligible for a shorter review time, including some applications for products that are on FDA's drug shortage list at the time of ANDA submission. Our GDUFA II commitment also introduced a formal pre-ANDA program designed to support the development of complex generic drug products.

The formal pre-ANDA program features meetings between FDA and prospective applicants at various stages of drug development to address three key goals:

- Help clarify regulatory expectations early in product development,
- Assist prospective applicants to develop more complete applications, and
- Reduce the number of review cycles required to obtain approval.

These types of meetings can help clarify regulatory expectations for prospective applicants early in a generic drug's development cycle and can assist them in developing more complete application submissions, which in turn can help them reduce their time in the pipeline from concept to development to market. In 2019, FDA received 105 product development and pre-submission pre-ANDA meeting requests.

Spotlight: 35th Anniversary of the Hatch-Waxman Amendments

In 2019, FDA marked the 35th anniversary of the [Drug Price Competition and Patent Term Restoration Act of 1984](#), also known as the Hatch-Waxman Amendments. These amendments established the modern-day approval pathway for generic drugs. When the Hatch-Waxman Amendments were enacted 35 years ago, generic drugs accounted for only 19% of all prescription drugs dispensed in the United States. Due to FDA's actions and policies advanced under the Hatch-Waxman Amendments along with the [Generic Drug User Fee Amendments](#) (GDUFA), today, almost 90% of prescriptions are filled with generic drugs.

When FDA announced approval of the first generic Advair Diskus (a complex generic drug-device combination product) in January 2019, OGD heard heartfelt remarks from people who were now able to afford their asthma medication. One such comment relayed:

“Thank you so very, very much for this — you have no idea how this generic brand will change the lives of untold numbers of people who were struggling to pay for their asthma medicine...

I paid \$398.96 for my inhaler back in January, and today, when the cashier at the pharmacy told me that my total was only \$188.65, I almost broke down in tears! ...

Again, thank you from the bottom of my heart!”

— anonymous patient

Selected Accomplishments

What Our Commitment to the Scientific Assessment of Complex Generics Means for the American Public

Generic drug-device combination products are products that have a drug component and a device component, often to deliver the drug. FDA specially assesses these products to ensure that users would not need re-training to use the proposed generic product. This often-complex endeavor is supported by agency scientists from many different fields. For example, in 2000, FDA approved the brand-name dry powder inhaler ADVAIR (Fluticasone Propionate/Salmeterol Xinafoate) to treat asthma and COPD (Chronic Obstructive Pulmonary Disease). Asthma affects approximately 25 million children and adults in the US, and COPD affects at least 16 million adults. Advair was the only dry powder inhaler combination product available for many years, and its manufacturer averaged about \$5 billion a year in revenue for this one treatment. Because it is a combination of two drugs administered by an inhaler (the device component), it is a very complex product to copy. We worked diligently to address many questions about sameness and substitutability and were able to approve the first generic inhaler product, Fluticasone Propionate/Salmeterol Xinafoate Inhalation Powder, in January 2019.

The Importance of Our International Efforts

In 2019, OGD’s Global Affairs Team successfully led the effort to have a generic drug topic proposal on “Bioequivalence (BE) for Immediate-Release (IR) Solid Oral Dosage Forms” endorsed by the International Council for Harmonisation (ICH) Management Committee (MC). The ICH-MC endorsement will lead to the development of the first ever ICH guideline (M13) focusing on generic drugs. In addition, the ICH M9 Guideline and Q&As on Biopharmaceutics Classification System (BCS)-based biowaivers was finalized in November 2019 and is ready for ICH regulatory member adoption. The outcome of these harmonization efforts would reduce the costs and time of product development, and ultimately enhance the quality, approvability, and affordability of generic drug applications with international components of development, study, and manufacture. This change would accelerate access to affordable, safe, effective, and high-quality medicines for the American public.



Monitoring and Evaluating to Ensure Generic Drugs Are High-Quality, Safe, and Effective

OGD maintains a robust drug lifecycle management program for evaluating generic drug safety. Effective premarketing and postmarketing surveillance of generic drugs is essential to continuing to ensure that, when substituted for the brand-name drug, the FDA-approved generic drug remains safe and effective for its approved use. OGD's Clinical Safety Surveillance Staff (CSSS) facilitates broad surveillance projects with an interdisciplinary team of physicians, pharmacists, epidemiologists, chemists, and other scientists. CSSS tracks and evaluates information related to generic drug product quality, adverse events, or potential differing therapeutic effects from the brand-name drug.

For example, in 2019, CSSS engaged within OGD and throughout CDER to address safety concerns related to nitrosamine impurities in several generic over-the-counter and prescription drug products. CSSS also supported changes in loperamide tablet packaging to promote safe use. Through surveillance projects and engagement, OGD supports the continued availability of safe, effective, and high-quality generic drugs.

Highlighted Postmarketing Safety Activities:

- [Nitrosamines in Angiotensin II Receptor Blocker \(ARB\) Products](#)⁴
- [Nitrosamines in Ranitidine Products](#)⁵
- [Loperamide Packaging to Promote Safe Use](#)⁶

4 <https://www.fda.gov/news-events/press-announcements/statement-agencys-ongoing-efforts-resolve-safety-issue-arb-medications>

5 <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine>

6 <https://www.fda.gov/drugs/drug-safety-and-availability/fda-limits-packaging-anti-diarrhea-medicine-loperamide-imodium-encourage-safe-use>

Communicating Safety Surveillance Results

In addition to generic drug safety and surveillance, in 2019 we presented our scientific approach for conducting safety evaluations to several major stakeholder audiences. Some of these presentations are available at the following links:

- [Drug Information Association \(DIA\) 2019 Pharmacovigilance and Risk Management Strategies Conference – Session 1 FDA updates⁷](https://www.diaglobal.org/en/conference-listing/meetings/2019/01/pharmacovigilance-and-risk-management-strategies-conference/agenda/28/session-1-fda-updates?ref=Session1FDAUpdates)
- [Public Meeting #2 Electronic Submissions of AE reports using \(ICH\)E2B standards⁸](https://www.fda.gov/media/129211/download)
- **Podcast:** [Challenges in Generic Drug Safety & Surveillance⁹](https://diapublications.podbean.com/e/challenges-in-generic-drug-safety-surveillance/) posted by DIA on their *Driving Insights to Action* website. This podcast summarizes efforts regarding ongoing safety surveillance efforts featuring multiple real-life examples.

⁷ <https://www.diaglobal.org/en/conference-listing/meetings/2019/01/pharmacovigilance-and-risk-management-strategies-conference/agenda/28/session-1-fda-updates?ref=Session1FDAUpdates>

⁸ <https://www.fda.gov/media/129211/download>

⁹ <https://diapublications.podbean.com/e/challenges-in-generic-drug-safety-surveillance/>



Policies that Support the Efficient Development of Safe, High-Quality, and Affordable Generic Drugs

Our efforts to improve patient access to generic drugs start with ensuring we are transparent with our recommendations to generic drug developers on how to meet the scientific and regulatory requirements for approval. Timely recommendations from the Agency allow generic drug applicants to build those recommendations into their research and development programs, which helps them submit higher quality ANDAs. There are a variety of ways OGD makes its regulatory and scientific policies available to applicants and the general public, including:

REGULATORY GUIDANCES

OGD publishes guidances that, when finalized, describe the Agency's current thinking and recommendations to industry on generic drug development. Guidances are available online in the [FDA Drugs Guidances database](#) by choosing the "Generics" category.

MANUALS OF POLICIES AND PROCEDURES

Manuals of Policies and Procedures (MAPPs) describe internal agency policies and procedures and are accessible to the public to help make the Agency's operations more transparent. MAPPs are available online in the [CDER Manual of Policies and Procedures](#).

In the two months after the first generic for pregabalin (Lyrica) entered the market, the price lowered from \$7 per capsule to about \$0.13 per capsule.

Generic Drugs: Competition Can Help Lower Prices

Addressing the high cost of medicines by bringing more drug competition to the market is a top priority for FDA. As part of OGD’s commitment to providing information and guidance on the generic drug program, 2019 brought a particular focus on policies that can expedite the availability of generic drug products and help lower prices for American patients.

The [Drug Competition Action Plan \(DCAP\)](#) aims to further encourage robust and timely market competition for generic drugs and help bring greater efficiency and transparency to the generic drug review process, without sacrificing the scientific rigor underlying our generic drug program. Through this Plan, FDA is helping remove barriers to generic drug development and market entry in an effort to spur competition so that consumers can get access to the medicines they need at more affordable prices.

One notable example of a generic drug considerably lowering the price for patients is for pregabalin (brand-name Lyrica), which is widely used to treat certain types of seizures as well as neurologic pain and fibromyalgia. The average price during the 12 months before a generic entered the market was more than \$7 per capsule. During the first two months of sales of generic pregabalin — July and August 2019 — the average price for the generic pregabalin capsules lowered to about \$0.13 per capsule. During those first two months of availability, generic pregabalin accounted for 57% of the total market share.

In 2019, OGD made significant progress with the three major components of DCAP:

1. Improving the efficiency of the generic drug development, review, and approval process;
 2. Maximizing scientific and regulatory clarity with respect to complex generic drugs; and
 3. Closing loopholes that allow brand-name drug companies to “game” FDA rules in ways that delay the generic competition Congress intended.
1. Efforts to improve the efficiency of the generic drug development, review, and approval process included:
 - Publishing a draft guidance for industry, [ANDAs Submissions — Amendments and Requests for Final Approval to Tentatively Approved ANDAs](#), to provide recommendations on the timing

and content of amendments to tentatively approved ANDAs to facilitate submission in a timely fashion to enable final approval on the earliest lawful approval date.

- Publishing a draft guidance for industry, [*Competitive Generic Therapies*](#), to describe the process that applicants should follow to request designation of a drug as a competitive generic therapy (CGT) and the criteria for designating a drug as a CGT.
 - Publishing a final guidance for industry, [*Determining Whether to Submit an ANDA or a 505\(b\)\(2\) Application*](#), to assist applicants in determining which abbreviated approval pathway under the Federal Food, Drug, and Cosmetic Act (FD&C Act) is appropriate for the submission of a marketing application to FDA.
 - Updating FDA’s website on [*Patent Certifications and Suitability Petitions*](#) to include additional data that may help subsequent generic drug applicants determine when their products can be approved and marketed.
2. Efforts to maximize scientific and regulatory clarity with respect to complex generic drugs included:
- Publishing 269 PSGs (new and revised) for complex generic drug products to increase transparency on methodologies for developing these products and generating evidence needed to support generic approval.
 - Launching a new website, [*Upcoming Product-Specific Guidances for Complex Generic Drug Product Development*](#), to provide information related to upcoming new and revised PSGs to support the development and approval of safe, effective, and high-quality complex generic drug products.
 - Publishing a MAPP, [*Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings*](#), describing OGD and OPQ policies and procedures for evaluating requests from prospective ANDA applicants for a product development or a pre-submission pre-ANDA meeting and conducting such meetings.
 - Holding a public workshop, [*Complex Generic Drug Product Development*](#), to communicate to the generic industry how FDA research outcomes guide and facilitate complex generic drug product development.

3. Efforts to close loopholes that allow brand-name drug companies to “game” FDA rules in ways that delay the generic competition Congress intended included:
 - Updating the [list of all drug products about which FDA has received inquiries related to reference listed drug access](#) in February and September to provide transparency regarding these inquiries.
 - Publishing a MAPP, [Development of a Single, Shared System \(SSS\) Risk Evaluation and Mitigation Strategy \(REMS\) or a Separate REMS with Elements to Assure Safe Use \(ETASU\): Responsibilities and Procedures](#), describing the CDER policy, responsibilities, and procedures for developing an SSS REMS with ETASU for a reference listed drug (RLD) and ANDAs that reference the RLD during the review of the ANDAs, and developing a separate REMS with ETASU (if applicable) for an ANDA.
 - Publishing the final 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.
 - Updating the [List of Off-Patent, Off-Exclusivity Drugs without an Approved Generic](#) in June and December to ensure continued transparency and encourage the development and submission of ANDAs in markets with limited competition.



Regulatory Science and Research at OGD

How the Generic Drug Program's Research Makes a Difference

OGD's GDUFA regulatory science research provides needed information and tools for industry to develop new generic drug products and for the Agency to evaluate the equivalence of proposed generic drugs. We consult with and solicit input from the public, industry, and academia to develop an annual list of GDUFA regulatory science initiatives specific to research on generic drugs. In 2019, FDA awarded [14 new research contracts and 3 grants](#)¹⁰ for innovative research projects on generic drugs. FDA also utilized its laboratories and computer systems to conduct more than 50 GDUFA Science and Research projects.

The Importance of Scientific Research for Complex Generic Drug Development

Ongoing [scientific research under GDUFA](#) enables us to make recommendations that support appropriate science-based methodologies and evidence for the development of many generic drugs including complex generics. In 2019, FDA-supported research related to complex generic drugs also resulted in numerous articles for peer-reviewed publications. Looking ahead, we will be investigating additional ways to make our complex generics regulatory science activities and outcomes even more easily available to generic drug developers. In total, 110 complex drug products were approved by FDA in 2019.

We are committed to spurring competition so that consumers can get access to the medicines they need at affordable prices while steadfastly maintaining FDA's gold standard for rigorous, science-based regulation.

¹⁰ 14 new research contracts and 3 grants

Guidances and Recommendations Based on Scientific Research and Health Priorities

OGD provides important scientific guidance and recommendations to give generic drug applicants better opportunities to efficiently develop generic drug products and to prepare more complete ANDAs. We develop these recommendations based on public health priorities, requests from industry, current and anticipated patient and industry needs, and on scientific research.

Our recommendations are often described in [product-specific guidances](#) (PSGs). PSGs provide the Agency's current thinking and expectations on how to develop generic drugs that are therapeutically equivalent to specific brand-name, reference listed drugs. PSGs also help applicants submit ANDAs with fewer deficiencies, which can lead to more first-cycle approvals.

PSGs are intended to help make industry's research and development decisions more efficient and cost-effective by identifying the most appropriate methodology and evidence needed to support a specific generic drug's approval.

In 2019, OGD issued 269 PSGs. As of December 31, 2019, FDA had published nearly 1,800 PSGs on FDA's website at [Product-Specific Guidances for Generic Drug Development](#).

OGD also published a new web page, [Upcoming Product Specific Guidances for Complex Generic Drug Product Development](#), to describe FDA's plans for issuing new and revised PSGs for complex drug products (as defined by the GDUFA II Commitment Letter) in the next 12 months. The webpage responds to a [GAO report](#) requesting FDA to announce its plans to issue and revise PSGs for complex generic drug products. This advanced notice seeks to help generic drug companies plan their development of complex generic drug products and support the development and approval of safe and effective complex generic drug products. More than half of the PSGs FDA issued in 2019 were for complex products.

How OGD-Funded Research Plays a Role in Ensuring Quality and Safety of Generic Drugs

In 2019, the generic drug program funded approximately \$20 million in regulatory science research programs. We awarded funding for 14 new contracts and 3 new grants, as well as 2 ongoing grants and 23 contracts to conduct regulatory science research. OGD had 57 ongoing external research collaborations in 2019, with many projects awarded

in previous years continuing in 2019. In keeping with FDA's commitment to promote quality and clinically-relevant science, OGD staff and/or external collaborators published more than 50 peer-reviewed scholarly articles and book chapters, presented more than 100 external talks, and exhibited nearly 50 posters at national and international scientific and medical conferences.

In 2019, we published a new web page, [GDUFA Science and Research Outcomes](#), which lists all research outcomes for the previous fiscal year in one easily accessible place. We compiled this list as part of our GDUFA commitments. It provides greater public transparency regarding the important work the generic drug program engages in to advance the science of generic drugs. This information is provided to generic drug developers, applicants, and assessors, along with essential tools and information to help expedite the availability of safe, effective, and high-quality generic drugs. The new web page provides information on GDUFA research supporting:

- the development of generic drug products,
- the generation of evidence needed to support efficient review and timely approval of ANDAs, and
- the evaluation of generic drug equivalence throughout a given fiscal year.

These outcomes are also included in the [FY 2018 GDUFA Science and Research Report](#), which was updated in 2019 to include all topic areas.

On May 1, 2019, FDA held the [FY 2019 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 FY2020 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 2020](#).

The FY2020 generic drug regulatory science priority initiatives identified are grouped into the following topic areas:

- Topic A: Complex active ingredients, formulations, or dosage forms
- Topic B: Complex routes of delivery
- Topic C: Complex drug-device combinations
- Topic D: Tools and methodologies for bioequivalence and substitutability evaluation

Selected Significant 2019 Research Accomplishments

• OPHTHALMIC DRUG PRODUCTS

In 2019, we published results from an ophthalmic absorption model for dexamethasone ophthalmic suspensions that was developed and validated using published and in-house-generated rabbit pharmacokinetic (PK) data. The model simulated the ocular drug PK profiles of dexamethasone formulations that are qualitatively and quantitatively similar but have differences in drug particle size, formulation viscosity, and strength. The model describes the dose-dependent (0.01 to 0.1%) non-linear PK in ocular tissues and illustrates that ocular bioavailability is dictated by the interplay between formulation properties and physiological clearance, through drainage and tear turnover rates in the pre-corneal compartment.¹¹

• COMPLEX MIXTURES AND PEPTIDES

Peptide impurity profiles of teriparatide drug substance and product were identified and quantified using ultra-high-performance liquid chromatography-mass spectrometer (UHPLC-MS). More than 30 impurities were identified and

11 AAPS J. 21:65 (2019). DOI:10.1208/s12248-019-0334-x

We consult with and solicit input from the public, industry, and academia to develop an annual list of regulatory science initiatives.

quantified, including 16 impurities above the reporting threshold of 0.05%. These impurities could be categorized either as degradation products that accumulated over time or process impurities produced during the manufacturing process.

- **LONG-ACTING INJECTABLES**

Poly-lactic-co-glycolic acid (PLGA) is a biodegradable polymer that is widely used in long-acting injectable products. It is the product component that controls the drug release rate. PLGAs are complex in nature and their properties can be altered during manufacturing, which can make reverse engineering difficult. Based on our current understanding, comparative characterization data on polymer molecular weight/weight distribution, monomer ratio, and polymer structure (linear vs. branched) are critical. In 2019, FDA and our collaborators successfully developed and validated an analytical technique using a series of in-house synthesized branched-PLGA standards. The method was used to determine the branching parameters of glucose-PLGA extracted from Sandostatin LAR, as well as glucose-PLGAs obtained from three different suppliers in the U.S.¹²

- **COMPLEX INJECTABLES AND NANOMATERIALS**

An internal FDA research project focused on developing innovative analytical methods to quantify unencapsulated drug, excipients, and potential impurities in liposome formulations. This collaborative research with FDA's Office of Regulatory Affairs (ORA) resulted in three publications¹³ that will aid the development of generic liposome products.

- **ORALLY INHALED AND NASAL DRUG PRODUCTS**

To address challenges with conducting comparative clinical endpoint bioequivalence studies for metered dose inhaler (MDI) products, we conducted research to help identify and develop more predictive, clinically relevant in vitro methodologies for characterizing the aerosolized particles and their deposition and dissolution, as well as new computational modeling and simulation approaches to correlate these results with the delivered dose measured in vivo. As a result of this research, in 2019, the Agency posted the first PSG for a solution-based MDI product (Beclomethasone Dipropionate).¹⁴

¹² Journal of Controlled Release. (2019); DOI: 10.1016/j.jconrel.2019.03.002.

¹³ International Journal of Pharmaceutics, (2019) 569: 118603; International journal of pharmaceutics, (2019) 569: 118576; and International journal of pharmaceutics (2018) 549 (1-2), 109-114.

¹⁴ https://www.accessdata.fda.gov/drugsatfda_docs/psg/Beclomethasone%20dipropionate%20Inhalation%20Aerosol%20Metered%20NDA%20207921%20PSG%20Page%20RC%20May%202019.pdf

- **TOPICAL DERMATOLOGICAL DRUG PRODUCTS**

An in vivo dermal open-flow microperfusion (dOFM) study was conducted in human subjects to characterize the dose-response relationship and the influence of potentially confounding factors such as local “cross-talk” between probes in adjacent treatment sites, or redistribution of the drug via clearance into the systemic circulation and recirculation into the skin. Six healthy subjects were enrolled in this pilot, single center, open-label study. The absence of probe contamination from systemic redistribution, and the lack of any substantial “cross-talk” between adjacent test sites indicates that individual probes can monitor the local rate and extent of lidocaine and prilocaine specifically, and without interference from different treatments at other sites.

- **LOCALLY ACTING PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODELING**

FDA scientists collaborated with external experts to develop, evaluate, and improve physiologically-based models for challenging routes of delivery for generic drug development: ophthalmic,¹⁵ inhalation,¹⁶ and dermal.¹⁷ These models can aid generic drug development and help FDA’s evaluation of new bioequivalence approaches for these routes of delivery. In FY2019, a PBPK model that allowed the quantitative description of drug absorption through the skin was utilized to support the approval of a generic topical gel product referencing Voltaren® (diclofenac sodium) topical gel, 1% (Reference Listed Drug [RLD] — NDA 022122) for the topical treatment to relieve pain associated with osteoarthritis.

- **QUANTITATIVE CLINICAL PHARMACOLOGY (QCP)**

QCP approaches are used to integrate physiological, biological, and drug properties to set up clinically relevant BE criteria, evaluate post-marketing signals on generic switches, and explore alternate BE study designs.¹⁸ Two projects were conducted in FY2019 to evaluate new approaches for assessment of BE in PK study designs with sparse sampling, e.g., for ophthalmic product BE studies that only have one PK sample per subject. Model-based BE analysis strategies can be used to increase the efficiency of generic drug development and regulatory decision-making.

- **DATA ANALYTICS**

We conducted time-to-event analysis based on machine learning (ML) to predict the time to the first submission of ANDAs referencing new chemical entities (NCEs).¹⁹ This research is important to inform ANDA workload and to prioritize research efforts.

Communicating Regulatory Science Research Outcomes to 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 2019, CDER connected with the generic drug industry and other stakeholders through public events, webinars, podcasts, workshops, meetings, and publications.

15 AAPS J. (2019) 21(4):65. DOI: [10.1208/s12248-019-0334-x](https://doi.org/10.1208/s12248-019-0334-x)

16 CPT: Pharmacometrics & Systems Pharmacology. 2019;8(6):359-370.

17 Tsakalozou, E. Physiologically-based Pharmacokinetic Modeling and Simulation Approaches: Best Practices for Regulatory Applications Related to Locally-acting Generic Drugs. Presentation at Complex Generic Drug Product Development Workshop. College Park, MD, Sept. 26, 2019 (<https://sbiaevents.com/cgp2019/>)

18 Clin Pharmacol Ther. (2019) 105(2):338-349. DOI: [10.1002/cpt.1282](https://doi.org/10.1002/cpt.1282)

19 Clin Pharmacol Ther. (2019) 106(1):174-181.

Online Resources for Science and Research

- “[Building Confidence in Generic Narrow Therapeutic Index Drugs](#)” live Webinar for continuing education credit in CDER’s Division of Drug Information
- Industry updates, such as CDER’s Small Business & Industry Assistance newsletter ([FDA/CDER SBIA Chronicles](#)), and listserv for industry ([Small Biz Buzz](#)), as well as two generic drug [Listserves](#) 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

The FDA Generic Drug Program— A Special Thank You to Our Collaborators

To carry out the FDA Generic Drug Program, the Office of Generic Drugs (OGD) serves as the primary contact for those submitting ANDAs. OGD benefits from and relies on the efforts of many FDA offices that cooperate within the Program, including:

Center for Biologics Evaluation and Research

Center for Devices and Radiological Health

Center for Drug Evaluation and Research

- | | | |
|----------------------------|------------------------------------|---|
| • Office of Communications | • Office of New Drugs | • Office of Surveillance and Epidemiology |
| • Office of Compliance | • Office of Pharmaceutical Quality | • Office of Translational Sciences |
| • Office of Management | • Office of Regulatory Policy | |
| • Office of Medical Policy | • Office of Strategic Programs | |

Office of Chief Counsel

Office of the Commissioner

Office of Regulatory Affairs

We would like to thank our 2019 internal collaborators, especially the Office of Pharmaceutical Quality (OPQ), who greatly contributed to our successes in 2019. We look forward to future collaborations that will continue to help us enhance access to generic drugs for the American public.

Appendix

Regulatory Guidances issued in 2019

DRAFT GUIDANCES:²⁰

- [ANDA Submissions — Amendments and Requests for Final Approval to Tentatively Approved ANDAs Guidance for Industry](#), January 2019
- [Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format Guidance for Industry](#), January 2019
- [Competitive Generic Therapies](#), February 2019
- [Using the Inactive Ingredient Database Guidance for Industry](#) (led by Office of Pharmaceutical Quality), July 2019
- [Harmonizing Compendial Standards With Drug Application Approval Using the USP Pending Monograph Process Guidance for Industry](#) (led by Office of Pharmaceutical Quality), July 2019
- [Drug Master Files Guidance for Industry](#) (led by Office of Pharmaceutical Quality), October 2019
- [Assessing User Fees Under the Generic Drug User Fee Amendments of 2017 Guidance for Industry](#) (led by Office of Management), October 2019
- [Transdermal and Topical Delivery Systems — Product Development and Quality Considerations Guidance for Industry](#) (led by Office of Pharmaceutical Quality), November 2019

FINAL GUIDANCES:

- [Determining Whether to Submit an ANDA or a 505\(b\)\(2\) Application](#), May 2019
- [ANDA Submissions — Content and Format of Abbreviated New Drug Applications](#), June 2019
- [Citizen Petitions and Petitions for Stay of Action Subject to Section 505\(q\) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry](#) (led by the Office of Regulatory Policy), September 2019

Manual of Policies and Procedures (MAPP)

In 2019, OGD issued the following MAPPs:

- MAPP 5220.8, [Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings](#), September 2019

Meetings and Workshops

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

- At the FDA/American Society for Clinical Pharmacology and Therapeutics (ASCPT) we co-sponsored the Pre-conference on [PBPK Modeling for the Development and Approval of Locally Acting Drug Products](#) (March 13, 2019) that provided a forum for open discussion on the challenges and critical role of PBPK for locally-acting drug products (e.g., inhalation drug products, dermal drug delivery and ophthalmic drug products) in drug development and regulatory decisionmaking. This workshop was especially valuable to industry developing products that need to demonstrate bioequivalence to a locally acting drug product.

²⁰ When final, these guidances will represent the FDA's current thinking on these topics.

- At the [CDER Small Business and Industry Assistance \(SBIA\) Regulatory Education for Industry \(REdl\) Public Meeting: Generic Drug Forum 2019](#) (April 3–4, 2019) we updated industry on current trends around GDUFA and FDA’s generic drug program. Topics were drawn from stakeholder feedback from previous meetings.
- At the FY2019 [Generic Drug Regulatory Science Initiatives Public Workshop](#) (May 1, 2019) we 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 2020 research priorities.
- At the [2019 CDER SBIA and REdl Complex Generic Drug Product Development Public Workshop](#) (September 25–26, 2019) we communicated to industry how FDA research outcomes guide and facilitate complex generic drug product development. The workshop drew more than 3,800 registrants.
- As lead for the [Complex Product Workshop at 2019 Generic + Biosimilar Medicines Conference](#) (November 6, 2019) we provided a half-day hands-on training on pre-ANDA meetings with examples from liposomal ophthalmic, topical dermatological cream, and orally-inhaled drug-device combination products.
- At the FDA/American Society of Pharmaceutical Scientists (AAPS)/European Federation for Pharmaceutical Sciences (EUFEPS), we co-sponsored the [Fourth International Workshop on Global Bioequivalence Harmonization Initiative \(GBHI\)](#) (December 12–13, 2019), which delivered cutting edge science in a focused and “state-of-the-art” meeting. Key areas of focus included: 1) fasted and fed bioequivalence requirements for immediate-release products; 2) evaluation of bioequivalence of long-acting injectables and implants; and 3) Bioequivalence assessment of orally inhaled products.

Webinars, Articles, and Activities Reports

- OGD experts presented in two SBIA Webinars: [Financial Incentives for CDER Medical Products](#) (June) and [How Should I Measure This? An FDA perspective on the Bioanalytical Method Validation \(BMV\)](#) (June).
- The article [FDA Q&A: Generic Versions of Narrow Therapeutic Index Drugs: A National Survey of Pharmacists Substitution Beliefs and Practices](#) was posted online in the DIA Global Forum (July 2019).
- [Monthly Activities](#) reports and [GDUFA II Quarterly Performance](#) reports
- [First Generics Approvals](#)
- [Competitive Generic Therapy Approvals](#)
- [Activities Metrics](#)
- Additional information is available online at [Approvals & Reports](#)

Resources

- **About the Office Of Generic Drugs:** OGD comprises an immediate office and four subordinate offices, with a total of approximately 500 employees. Find out more about OGD here: www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-generic-drugs
- **Activities Report of the Generic Drug Program:** www.fda.gov/drugs/abbreviated-new-drug-application-anda/generic-drugs-program-activities-report-monthly-performance
- **CDER Small Business and Industry Assistance:** www.fda.gov/drugs/development-approval-process-drugs/cder-small-business-industry-assistance-sbia
- **First Generic Drug Approvals:** www.fda.gov/drugs/drug-and-biologic-approval-and-ind-activity-reports/first-generic-drug-approvals
- **Generic Drugs Web Pages:** www.fda.gov/GenericDrugs
- **Generic Drug User Fee Amendments:** www.fda.gov/GDUFA
- **GDUFA II Commitment Letter:** www.fda.gov/media/101052/download
- **GDUFA II Features Videos:** www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-ii-videos-and-resources
- **GDUFA Science and Research:** www.fda.gov/GDUFAregscience
- **Guidances and MAPPs Related to the Generic Drug User Fee Amendments:** www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-guidances-and-mapps
- **Orange Book:** www.fda.gov/OrangeBook



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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 DCAP and GDUFA II goals.

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