



OFFICE OF GENERIC DRUGS

2020 ANNUAL REPORT

Ensuring Access to Safe, Effective,
High-Quality, and More Affordable Generic Drugs





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Director's Message

Welcome to the sixth 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). Access to more affordable medicines remains a significant public health priority for FDA, and competition from generic drugs can help lower drug prices and improve access for American patients and consumers. Amid rapidly advancing science and unprecedented global challenges, the FDA's generic drug program has continued its steadfast efforts to help increase the availability of more affordable, high-quality drugs in the United States. Right now, 9 out of 10 prescriptions in the United States are filled by generic drugs. Generic drugs have saved the health care system \$2.2 trillion dollars in the past decade.¹ That is good news for the public health of Americans.

OGD's work in 2020 continued at a steady pace even as the COVID-19 global pandemic presented additional complexities, resulting in new realities and unique challenges. Our work this year, both routine and unexpected, may never have been as important.

Generic Drugs in the Time of a Pandemic

In 2020, we were encouraged to see how past efforts to improve the FDA generic drug program's efficiency, quality, and predictability were even more critical as OGD focused on supporting the approval of safe and effective generic medicines for use in fighting COVID-19.

During the COVID-19 public health emergency, FDA and OGD quickly pivoted to prioritizing the assessment of generic drug submissions for products that could help address COVID-19 as the top priority. More than 660 supplements and 50 original applications were approved for drug products used to treat patients with COVID-19. In addition to our emergency response to the pandemic, OGD and the entire generic drug program maintained FDA's rigorous standards for evaluating non-COVID-19 products based on quality data and sound science.

We identified and pursued tools and strategies to aid in the fight against COVID-19. OGD created a system for identifying generic drugs that are critical to the treatment of patients with COVID-19 and subsequently took regulatory and scientific action to accelerate review of those products. This system included establishing the infrastructure to rapidly complete tasks and resolve review issues in support of taking timely actions on critical generic drugs used in the pandemic.

¹ Association for Accessible Medicines' 2020 Report: Generic Drug and Biosimilars Access and Savings in the U.S. using data from IQVIA, found online, <https://accessiblemeds.org/2020-Access-Savings-Report>, December 2020.

OGD also worked diligently to support manufacturers of approved generic drugs who needed to make changes to manufacturing processes or facilities to address disruptions caused by the pandemic. The drug products they produce included antibiotics, sedatives used in ventilated patients, anticoagulants, and pulmonary medications, among others.

We also developed regulatory and scientific approaches to help efficiently restart generic drug development programs interrupted by the pandemic. For instance, we directly assisted applicants with resuming bioequivalence studies, including answering their questions about protocol revisions and information collection.

OGD Continued To Ensure Access to More Affordable Medicine

As OGD and the rest of FDA worked on the response to COVID-19, OGD also made significant progress this year with its everyday mission of improving access to generic drugs, which results in more competition in the market and more affordable medicines for the American public.

In the prescription drug market, OGD helped increase competition by approving or tentatively approving 948 Abbreviated New Drug Applications (ANDAs), including 72 first generics. These were relatively consistent numbers compared to recent years and speak to the continued strength of the overall generic drug program. We also approved 35 generics with the Competitive Generic Therapy (CGT) designation, including a quarterly record of 17 CGT approvals in the first quarter of fiscal year (FY) 2020.

OGD's strategic, proactive approaches to supporting generic drug development and assessment have a real impact on American patients. For example, for the first time, patients with multiple sclerosis now have a generic Tecfidera ([dimethyl fumarate](#)), patients with toxoplasmosis now have a generic Daraprim ([pyrimethamine](#)), and patients experiencing severe hypoglycemia now have a generic [glucagon](#).

Providing manufacturers with information to develop and submit higher quality applications also helps increase competition. An important tool used to communicate with prospective generic drug applicants is called 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 opportunity for industry to submit controlled correspondence supports the creation and submission of higher quality generic drug applications. In 2020, FDA responded to 3,711 controlled correspondence inquiries submitted by industry – a record!

OGD's work in 2020 continued at a steady pace even as the COVID-19 global pandemic presented additional complexities, resulting in new realities and unique challenges.

The [pre-ANDA program](#), which was established under the Generic Drug User Fee Amendments of 2017 (GDUFA II), is another tool we continued to support throughout 2020 to provide product development assistance to generic drug developers. Through written communications and meetings, OGD is able to help clarify regulatory expectations early in the development process and during application assessment. This program has a special focus on complex generic drug products, such as some inhaled or injectable products, which can be more challenging for generic drug developers to copy, often leading to a lack of generic competition even after patents and exclusivities no longer block generic drug approval. In 2020 we received 121 product development and pre-submission pre-ANDA meeting requests.

Beyond approvals and helping improve the quality of applications, OGD also continued its implementation of the FDA's Drug Competition Action Plan (DCAP) by taking steps to: improve the efficiency of the generic drug development, review, and approval process; maximize scientific and regulatory clarity with respect to complex generic drugs; and close loopholes that allow brand-name drug companies to "game" FDA rules in ways that delay the generic competition Congress intended. This included publication of guidances for industry, Manual of Policy and Procedures, and other policy documents and actions.

Improving affordability of and patient access to generic drugs has long been, and continues to be, a top priority for the Agency for the foreseeable future. Under DCAP, we have been looking across all our regulatory work to consider how we can continue to take steps to facilitate generic drug competition and access, including beyond what might be considered more traditional regulatory tools.

For example, FDA opened public dockets and issued a guidance to seek user feedback on how to enhance the [Orange Book](#) to make this key resource as useful as possible for stakeholders, including any improvements that could be made to advance the Agency's goal of improving access to high-quality, more affordable treatment options for Americans. Our related efforts are listed on the [DCAP web page](#), which is updated regularly.

Additionally, October 31, 2020 marked the 40th anniversary of the first official [Orange Book](#). The Orange Book is consistently among the top search terms used on the FDA website and remains one of the Agency's most popular web resources. Along with other information, the Orange Book contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education on drug product selection and to foster containment of health care costs.

We also continued to leverage science and research through general recommendations and in [product-specific guidances](#) specifically to help applicants develop generic drugs that can meet our high approval standards. Recommendations in product-specific guidances 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 finding of therapeutic equivalence of a generic drug to a specific brand-name drug during OGD's assessment process, particularly for hard-to-copy complex generic drug products.

This year, OGD was excited to announce the award of a 5-year grant from the GDUFA Science and Research Program that went to the University of Maryland and the University of Michigan to establish [The Center for Research on Complex Generics](#). The \$5 million grant aims to enhance research collaborations with the generic drug industry to further OGD's mission of increasing access to safe, effective, high-quality, and potentially lower-cost generic drug products. This goal will be pursued through collaborative research, training, workshops, laboratory projects to meet development needs, a Complex Generics Scholars program, and exchange of resources between FDA, the generic drug industry, and stakeholders.

OGD's work also extends beyond our borders in an effort to ensure Americans continue to have access to lower-cost, safe, effective, and high-quality medicines. This year, we maximized our involvement in the International Pharmaceutical Regulators Programme (IPRP) and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) by sharing information with more than 30 regulatory agencies and leading harmonization initiatives to promote scientific and regulatory exchange and identify topics for potential international harmonization efforts for generic drugs. OGD is leading and collaborating with ICH experts to develop a new ICH guideline (M13) to harmonize bioequivalence standards for immediate-release solid oral dosage forms (M13). We also continued to leverage and strengthen bilateral partnerships with Health Canada and the European Medicines Agency to advance collaborative efforts intended to address complex scientific and regulatory issues for generic drugs.

Even with the unprecedented demands of the COVID-19 pandemic, OGD continued to exceed the majority of our performance goals for application assessments and other commitments. The generic drug program is stronger than ever, and we continue to take timely actions on COVID-19 and non-COVID-19 related ANDAs. That is good news for Americans.

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

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Generic Drugs by the Numbers

FDA's Office of Generic Drugs (OGD) hailed many successes during calendar year 2020 (CY2020), the third year of FDA's implementation of the reauthorization of the Generic Drug User Fee Amendments (GDUFA II), including:

948

Approved or tentatively approved generic drug applications, known as Abbreviated New Drug Applications (ANDAs).

187

Product-Specific Guidances (PSGs) issued for industry and other stakeholders in 2020 including 93 new draft PSGs and 92 revised draft PSGs.

3,711

Controlled correspondence inquiries submitted by industry — a record number.

121

Pre-ANDA meeting requests to discuss product development and/or pre-submission issues were received in 2020.

\$20 million

Provided (approximately) in funding for science and research programs.

72

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

1,865

Total PSGs for industry and other stakeholders can currently be found on the FDA website.

1,952

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

nearly 60,000

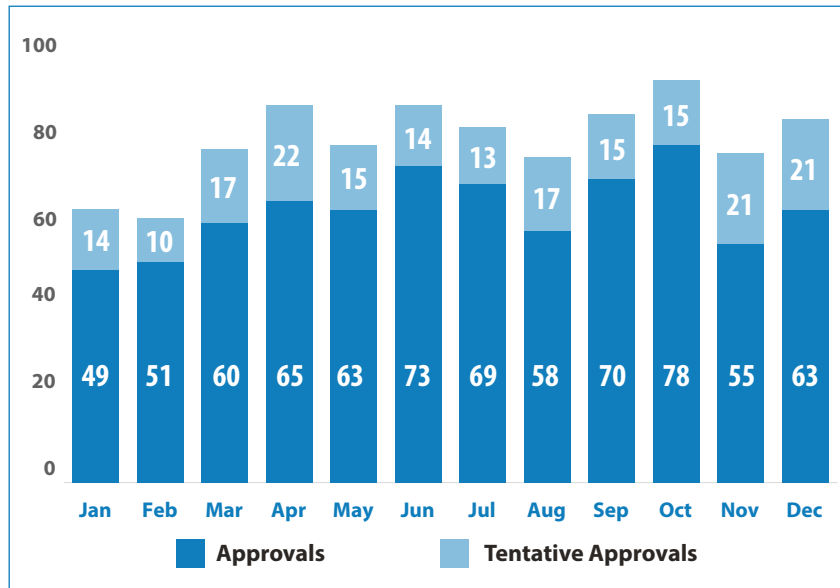
External stakeholders participated in eight conferences, workshops, public meetings, and pre-recorded webinars held to educate and inform about GDUFA and the generic drugs program.



Generic Drug Approvals

The impact of generic medicines on the consumer pocketbook is enormous — saving consumers more than a trillion dollars over the last decade.² In 2020, the generic drug program approved or tentatively approved 948 generic drug applications, known as Abbreviated New Drug Applications (ANDAs). Among the total approvals were 50 original applications and 668 supplement submissions for drug products used as potential treatments and supportive therapies for patients with COVID-19.

2020 Generic Drugs Approved and Tentatively* Approved



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

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

First Generics

First generic drugs provide access to needed therapies that treat a wide range of medical conditions and where little or no competition has previously existed. First generics are particularly important to public health, and OGD prioritizes the review of first generic drug submissions. In 2020, we approved 72 first generic drugs.

Significant First Generic Drug Approvals in 2020

Generic Drug Product	Brand Name	Indication of Use
Pyrimethamine Tablets	Daraprim	Treatment of toxoplasmosis
Dabigatran Etexilate Capsules	Pradaxa	Prevention of stroke and systemic embolism
Albuterol Sulfate Inhalation Aerosol	Proventil HFA	Treatment or prevention of bronchospasm
Efavirenz, Lamivudine, and Tenofovir Disoproxil Fumarate Tablets	SYMFI and SYMFI LO	Treatment of human immunodeficiency virus type 1 (HIV-1) infection
Dimethyl Fumarate Delayed-Release Capsules	Tecfidera	Treatment of multiple sclerosis
Glucagon for injection	Glucagon	Treatment of severe hypoglycemia

Highlighted 2020 Activities

Our Generic Drug Program in the Time of COVID-19

During the COVID-19 public health emergency, FDA and OGD identified and prioritized the assessment of generic drug submissions involving potential treatments and supportive therapies for patients with COVID-19. We pursued tools and strategies and took regulatory and scientific action intended to potentially help accelerate access to those products. This triaged system for identifying generic drug submissions for products that could help address the COVID-19 public health emergency included establishing the infrastructure to rapidly complete tasks and resolve review issues in support of taking actions on critical COVID-19 related generic drugs. These included products such as antibiotics, sedatives used in ventilated patients, anticoagulants, and pulmonary medications.

FDA expedited bioequivalence (BE) assessments of ANDAs, ANDA amendments, and responses to multiple controlled correspondences in order to assist the generic pharmaceutical industry with overcoming disruptions caused by the COVID-19 public health emergency and to help improve the supply chain for drug products critical in the fight against disease. The prioritization of specific generic drug ANDAs led to rapid BE assessments — many times in less than half the usual time.

We also developed regulatory and scientific approaches to help efficiently restart generic drug development programs interrupted by the pandemic. For instance, we directly assisted applicants with resuming bioequivalence studies, including answering their questions about protocol revisions and information collection.

Ensuring Standards and Assessing Methods for Bioequivalence

Additionally, we worked to communicate with applicants in the pre-ANDA space and to review BE studies, including those with pharmacokinetic, pharmacodynamic, and comparative clinical BE endpoints. We collaborated with a variety of stakeholders outside OGD to ensure regulatory standards were met for BE, and to assess new methodologies for demonstrating BE, especially for complex dosage forms which pose significant challenges to more traditional methods for the demonstration of BE.

For the first generic of Sucralfate Suspension, 1g/10ml, OGD developed a comprehensive understanding of the mechanism of local action of sucralfate which was critical to assess the important parameters necessary to support a determination of BE in the ANDA.

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In 2020, OGD performed more than 550 assessments related to the safety and therapeutic equivalence of generic drug products, including safety assessments of excipients, evaluation of safe levels for extractables and leachables, and comparative assessments of user interface for substitutability and therapeutic equivalence, to ensure that the proposed generics had the same safety profile as their reference listed drug (RLD). We provided expert review to develop new, highly sensitive methods for detecting and limiting impurities such as nitrosamines. Nitrosamines are probable human carcinogens. OGD worked with international stakeholders to evaluate the extent and severity of the concerns and take steps to mitigate the risks. We made assessments and set thresholds for these nitrosamine impurities across several generic drug classes. These assessments were pivotal to removing drug products contaminated with unacceptable levels of nitrosamine impurities from the market.

Of the assessments conducted, we performed more than 150 comparative analyses assessments. Comparative analysis helps to support findings of sameness of the generic product to its RLD, and to support therapeutic equivalence, the ability of a bioequivalent and pharmaceutically equivalent generic product to have the same clinical effect and safety profile as its RLD when administered to patients under the conditions specified in the labeling.

REMS and the CREATES Act

A [Risk Evaluation and Mitigation Strategy \(REMS\)](#) is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks. REMS strategies are designed to reinforce medication use behaviors and actions that support the safe use of the medication. While all medications have labeling that informs health care stakeholders about medication risks, only a few medications require a REMS.

In December 2019, Congress passed the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act to promote competition in the marketplace for drugs and biological products by facilitating the timely entry of lower-cost generic and biosimilar versions of those drugs and biological products. In 2020, OGD played a critical role in the Agency's coordinated and collaborative efforts to revise and develop regulatory and policy documents for the ANDA REMS program to implement the [CREATES Act](#) as it applies to generic drugs.

To meet the requirements of both the REMS safety program and the CREATES Act, OGD collaborated on a revised [Shared System REMS Manual of Policies and Procedures \(MAPP\)](#) and several REMS templates for Actions, and also created a new REMS template for Complete Response (CR) actions for pending developing REMS systems.

In 2020, several important outcomes resulted from OGD's efforts to merge the requirements of the REMS program and the CREATES Act:

- Approvals of Shared System REMS programs for products such as bosentan (treats pulmonary arterial hypertension), vigabatrin (treats seizures and infantile spasms), and the first generic for alvimopan (accelerates upper and lower gastrointestinal recovery following certain bowel resection surgeries).
- Nine REMS supplements were modified and approved in 2020, including one for ambrisentan (treats pulmonary arterial hypertension) for which a REMS modification eliminated the stand-alone ANDA REMS program, simplifying the process and increasing efficiency by merging it with a Shared Single System REMS program.

The Importance of Our International Efforts

OGD navigates the complex global landscape to provide the American public with access to high-quality, more affordable medicines. Global Generic Drug Affairs (GGDA), the OGD global affairs program, was formally established this year. In 2020, GGDA continued OGD efforts to create common global development standards for generic drugs by working with partners inside and outside the FDA. These OGD-led regulatory efforts are intended to advance the international harmonization of scientific and technical standards for generic drug development. The envisioned outcome of these efforts is reduced costs and product development time, which can contribute to improved patient access to more affordable medicines, while also enhancing the quality and approvability of generic drug applications.



Currently, OGD leads the International Council for Harmonisation (ICH) Generic drug Discussion Group (GDG). In June 2020, the GDG started its second year to focus on prioritizing future potential topics for harmonization that will include more complex products. The ICH M13 expert working group, formed in July 2020, represents the first ever ICH guideline (M13) focusing on harmonizing BE study design and standards for generic drugs. In addition to ICH engagement, GGDA continued leading efforts in numerous working groups within International Pharmaceutical Regulators Programme (IPRP) and Global Bioequivalence Harmonization Initiative (GBHI).

Throughout 2020, GGDA also fostered partnerships with international affairs entities across the Agency and is leveraging and strengthening collaboration with FDA's international offices, which improves the flow and transparency of information. Additionally, in 2020, we launched tailored regional outreach to increase the quality of generic drug application submissions, keeping global stakeholders up-to-date about OGD policies and practices. OGD's GGDA also represents OGD in responding to inquiries from entities such as the World Health Organization, foreign regulatory and health agencies, and the foreign generic drug industry. GGDA regularly engages with international stakeholders on bilateral and multi-lateral bases to discuss pressing matters affecting generic drugs in the global landscape.

Generic Drug User Fee Program

User Fee programs help FDA fulfill its mission of protecting the public health and accelerating innovation in industry. The Generic Drug User Fee program is based on the Generic Drug User Fee Amendments (GDUFA), which are negotiated between FDA and industry every 5 years.

OGD's GDUFA research programs support the investigation of drug development challenges and help us establish the scientific framework for ANDA assessments and product-specific guidance recommendations. GDUFA enables OGD 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 2020, FDA and the pharmaceutical industry entered their third year of the reauthorized generic drug user fee program, which was first enacted by Congress in 2012 and reauthorized in 2017 (GDUFA II). The GDUFA II program includes performance goals with specific timeframes for original ANDAs and prior approval supplements (PASs) for post-approval changes requiring a supplemental submission and approval, and amendments to PASs.

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.

Communicating with Industry

The Office of Generic Drugs (OGD) communicated with industry through more than 4,500 information requests (IRs), more than 2500 discipline review letters (DRLs), and 1,952 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 opportunity for industry to submit controlled correspondence supports the development

and submission of higher quality generic drug applications. In 2020, OGD responded to 3,711 controlled correspondence inquiries submitted by industry, which was a record number.

Under GDUFA II, certain applications may be eligible for priority review, including applications for products that are on FDA's drug shortage list. Also, our 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 and during review,
- 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 preparing more complete application submissions, which in turn can help them reduce their time in the pipeline from concept to development to market. In 2020, FDA received 121 product development and pre-submission pre-ANDA meeting requests.

Looking Ahead to GDUFA III

Although we are still two years away from the end of GDUFA II, FDA is gearing up for GDUFA's third iteration now. In July 2020, the Agency began the important process of considering public input, meeting with stakeholders, and engaging in negotiations with the generic drug industry as part of the process for Congress to reauthorize GDUFA for another five years (i.e., GDUFA III). FDA entered this reauthorization process building on the successes of GDUFA I and GDUFA II, which enabled the most robust generic drug review program to date. The continued work by FDA and the generic drug industry through a GDUFA III program will allow for critical funding of FDA's generic drug program so the Agency can continue to ensure that Americans will have access to safe, high-quality, more affordable generic drugs.



Monitoring and Evaluating Generic Drug Safety

OGD maintains a robust drug lifecycle management program for evaluating generic drug safety. Effective premarketing and postmarketing surveillance of generic drugs is essential to ensuring that, when substituted for a brand-name drug, an FDA-approved generic drug maintains the same safety and effectiveness profile as its RLD for the generic drug's approved use(s) throughout its lifecycle. OGD monitors and evaluates generic drug safety from the time a generic product is marketed until it is no longer available for sale in the United States. Effective safety surveillance of generic drugs is essential to making sure that FDA-approved generic drugs provide the same therapeutic effect and safety as brand-name drugs.

OGD's Clinical Safety Surveillance Staff (CSSS) performs these important surveillance functions by analyzing postmarket generic drug adverse event reports and trends, following generic drug distribution patterns, reviewing serious adverse events, and identifying emerging safety issues. Throughout 2020, OGD's CSSS:

- Supported the voluntary [market withdrawal of bacitracin injection products](#) due to the risks outweighing the benefits of the approved indication for treating infants with pneumonia or empyema.
- Provided proactive surveillance of more than 40 high-priority generic drugs to support OGD's COVID-19 Task Force in reinforcing the continued supply of these safe, effective, and important generic products.
- Led a cross-CDER effort to evaluate the need for regulatory action regarding fatal neurologic injury or death related to the accidental spinal rather than intravenous administration of vinca alkaloid drugs, a group of chemotherapy agents that includes vincristine sulfate, vinblastine sulfate and vinorelbine tartrate. This issue was included in the [April-June 2020 Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System \(FAERS\)](#).
- Aided (along with other discipline reviewers within OGD and throughout CDER) the Nitrosamine Impurities Task Force addressing evolving safety issues related to the presence of nitrosamine impurities in certain generic over-the-counter and prescription drug products — including angiotensin II receptor blockers, ranitidine, metformin, and rifampin products — providing scientific and clinical input on several [important public communications](#) regarding these products.
- Engaged with surveillance groups in the Office of Compliance and Office of Pharmaceutical Quality (OPQ) on an [albuterol sulfate inhaler voluntary recall](#).

Communicating Safety Surveillance Activities to Stakeholders in 2020

In 2020, OGD presented its scientific approach to conducting safety evaluations and postmarketing surveillance and engaged with several major stakeholder audiences, including:

JANUARY

“Challenges in Generic Drug Surveillance: Proactive Approaches for Complex Generic Drug Products” was presented at the [Drug Information Association \(DIA\) Pharmacovigilance and Risk Management Strategies Conference](#) in Washington, DC.

FEBRUARY

OGD joined CDER’s OPQ on several panel discussions with industry, provider, and pharmacist stakeholders at the Duke Margolis for Health Policy Meeting — [Understanding How the Public Perceives and Values Pharmaceutical Quality](#) in Washington, DC.

APRIL

“The Physician Reviewer’s Role in Premarket Safety Review of Generic Drugs,” “Post-market Pharmacovigilance Data Analysis and Decision Making,” and “Emerging Trends in Postmarketing Safety Surveillance for Generic Drugs” were presented at the [CDER Small Business and Industry Assistance Generic Drugs Forum](#) (virtual).

MAY

“Postmarket Surveillance of Generic Drugs” was one of four breakout sessions at the 2020 [Generic Drug Science and Research Initiatives Public Workshop](#) (virtual).

OCTOBER

“[Challenges and Opportunities in Post Marketing Pharmacovigilance and Lifecycle Management for Complex Generic Drug-Device Combination Products](#)” was co-led by OGD and the generic drug industry at the [DIA/FDA Complex Generic Drug-Device Combination Products Conference](#) (virtual).

NOVEMBER

“[Nitrosamines, Past, Present and Future](#)” and “[Pharmacovigilance: the Same Requirements for All](#)” were informative presentations and discussion panels at the [AAM GRx + BioSims 2020 Conference](#) (virtual).

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

OGD's efforts to improve patient access to generic drugs include ensuring transparency with our recommendations to generic drug developers on how to meet scientific and regulatory requirements for approval. Timely recommendations allow generic drug applicants to build that information 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 known and available to applicants and the general public. In 2020, FDA issued seven final and two draft guidances for industry related to generic drugs (not including product-specific guidances discussed below), two Federal Register Notices, and six MAPPs.

Regulatory Guidances

OGD publishes guidances that, when finalized, described 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 "Generic Drugs" topic. Below are the guidances issued in 2020.

FINAL GUIDANCES:

- [Competitive Generic Therapies](#)
- [Compliance Policy for the Quantity of Bioavailability and Bioequivalence Samples Retained Under 21 CFR 320.38\(c\)](#)
- [Marketing Status Notifications Under Section 506I of the Federal Food, Drug, and Cosmetic Act; Content and Format Guidance for Industry](#)
- [Amendments and Requests for Final Approval to Tentatively Approved ANDAs](#)
- [Referencing Approved Drug Products in Abbreviated New Drug Application \(ANDA\) Submissions](#)
- [Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA](#)
- [Controlled Correspondence Related to Generic Drug Development](#)

SPOTLIGHT: 40TH ANNIVERSARY OF THE ORANGE BOOK

October 31, 2020 marked the 40th anniversary of the first official publication of *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). The Orange Book is consistently among the top search terms used on the FDA website, and remains one of the Agency's most popular web resources. Among other information, the Orange Book contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education on drug product selection and to foster containment of health care costs.

DRAFT GUIDANCES:³

- [Orange Book Questions & Answers for Industry](#)
- [Failure to Respond to an ANDA Complete Response Letter Within the Regulatory Timeframe](#)

MANUAL OF POLICIES AND PROCEDURES

[CDER's Manual of Policies and Procedures \(MAPP\)](#) describe internal Agency policies and procedures and are accessible to the public to help make the Agency's operations more transparent. In 2020, FDA issued the following MAPPs:

- [Prioritization of the Review of Original ANDAs, Amendments, and Supplements \(MAPP 5240.3\)](#)
- [ANDA Amendments and Supplements Reviewed by the Division of Filing Review \(MAPP 5200.7\)](#)
- [Conversion of ANDA Approval to Tentative Approval Because of Court Order \(MAPP 5220.2\)](#)
- [Consolidation of ANDAs by the Office of Generic Drugs \(MAPP 5241.2\)](#)
- [Transfer of Ownership \(MAPP 5242.1\)](#)
- [ANDA Suitability Petitions \(MAPP 5240.5\)](#)

PRODUCT-SPECIFIC GUIDANCES

FDA's efforts to improve generic drug access involve providing critical guidance and support to generic drug developers. Timely guidance from FDA allows generic drug applicants to build Agency recommendations into their research and development programs, which helps applicants submit higher quality ANDAs. Certain recommendations are described in [product-specific guidances \(PSGs\)](#), which reflect the Agency's current thinking on the most appropriate methodology and evidence needed to support a specific generic drug's approval. These guidances give applicants better opportunities to efficiently develop generic drug products and to prepare more complete and more accurate ANDA application packages. PSGs help applicants submit ANDAs to FDA with fewer deficiencies, which helps lead to more first-cycle approvals.

PSGs also address uncertainties and provide the Agency's current thinking on product development questions, help make industry's research and development decisions more efficient and cost-effective, and advance the opportunity for discussion of new or alternative generic drug development strategies — especially for complex generic drug products.

OGD develops PSGs based on public health priorities, requests from industry, and current and anticipated patient and industry needs, and consistent with our GDUFA II commitments. OGD's [ongoing scientific research under GDUFA](#) enables the Agency to make recommendations to support the identification of appropriate science-based methodologies and evidence for the development of many complex drug products. Complex drug products are drugs that are harder to develop than generic drug products using traditional bioequivalence approaches because of the nature of their formulation or delivery system. In 2020, as a result of the GDUFA Science and Research Program, we developed PSGs for multiple complex drug products as well as non-complex drug products. FDA developed a new draft PSG for buprenorphine extended-release subcutaneous solution, a revised draft PSG for liposomal amphotericin B injection, and a new draft PSG for epinephrine metered dose inhaler, among others.

In total, FDA issued 187 PSGs in 2020, including 2 final (1 from existing draft guidance and 1 new), 93 new draft PSGs, and 92 revised draft PSGs (revisions to existing PGSs are generated, for example, as new information or scientific

³ When final, these guidances will represent the FDA's current thinking on these topics.

methodologies become available). As of December 31, 2020, FDA had published more than 1,865 PSGs, which can be found on FDA's website at the [Product-Specific Guidances for Generic Drug Development](#) section.

Generic Drug 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, in 2020 we continued to focus on policies that can expedite the availability of generic drug products and help lower prices for American patients. The FDA [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 and OGD are 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.

In 2020, OGD took a number of steps in support of DCAP. In addition to the guidances and MAPPs listed above, OGD's efforts included:

COMPETITIVE GENERIC THERAPY (CGT) DESIGNATIONS

In January 2020, FDA published a [new web page listing all approved ANDAs for products that received a Competitive Generic Therapy \(CGT\) designation](#). CGT-designated drug products have inadequate generic competition, meaning there is not more than one approved equivalent for that product included in the active section of the Orange Book. The list is updated on a bi-weekly basis and includes information about the approved application, drug product and any potential CGT exclusivity. Potential generic drug applicants can use this list to see whether CGT exclusivities have been awarded for particular drug products and the status of those exclusivities, to plan their own efforts accordingly.

In March, we finalized the [CGT guidance](#) to provide clarity for potential ANDA applicants on the new provisions the FDA Reauthorization Act of 2017 (FDARA) added to the FD&C Act related to competitive generic therapies (CGTs). These new provisions provide incentives for effective development, efficient review, and timely market entry of drugs for which there is inadequate generic competition. Among other things, the guidance provides a description of the process that applicants may follow to request designation of a drug as a CGT and the criteria for designating a drug as a CGT.

Timely recommendations from the Agency allow generic drug applicants to build our recommendations into their research and development programs, which helps them submit higher quality ANDAs.



ORANGE BOOK

This valuable resource, one of FDA’s most popular, lists approved prescription drug products, related patent and exclusivity information, and therapeutic equivalence evaluations, along with other information. The evaluations it contains serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education on drug product selection and to help keep health care costs down. The FDA has regularly sought to update and enhance the Orange Book to make it more accessible and useful to regulated industry and the public over time. In 2020, the Agency published an Orange Book-focused guidance, opened two additional public dockets to collect feedback, and planned two events to help educate and engage Orange Book users.

LIST OF OFF-PATENT, OFF-EXCLUSIVITY DRUG PRODUCTS WITHOUT AN APPROVED GENERIC

OGD maintains this list to improve transparency and encourage the development and submission of generic applications for drugs with limited competition. We update this list every six months to ensure continued transparency regarding drug products where increased competition has the potential to provide significant benefit to patients. This list is also useful within FDA as we develop additional product-specific guidances and other resources to assist prospective ANDA applicants. In 2020, the U.S. Pharmacopeia (USP) prioritized FDA’s list of off-patent, off-exclusivity branded drugs without approved generics, and launched a Call for Collaboration to advance our shared priorities. USP has identified opportunities where public quality standards can help increase access to medicines with great potential benefit to the public health.

PARAGRAPH IV PATENT CERTIFICATIONS

In 2020, OGD continued to help remove barriers to generic drug development and market entry by providing information and increased clarity related to 180-day patent challenge exclusivity. This information can help generic drug applicants make business decisions so that consumers can get access to the medicines they need at more affordable prices. For instance, throughout 2020, OGD provided biweekly updates with additional data in the existing [Paragraph IV Patent Certifications list](#), including the number of potential first applicants, the 180-day decision status, the date of first “first applicant” approval, the date of first commercial marketing, and the expiration date of last qualifying patent.

Science and Research at OGD

How the Generic Drug Program's Research Makes a Difference

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

In 2020, FDA funded approximately \$20 million in science and research programs. FDA awarded funding for 12 new contracts and 5 new grants, as well as 5 ongoing grants and 23 contracts to conduct science and research. OGD had 74 ongoing external research collaborations in 2020, with many projects that had been awarded in previous years continuing into 2020. In keeping with FDA's commitment to promote quality and clinically-relevant science, OGD staff or their external collaborators published 86 peer-reviewed scholarly articles, presented 106 external talks, and presented (virtually) 50 posters at national and international scientific and medical conferences.

In May, FDA held the [FY 2020 Generic Drug Science and Research Initiatives Public Workshop](#), which provided an overview of the status of the generic drug science and research program and an opportunity for public input in developing the FY2021 science and research priorities. Information obtained during the public workshop, along with other input such as comments to the public docket, were considered in developing the [GDUFA Science and Research Priority Initiatives for Fiscal Year 2021](#).

In August, FDA awarded a 5-year grant to the University of Maryland and the University of Michigan to establish the [Center for Research on Complex Generics](#) (CRCG). The CRCG aims to enhance research collaborations with the generic industry to further the FDA's mission of increasing access to safe and effective generic products. This goal will be pursued through collaborative research, training, and exchange of resources between FDA, the generics industry, and stakeholders. The [CRCG](#) will offer collaborative research and training, webinars, workshops, laboratory projects, and a Complex Generics Scholars program, among other initiatives, in support of the generic industry and other stakeholders. This cutting-edge center, the first of its kind, will stimulate innovative dialogue, disseminate current understanding of complex products and practices, and generate new knowledge. The specific areas of focus for the CRCG during FY2021 will align with the FY2021 generic drug science and research priorities.

In September, FDA held the [Advancing Innovative Science in Generic Drug Development Workshop](#), which focused on common scientific issues seen in ANDAs. The presentations linked GDUFA science and research related to complex products and complex scientific issues to PSG development, pre-ANDA meetings and the assessment of information and data submitted in ANDAs, as well as examining various areas of the science behind generic drug development.

In 2020, FDA published research outcomes for FY2019 [on an easily accessible web page](#). On the same [page](#), updated FY2018 outcomes are listed as well. FDA compiled the list as part of our GDUFA II commitments. The list provides greater public transparency regarding the important work the generic drug program engages in to advance the science of generic drugs and provide generic drug developers, applicants, and FDA reviewers essential tools and information to help expedite the availability of high-quality, lower-cost, safe, and effective generic drugs. The web page also provides information on 1) GDUFA research supporting the development of generic drug products, 2) GDUFA research supporting the generation of evidence needed to support efficient review and timely approval of ANDAs, and 3) GDUFA research supporting the evaluation of generic drug equivalence throughout a given fiscal year. The outcomes on this page are also included in the [FY 2019 GDUFA Science and Research Report](#), which was updated in 2020 to include all topic areas.



Select 2020 Research Accomplishments

In addition to serving as the scientific basis for the development of PSGs, specific pre-ANDA communications, and generic drug application assessment, research outcomes from intramural and extramural research are published in peer-reviewed scientific literature and are presented and discussed at major medical and scientific meetings to contribute to general guidance development, to facilitate the path toward generic drug product development, and to support efficient review and timely approval of ANDAs. [GDUFA science and research](#) includes the following 13 research programs, each highlighted with a key FY2020 outcome.

- **ABUSE-DETERRENT OPIOID PRODUCTS**
FDA is developing in vitro methods that may be (bio)predictive of drug delivery following the nasal insufflation of milled oxycodone hydrochloride extended release tablets. In 2020, FDA published a study that described a dissolution method for manipulated abuse deterrent formulations using the United States Pharmacopeia (USP) Apparatus 4, where the model drug was metoprolol succinate.⁴
- **COMPLEX INJECTABLES, FORMULATIONS, AND NANOMATERIALS**
In 2020, FDA developed a high resolution cryo-transmission electron microscopy method to characterize the particle size and morphology of four therapeutically equivalent propofol products.
- **COMPLEX MIXTURES AND PEPTIDE PRODUCTS**
Complex mixtures and therapeutic peptides represent a unique challenge from a quality perspective. To support assessments of active ingredient sameness between reference and generic products, FDA developed advanced analytical methods and statistical analysis for the characterization and comparison of complex active ingredients.

⁴ Feng, X., Zidan, A., Kamal, N. S., Xu, X., Sun, D., Walenga, R., Boyce, H., Cruz, C. N., and Ashraf, M. *Assessing Drug Release from Manipulated Abuse Deterrent Formulations*. *AAPS PharmSciTech*. (2020) 21(2):40. doi: 10.1208/s12249-019-1595-5. PMID: 31897805.

- **DATA ANALYTICS**

To identify measures that might accelerate the development of generic drug products, FDA researchers investigated factors that might predict the likelihood that an ANDA, relying on a given RLD product, would be submitted to FDA.

- **DRUG-DEVICE COMBINATION PRODUCTS**

Research involving drug-device combination products has meaningfully improved our scientific understanding of such products and contributed to regulatory decision making in ANDA reviews for suspension-based metered dose inhalers (MDIs).

- **INHALATION AND NASAL DRUG PRODUCTS**

Research results for aerodynamic particle size distribution (ASPD) testing with MDIs suggest that the consideration for using Next Generation Impactor (NGI) stage coating during an APSD study cannot be generalized across all MDIs and may be dependent on the particular formulation being tested, which has direct implications for the corresponding BE study recommendations for such products.

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

Research in this area during 2020 expanded the knowledge base for various types of models, including PBPK and computational fluid dynamics (CFD) models, to facilitate reliable predictions of local drug delivery to the site of action (e.g., in the lung or nasal tissues).

- **LONG-ACTING INJECTABLES AND IMPLANTED PRODUCTS**

A revised draft PSG for generic levonorgestrel intrauterine system (LNG-IUS) was posted, recommending an in vitro and in vivo combination approach for establishing the BE of generic LNG-IUS.⁵

- **OPHTHALMIC DRUG PRODUCTS**

A key outcome from the FY2020 research on ophthalmic drug products relates to developing a new analytical method to investigate the process of drug transfer and the mechanism of drug release from emulsions. With the new method, the diffusion rate constants for both the oil-to-aqueous and aqueous-to-oil were determined.

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

5 Revised Draft Guidance for Levonorgestrel Intrauterine Device. (Jan. 22, 2020) Accessible at https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021225.pdf.

- **ORAL ABSORPTION MODELS AND BIOEQUIVALENCE**

The findings of research on the impact of excipients on drug absorption indicated a potential influence of excipients on the bioavailability of drugs that are OATP2B1 substrates.⁶

- **PATIENT SUBSTITUTION OF GENERIC DRUGS**

Two studies completed in 2020 demonstrated the comparability of treatment outcomes for generic vs. brand narrow therapeutic index (NTI) drug products, one in patients with hypothyroidism and another in a senior population treated with anticoagulation agents. These studies provide real-world evidence to support public confidence in generic NTI drugs.

- **QUANTITATIVE CLINICAL PHARMACOLOGY**

During 2020, as part of its effort to develop efficient model-based BE methods, FDA evaluated three alternative approaches for calculation of standard error (SE) for pharmacokinetic (PK) BE studies with sparse sampling.

- **TOPICAL DERMATOLOGICAL PRODUCTS**

During 2020, a dermal open flow microperfusion (dOFM) clinical study with 20 healthy subjects was conducted to assess the accuracy, reproducibility, and discrimination sensitivity of a dOFM BE study with lidocaine and prilocaine cream and gel products.

Enhancing Communication about Research with Industry and Stakeholders

Communicating the results of science and research to external stakeholders provides transparency and clarity to industry, which strengthens the generic drug program. In 2020, OGD connected with the generic drug industry and other stakeholders through public events, webinars, workshops, meetings, and conferences. FDA sponsored eight virtual conferences, meetings, workshops, and webinars that focused on generic drug development, science and research, or GDUFA.

6 Zou, L., Spanogiannopoulos, P., Pieper, L. M., Chien, H. C., Cai, W., Khuri, N., Pottel, J., Vora, B., Ni, Z., Tsakalozou, E., Zhang, W., Shoichet, B.K., Giacomini, K. M., and Turnbaugh, P. J. *Bacterial Metabolism Rescues the Inhibition of Intestinal Drug Absorption by Food and Drug Additives*. Proc Natl Acad Sci U S A. (2020) 117(27):16009; doi: 10.1073/pnas.1920483117. PMID: 32571913.

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

To carry out the FDA Generic Drug Program, 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 Compliance
- Office of Generic Drugs
- 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 the Chief Counsel

Office of the Commissioner

Office of Executive Programs

Office of Regulatory Affairs

We would like to thank our 2020 internal collaborators, especially the Office of Pharmaceutical Quality, who greatly contributed to our successes in 2020. We look forward to future collaborations that will help us further increase access to generic drugs for the American public.

Appendix

Conferences, Public Meetings, Workshops, and Webinars

[Regulatory Education for Industry \(REdI\) Conference: Generic Drugs Forum](#)

The annual REdI Generic Drugs Forum was held (virtually) in April to update industry stakeholders on current trends related to GDUFA and relevant to FDA's generic drug program. Presentations by FDA offered practical advice, illustrated case studies, and enabled discussions about scientific issues related to ANDAs that were designed to help prospective generic drug developers reduce certain risks in their development programs and minimize the likelihood of deficiencies in their ANDAs. The virtual event, which featured presentations from the FDA's Office of Generic Drugs and the Office of Pharmaceutical Quality, had more than 2,600 attendees representing 77 countries.

[FY2020 Generic Drug Science and Research Initiatives Public Workshop](#)

The annual spring Generic Drug Science and Research Initiatives Public Workshop was held (virtually) in May. This science-focused public workshop provided an overview of ongoing work and outcomes from research advanced under the FY2020 GDUFA science and research priorities. A key objective of this workshop was to solicit public input related to the development of next year's (FY2021) GDUFA science and research priorities. More than 500 attendees joined the workshop.

[Public Meeting on the Reauthorization of the Generic Drug User Fee Amendments \(GDUFA\)](#)

This public meeting was held in July (virtually) to discuss the reauthorization of GDUFA for FY2023 through FY2027.

[REdI Conference: Advancing Innovative Science in Generic Drug Development Workshop](#)

This workshop was held (virtually) in September and focused on common scientific issues seen in ANDAs. The presentations linked GDUFA science and research related to complex products and complex scientific issues to PSG development, pre-ANDA meetings and the assessment of information and data submitted in ANDAs, as well as examining various areas of the science behind generic drug development. The workshop advanced concepts that help the generic drug industry, scientists, researchers, and regulatory affairs professionals pave a clear scientific pathway for generic drug development. This year's workshop had more than 1,800 attendees from more than 90 countries.

[FDA/DIA Complex Generic Drug-Device Combination](#)

[Products Conference](#)

This workshop was held (virtually) in October and examined the current state of knowledge about complex drug-device combination products as well as ongoing scientific research by FDA supporting the evidence-based development, assessment, and approval of complex generic drug-device combination products. Speakers discussed these topics, including common issues that arise during the assessment of information and data submitted in ANDAs, general expectations for industry after product approval, and future directions for the development of these important generic products.

[Celebrating 40 Years: An In-Depth Examination of the FDA Orange Book](#)

[REdI Conference](#)

In October 2020, FDA (virtually) hosted the first-ever Orange Book Conference, which showcased the Orange Book and provided a roadmap to navigate and utilize the wealth of information it contains including therapeutic equivalence ratings, patents, exclusivities, and more. The conference, geared to the brand and generic drug industry, as well as other public health stakeholders, featured Orange Book experts who provided insights and feedback related to its use and functionality including possible future enhancements to the Orange Book.

[Orange Book Q & A Webinar](#)

This webinar was designed to assist stakeholders in utilizing the Orange Book. It addressed some of the most frequently asked questions that the FDA has received from interested parties regarding the Orange Book.

[Referencing Approved Drug Products in ANDA Submissions Webinar](#)

This webinar was intended to help applicants submitting an ANDA seeking approval of a generic drug to identify: RLD, i.e., a previously approved drug product on which an applicant relies in seeking approval of a generic drug; a reference standard, i.e., the previously approved drug selected by FDA that an applicant must use in conducting any in vivo bioequivalence testing required to support approval of its ANDA; and the basis of submission for the ANDA.

Resources

- [About the Office Of Generic Drugs](#)
- [Activities Report of the Generic Drug Program](#)
- [Approvals & Reports](#)
- [CDER Small Business and Industry Assistance](#)
- [Competitive Generic Therapy \(CGT\) Approvals](#)
- [FDA Drug Competition Action Plan](#)
- [First Generic Drug Approvals](#)
- [First Generic Drug Approvals Previous Years](#)
- [Generic Drugs Web Pages](#)
- [Generic Drug User Fee Amendments](#)
- [GDUFA II Commitment Letter](#)
- [GDUFA II Videos and Resources](#)
- [GDUFA Science and Research](#)
- [Guidances and MAPPs Related to the Generic Drug User Fee Amendments](#)
- [List of Off-Patent, Off-Exclusivity Drug Products without an Approved Generic](#)
- [Orange Book](#)
- [Paragraph IV \(PIV\) Patent Certifications](#)
- [Product-Specific Guidances \(PSGs\)](#)
- [Upcoming Complex PSGs](#)



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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 and DCAP goals.

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