U.S. FOOD & DRUG ADMINISTRATION

OFFICE OF GENERIC DRUGS

2021 ANNUAL REPORT

Ensuring High-Quality, Affordable Generic Drugs are Available to the American Public

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

Director's Message

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

Ensuring that patients who need safe and effective medicines have greater access to them is a public health priority for the FDA. As you will read in this Report, the priority of access to more affordable medicines fits hand-in-hand with OGD's mission to ensure high-quality, affordable generic drugs are made available to the American public. In this Report, I am pleased to share with you a snapshot of our successes.

Currently 90 percent—9 out of 10—of all prescriptions dispensed in the United States are for generic drugs. To make that possible, the generic drug program approves safe, effective, high-quality drugs and monitors those drugs once they are on the market.

How Did We Do in 2021?

This past year, the generic drug program approved hundreds of abbreviated new drug applications (ANDAs) and thousands of application supplements. Our office prioritized the assessment of generic drug submissions for potential treatments and supportive therapies for patients with COVID-19, approving more than 75 original ANDAs, some in record time,[1] and since the beginning of the pandemic, more than 1,200 supplements. We funded approximately $20 million in generic drug science and research programs. We issued 149 product-specific guidances for generic drug development, including 54 for harder-to-develop complex drugs, to relay the agency's thinking on the most appropriate methodology and evidence needed to support the development of specific generic drugs.

Innovation Helped Ensure the Public's Access to More Affordable Medicines

In 2021, OGD scientific and programmatic innovations supported our generic drug assessment work. For instance, we established the scientific foundation to support alternative bioequivalence (BE) approaches for several generic drug products. One such example included a novel in vitro BE approach that directly resulted in the development, assessment, and approval of the first generic difluprednate ophthalmic emulsion (generic Durezol) used to treat eye swelling and pain after eye surgery.

Another innovation came with this year's approval of the first generic paliperidone palmitate extended-release injectable suspension (generic Invega Sustenna), a long-acting injectable product indicated for the acute and maintenance treatment of schizophrenia in adults. The FDA developed modeling and simulation approaches for pharmacokinetic study designs and BE evaluations, which the applicant used. In yet another example, we approved the first complex generic for ferumoxytol injection (generic Feraheme), a parenteral (non-oral) iron product that treats iron deficiency anemia. Our scientific investment in the characterization of the product and advanced BE study designs was essential to this approval. Another successfully deployed programmatic innovation was an increase in the frequency of certain updates from monthly to semi-monthly in the FDA's electronic Orange Book. This change in update frequency is providing even more timely information about listed drug products, including their market status.

1 Record numbers in the era of the Generic Drug User Fee Amendments (GDUFA) — 2012–present.

Scientific and Regulatory Collaboration Moved the Needle

Scientific and regulatory collaborations helped us create new approaches to support assessment of generic drug products in 2021.

FDA's partnership with the University of Maryland and the University of Michigan (the Center for Research on Complex Generics) reached thousands of stakeholders worldwide with workshops that stimulated innovative dialogue and generated new knowledge about science and research crucial for the development of complex generic medicines.

Additionally, continued implementation of the congressionally established Competitive Generic Therapy (CGT) pathway helped us reach a milestone in 2021—approving 100 ANDAs designated as CGTs. The CGT pathway for generic drugs helps incentivize the entry of drugs with "inadequate generic competition" to the market. This milestone is a sign the CGT program is achieving its goal – the development and market availability of safe, effective generic drugs in areas of the market that previously had little to no competition.

Globally, 2021 marked the launch of a joint FDA and European Medicines Agency pilot program to provide parallel scientific advice to developers of complex generic drug products. The pilot allows assessors from the two agencies to concurrently communicate their views on scientific issues, in real time, to manufacturers working to develop complex generic drugs. This collaboration can help shorten the time it takes for these important products to obtain regulatory approval. The FDA also launched the Global Generic Drug Cluster, the first forum established for leading regulatory agencies to increase scientific alignment around topics relevant to the development of generic drugs.

In 2021, even with the unique challenges caused by the ongoing pandemic, OGD continued to innovate and conduct scientific research to keep the generic drug program moving forward. Today, the generic drug program is stronger than ever and continues to take timely actions to improve access to generic drug products. As always, this is good news for the American public.

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

In 2021, even with unique challenges caused by the ongoing pandemic, we continued our work to ensure timely access to generics while also helping to fight the pandemic.

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2021 Generic Drug Program At-A-Glance

FDA's Office of Generic Drugs (OGD) hailed many successes as we continued to implement the reauthorization of the Generic Drug User Fee Amendments (GDUFA II), including:

776

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

108

Pre-ANDA meeting requests responded to regarding product development and/or pre-submission issues.

149

Product-specific guidances (PSGs) for industry and other stakeholders were issued including 88 new draft PSGs, and 61 revised draft PSGs.

1,949

Total number of PSGs including those published in 2021 that can be found on the FDA website here.

3,901

Controlled correspondence inquiries received from industry.

1,787

Complete response letters were issued detailing the deficiencies applicants needed to resolve before FDA could grant approval.

> 16,000

External stakeholders who participated and virtually viewed 6 public workshops, 2 webinars, and 1 public forum worldwide held by FDA. Topics included Immunogenicity, In Vitro/In Vitro Permeation Test Methods, GDUFA Science and Research, Modeling and Simulation Approaches, Common Labeling Deficiencies, and Product-Specific Guidances.

$20 million

Funding provided to a variety of researchers for generic drug science and research programs.

Success Highlights

FDA's generic drug program was created to enhance the availability of affordable, high-quality generic drugs in the United States. More than 10,000 generic drugs have now been approved by the FDA. Generic drugs continue to demonstrate their value proposition in the United States – representing more than 90% of all prescriptions dispensed, but only 18% of spending.[2] According to the Association for Accessible Medicines (AAM) savings from generics and biosimilars totaled $338 billion in 2020 alone, a savings increase of $23.5 billion from 2019 to 2020.[3] Increasing the availability of generic drugs helps create competition in the marketplace, which helps reduce the cost of treatment and increase access to health care for more patients.

In 2021, FDA's generic drug program worked to expand access to critical drug products necessary for the treatment of patients with COVID-19, increased critical partnerships domestically and around the world, continued to approve novel first generic drug products, encouraged competition through our program, conducted and funded an extensive amount of scientific research, modernized technology infrastructure to improve program efficiency, and increased access to critical drug products.

One example of how OGD's work expanded access to critical drug products is the February 2021 approval of a complex generic for loteprednol etabonate ophthalmic (eye-related) suspension. This drug, which treats eye inflammation, was able to use a new in vitro bioequivalence approach to support its approval. Without the new approach, generic

2 2021 AAM U.S. Generic & Biosimilar Medicines Savings Report: accessiblemeds.org/sites/default/files/2021-10/AAM-2021-US-Generic-Biosimilar-Medicines-Savings-Report-web.pdf, p. 8. October 2021.

3 Ibid. p. 7.

drug applicants would have had to recruit hundreds of cataract surgery patients to demonstrate bioequivalence. Investments in particle size characterization and eye models supported this more efficient bioequivalence method.

Overall, to enhance patient access to complex generics, in 2021 FDA awarded 6 new research contracts and 10 new grants for innovative extramural projects to support the development of generic drugs and to supplement and continue existing research projects. FDA also utilized its laboratories and computer systems to conduct more than 80 intramural Generic Drug User Fee Amendments (GDUFA) Science and Research projects focused on how to best use resources to improve generic drug development and regulatory assessment.

Potential Treatments and Supportive Therapies for COVID-19

Since the beginning of the COVID-19 pandemic, FDA has prioritized the assessment of potential generic drug treatments and supportive therapies for patients with COVID-19. OGD worked closely with Center for Drug Evaluation and Research (CDER) staff to identify products that needed to be prioritized, including products being used for patients with COVID-19 that could be in drug shortage. In 2021, this included 75+ original ANDAs and, since the beginning of the pandemic, more than 1,200 supplements. Throughout this work, OGD maintained FDA's gold standard for evaluating drug products based on quality data and sound science. Examples of supportive therapies for patients with COVID-19 include:

- Dexamethasone injection – used to treat conditions such as arthritis, blood disorders, hormone disorders, allergic reactions, skin diseases, eye disorders, breathing problems, bowel disorders, cancer, and immune system disorders
- Succinylcholine chloride injection—indicated, in addition to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation
- Propofol emulsion injection—an intravenous general anesthetic and sedation drug
- Dexmedetomidine hydrochloride injection—indicated for sedation of initially intubated and mechanically ventilated patients during treatment in an intensive-care setting and sedation of non-intubated patients prior to and/or during surgical and other procedures

Since the beginning of the COVID-19 pandemic, FDA has prioritized the assessment of potential generic drug treatments and supportive therapies for patients with COVID-19. OGD staff worked closely with colleagues throughout the Center for Drug Evaluation and Research (CDER) to identify products that could be in shortage/ needed to be prioritized.

In addition, FDA recognized that the pandemic could impact the development of generic drug products by interrupting or delaying generic drug applicants' bioequivalence studies and their submission of ANDAs to FDA for assessment. To assist applicants during the pandemic, FDA published two key guidances in 2021:

- "Protecting Healthy Patients in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency Guidance for Industry" (January)
- "Development of Abbreviated New Drug Applications During the COVID-19 Pandemic—Questions and Answers Guidance for Industry" (April with a revision in September).

Complex Generics Program

FDA's generic drug science and research program supports the development of innovative BE methodologies and more efficient BE tools that aid the development of safe, effective, and high-quality generic drug products. This research is particularly important for certain pharmaceutical products, known as complex products, which are harder to develop as generics using traditional BE methods. Complex products often have few generics or none at all. In the absence of market competition from generic products, these medicines can be so expensive that patients who need them may not be able to afford them. To facilitate access to complex generics, FDA actively engages in research to address scientific, technological, and regulatory challenges that may impact the development of complex generic products.

It is essential that FDA's regulatory decision-making is based on sound scientific methodologies and appropriate risk-based frameworks that utilize current scientific evidence; the generic drug science and research program has delivered new approaches in many categories of complex products and has allowed FDA to build a scientific and evidence-based foundation for the efficient development of these products.

Examples of complex generic drugs approved in 2021 based on research and science recommendations from FDA include:

- A generic for loteprednol etabonate ophthalmic suspension to treat eye inflammation. Our scientific investments in particle size characterization and eye models provided a new efficient in vitro bioequivalence approach. Without the new approach, applicants would have had to recruit hundreds of cataract surgery patients to demonstrate bioequivalence.
- An in vitro bioequivalence approach, developed through FDA science and research, supported approval of another generic

ophthalmic product, tobramycin, and dexamethasone ophthalmic suspension USP, 0.3%/0.1% (generic to Tobradex)—the first generic product approved for this drug since 1999—to treat the symptoms of ocular inflammation and bacterial infection of the eye.

Global Collaborations

OGD navigates the complex international landscape to help provide the American public with high-quality, more affordable medicines through its Global Generic Drug Affairs program.

In 2021, OGD strengthened international partnerships to leverage collaborations among leading global regulatory agencies and to advance generic global drug development and innovation. Global collaborations allow for:

- Information collection and dissemination to enhance regulatory decision making;
- Identification of emerging regulatory changes; and
- Proactive engagement with international partners.

All of these efforts support FDA's public health mission of assuring the safety, efficacy, and quality of FDA-regulated products for the American public.

In September 2021, FDA launched a Parallel Scientific Advice (PSA) program with the European Medicines Agency (EMA). This pilot program provides parallel scientific advice to prospective generic drug applicants of FDA's ANDAs for complex generic drug products and of EMA's marketing authorization applications (MAAs) for hybrid products. The PSA pilot program allows FDA and EMA assessors to concurrently exchange their views on scientific issues with applicants during the development phase of complex generic drug products. Additionally, in June, OGD launched the Global Generic Drug Cluster, the first forum established for leading regulatory agencies across the world specifically for generic drug development. The goal of the Generic Drug Cluster is to increase scientific alignment among these leading generic drug regulatory agencies.

Another organization with whom OGD collaborates is the International Council for Harmonisation (ICH). In 2021, the ICH Generic Drug

Discussion Group assessed feasibility of harmonization and the impact on public health of several complex generic product categories by creating a comprehensive map of topics to recommend for the development of future ICH guidelines. Additionally, the ICH M13 Expert Working Group continued to develop guidelines on bioequivalence for immediate release oral solid dosage forms.

OGD is also involved in two working groups with the International Pharmaceutical Regulators Programme, or IPRP: the IPRP Bioequivalence for Generic and Nanomedicines Working Groups.

- The Bioequivalence Working Group for Generics is interested in the application and interpretation of BE requirements, and information and procedures for BE assessment.
- The Nanomedicines Working Group covers the exchange of non-confidential information on nanomedicines and nanomaterial in drug and combination products.

Center for Research on Complex Generics (CRGC)

One of the greatest challenges to the development of complex generics, as reported to FDA in industry and stakeholder feedback, is uncertainty about how to implement scientific insights from generic drug research in a manner consistent with FDA's regulatory expectations. This includes the development of suitable test procedures, study designs, model integrated evidence, or other data and information needed to support generic drug applications. The CRCG, established in 2020 by an FDA grant, plays a vital role in addressing these challenges by supporting FDA's efforts to enhance research collaborations with the generic industry. For example, public workshops in 2021 worked to advance programs and stimulate scientific dialogue, disseminate current insights about complex generics, and generate new knowledge in support of FDA's mission of increasing access to safe and effective generic medicines.

FDA-CRCG workshops held in 2021:

In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions

August 18-20, 2021

The purpose of this workshop was to discuss the scientific principles and practical considerations that inform current FDA thinking and United States Pharmacopeia (USP) recommendations for IVRT and IVPT studies, to identify areas that would benefit from further research, and to discuss opportunities for further coordination and collaboration between the FDA, USP, academic institutions, product manufacturers, diffusion cell equipment manufacturers, contract research organizations, consultants, and other stakeholders.

Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches

September 30 – October 1, 2021

The generic drug industry and other stakeholders discussed how mechanistic modeling and simulation could support product development and regulatory submissions, shared the current state of mechanistic modeling for bioequivalence (BE) assessment through case studies, established a consensus on best practices for using physiologically-based pharmacokinetic (PBPK) and computational fluid dynamic (CFD) modeling for BE assessment to help drive further investment by the generic drug industry into mechanistic modeling and simulation, and discussed the roll out of the concept of a Model Master File to improve model-sharing between model developers, industry, and FDA.

Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products

November 30, 2021

This workshop engaged experts in the field of modeling and simulation in the generic and new drug industries, academia, and relevant stakeholders who explored, identified, and recommended best practices for the development and assessment of model integrated approaches for BE assessment of long-acting injectables and implants. The workshop focused on how model-integrated approaches support innovative study designs and data analyses and how they can be validated and verified.

Competitive Generic Therapy (CGT) Approvals

The U.S. Congress established the Competitive Generic Therapy (CGT) pathway for generic drugs in 2017 to incentivize the development and market entry of drugs with "inadequate generic competition." This inadequacy exists when there is only one or no company marketing a product (e.g., sole-source drugs) which often arises when products have limited markets or are difficult to develop. In a two-step process, generic applicants (i.e., manufacturers) may, before or at application submission, request a CGT designation and, if granted then potentially become eligible for 180-day CGT exclusivity upon approval of the product. In a study conducted by FDA and published in the Journal of the American Medical Association, it was shown that, among the approved CGT-designated drugs analyzed in the study eligible for CGT exclusivity, approximately 85% began commercial marketing within a median of 2.5 days from approval. As of December 31, 2021, FDA had approved 119 generic drug products with a CGT designation. Of that total, 52 were approved in 2021.

SPOTLIGHT: 100 CGT APPROVALS MILESTONE

In 2021, FDA reached the milestone of approving 100 ANDAs with a Competitive Generic Therapy (CGT) designation, with more than half receiving exclusivity. There has been incredible interest in the CGT program since its inception for a broad range of products and therapeutic areas. Approving 100 ANDAs with CGT designations is a sign the program is achieving what was hoped—spurring both the development and market availability of safe and effective generic drugs in areas of the market that previously had little to no competition, giving patients more affordable access to medicines.

Modernizing OGD's Information Infrastructure

In conjunction with FDA's Office of Information Technology and CDER's Center IT Liaison Office, OGD rolled out new information technology platforms to support multiple ways for internal collaboration and communication, as well as new productivity and cybersecurity tools that support advancements in drug safety priorities and drug supply chains. For example, in 2021, OGD successfully completed three IT modernization pilots.

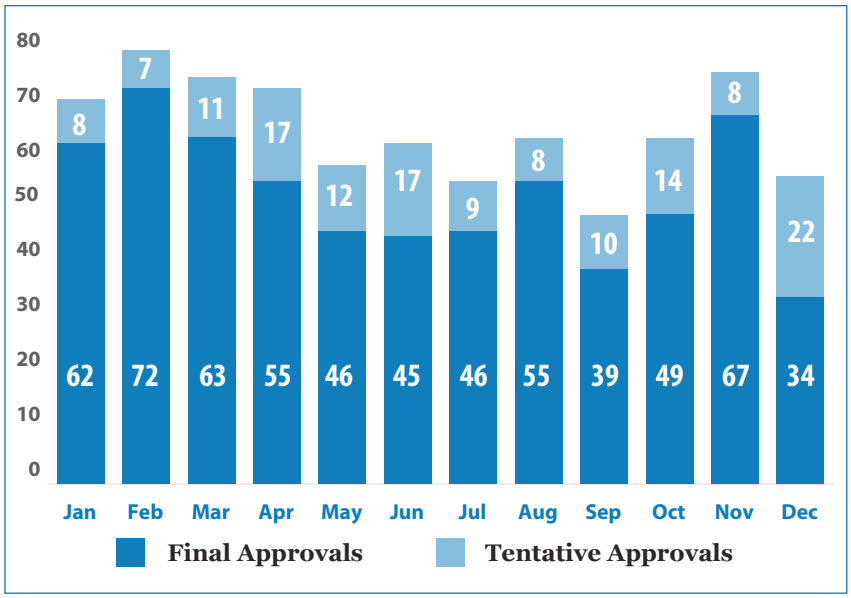
These pilots included the transition of the Controlled Correspondence process [inquiries submitted to the Agency by (or on behalf of) a generic drug manufacturer or related industry, requesting information on a specific element of generic drug product development] to a more modernized IT platform. They also included updating an internal tool used for reviewing generic drug labeling and creating a new patent review workflow for the Orange Book. OGD also launched a process development effort to apply structured review technology to its bioequivalence reviews of generic drug applications. In addition, OGD continued its involvement in many activities and initiatives around CDER data and informatics modernization, including work to facilitate overall systems integration approaches for all analytics and data needs.

In June 2021, OGD completed a pilot initiative to implement "Bioequivalence Assessment Mate (BEAM)"—a BE assessment tool in the in vivo pharmacokinetic BE study review process. A total of 60 ANDA BE reviews were completed using BEAM. Based on knowledge and experience gained from BEAM, we were able to initiate a knowledge-based, computer-aided BE structured review template. The modernized BE review template resource created an efficient and productive BE structured review template with high data automation and knowledge management capabilities.

Generic Drug Approvals

Generic medicines continue to account for approximately 90% of all prescription drugs dispensed in the U.S. FDA's generic drug program continued to maintain a robust generic drug assessment program to review and approve safe, effective, high-quality drugs and to monitor generic drugs once they are on the market.

2021 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.*

First Generics

First generic drugs provide access to needed therapies that treat a wide range of medical conditions and where no competition previously existed. Because of their importance to public health, FDA prioritizes review of submissions for these products. In 2021, OGD approved 93 first generic drugs.

Significant First Generic Drug Approvals in 2021

Generic Name	Brand Name	Indication	Approval Date
Linaclotide Capsules	Linzess Capsules	Irritable bowel syndrome with constipation and chronic idiopathic constipation	2/9/2021
Apremilast Tablets	Otezla Tablets	Moderate to severe plaque psoriasis	2/18/2021
Hydrocodone Bitartrate Extended-Release Tablets	Hysingla ER Tablets	Severe pain	3/1/2021
Ibrutinib Capsules	Imbruvica Capsules	Mantle cell lymphoma (MCL)	3/31/2021
Enzalutamide Capsules	Xtandi Capsules	Prostate cancer	5/14/2021
Lenalidomide Capsules	Revlimid Capsules	Multiple myeloma, anemia, and certain lymphomas	5/21/2021
Tofacitinib Tablets	Xeljanz Tablets	Certain types of arthritis and ulcerative colitis	6/1/2021
Difluprednate Opthalmic Emulsion	Durezol Ophthalmic Emulsion	Inflammation/pain associated with ocular surgery and treatment of endogenous anterior uveitis	8/9/21
Varenicline Tablets	Chantix Tablets	Smoking cessation	8/11/2021
Linagliptin Tablets	Tradjenta Tablets	Type 2 Diabetes Mellitus	8/31/2021
Dasatinib Tablets	Sprycel Tablets	Chronic myeloid leukemia	11/23/2021

Communicating with Industry

OGD communicated with industry through more than 4,250 information requests (IRs), more than 2,275 discipline review letters (DRLs), and 1,787 complete response letters (CRLs). These requests and letters identify issues that need to be addressed by applicants before the FDA can approve an application. Another important tool used to communicate with prospective generic drug applicants is controlled correspondence. A controlled correspondence is an inquiry 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 helps support the submission of higher quality generic drug applications. In 2021, OGD received more than 3,900 controlled correspondence inquiries submitted by industry.

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) first enacted by Congress in 2012. The fees are negotiated between FDA and industry every 5 years. The implementation of GDUFA by FDA encompasses a wide range of human generic drug activities and includes a commitment to meet specific performance goals. GDUFA includes a science and research program that is carried out through extensive intramural research collaborations among FDA scientists as well as through numerous extramural collaborations with research institutions around the world. Of note, GDUFA science and research provides data to support the assessment and approval of ANDAs referencing complex products, which ultimately improves patient access to complex generics that were unfeasible to develop even just a few years ago.

For example, in August 2021 FDA approved an ANDA for the first generic difluprednate ophthalmic emulsion. Ophthalmic emulsions like this one have been challenging to develop as generics because they have a complex dosage form and are administered by a complex route of delivery. After generic industry stakeholders and FDA collaboratively established a research priority to develop new bioequivalence methods and pathways for locally acting drug products, the GDUFA Program coordinated intensive collaboration among experts in multiple offices across OGD and the Office of Pharmaceutical Quality (OPQ) as well as the Center for Devices and Radiological Health (CDRH). The collaborations resulted in numerous scientific innovations, including several research breakthroughs that established the scientific foundation for bioequivalence recommendations in a PSG for difluprednate ophthalmic emulsion, and directly facilitated the development, assessment, and approval of the first generic difluprednate ophthalmic emulsion.

Looking ahead to GDUFA III

In 2021, together with stakeholders, OGD made progress toward the reauthorization of GDUFA for FY23-FY27, known as GDUFA III. Every 5 years, this stepwise process leads to Congressional reauthorization of critical GDUFA funding that allows FDA to continue to ensure patients have access to high-quality, safe, and effective generic medicines. Amidst the backdrop of the ongoing pandemic, FDA and industry concluded the negotiations in September 2021 and reached a proposed agreement for GDUFA III. The successful negotiations will enable the proposed agreement to go to Congress for enactment in 2022.

Some of the proposals in the agreement include:

Pre-ANDA Program Enhancements

- FDA's process for reviewing and responding to suitability petitions will be enhanced. Beginning in FY 2024, any newly submitted suitability petition will undergo a completeness assessment, receive a goal date, and receive a prioritization assessment under defined parameters in the proposed Commitment Letter.
- The product-specific guidance (PSG) program will be enhanced through new goals around PSG development for complex products to further aid in the development of complex generics, and by providing information on FDA.gov about upcoming new and revised PSGs and PSG prioritization.
- Other proposed enhancements include allowing certain ANDA applicants to request a "PSG Teleconference" to obtain FDA feedback on the potential impact of new PSG recommendation(s) on ongoing in vivo bioequivalence studies.

ANDA Assessment Program Enhancements

- The ANDA assessment process will be enhanced to include additional methods for FDA to work with applicants to resolve issues during the review cycle, even when this may require goal date extensions, in order to reduce the number of assessment cycles and facilitate timely access to generic drugs.
- The definition of controlled correspondence will be expanded to include correspondence seeking regulatory and/or scientific advice after issuance of a CRL, tentative approval, or ANDA approval.
- Under certain circumstances, a new Enhanced Mid-Cycle Review Meeting will be available for applicants to ask questions related to a proposed scientific path to address deficiencies identified in a mid-cycle discipline review letter (DRL).

A full description of all the proposed recommendations, the GDUFA Reauthorization Performance Goals, and the Program Enhancements for Fiscal Years 2023-2027, also known as the GDUFA III Commitment Letter, can be found at www.fda.gov/media/153631/download.

GDUFA Science and Research in OGD

How the Generic Drug Program's Research Makes a Difference

The GDUFA Science and Research Program supports the development of innovative methodologies and more efficient tools that help establish drug equivalence standards and ensure the development of safe, effective, and high-quality generic drug products for the American public. The results of OGD's GDUFA science and research provide needed information and tools for industry to develop new generic drug products and for FDA to evaluate the bio- and/or therapeutic equivalence of proposed generic drugs. In 2021, this research was particularly important for certain pharmaceutical products, known as complex products, which are harder to develop as generics. Complex products frequently have little to no generic competition. In the absence of market competition from generic products, these medicines can be so expensive that patients who need them may not be able to afford them.

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 priorities and projects. In 2021, FDA funded approximately $20 million in science and research programs. FDA awarded funding for 6 new contracts and 10 new grants, as well as 10 ongoing grants and 20 contracts to conduct science and research. OGD continued 80 ongoing external research collaborations, and in keeping with FDA's commitment to promote high quality, clinically relevant science, OGD staff or their external collaborators published 53 peer-reviewed scholarly articles, presented 80 external talks, and presented (virtually) 68 posters at national and international scientific and medical conferences.

In 2021, FDA published GDUFA Science and Research Outcomes for FY 2020 on an easily accessible web page. The web page provides information throughout a given fiscal year 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. FDA provided the information to create public transparency regarding the important work of the generic drug program to advance the science of generic drugs. More details about outcomes are included in the FY 2020 GDUFA Science and Research Report.

FDA conducts ongoing research to evaluate generic substitution in various ways, including through clinical studies of substitution in patients, analyzing medical informatics data, and surveying studies of patient and provider perceptions impacting generic substitution.

Generic Substitution and Safety of Generic vs. Brand-Name Drugs

As part of its GDUFA-funded research projects, FDA is conducting ongoing research to evaluate generic substitution in various ways, including through clinical studies of substitution in patients, analyzing medical informatics data to evaluate generic utilization and substitution, and surveying studies of patient and provider perceptions impacting generic substitution.

In 2021, FDA reviewed the feasibility of using Sentinel data to investigate generic performance in terms of therapeutic equivalence with the reference product. Sentinel is FDA's national medical product monitoring system and houses the largest multisite distributed database in the world dedicated to medical product safety.

Additionally, ongoing research efforts focused on evaluating the substitutability of approved generic products and their corresponding reference products. For instance, FDA collaborated with the Yale University-Mayo Clinic (Yale-Mayo) Center of Excellence in Regulatory Science and Innovation (CERSI) to characterize whether users of different generic levothyroxine products used to treat underactive thyroid and other conditions had equivalent clinical outcomes, in particular thyroid stimulating hormone (TSH) levels. Preliminary results showed that there were no significant differences among the various generic levothyroxine products and there is no need to caution against switching between different generic products. A second award with the Yale-Mayo CERSI was designed to control for unobserved confounding that is ubiquitous in observational studies. Preliminary results showed the global treatment effect was not significantly different between generic levothyroxine and brand levothyroxine products.

Other ongoing internal research efforts include monitoring postmarket performance of a first generic, Wixela Inhub®, which is an approved generic of Advair Diskus® for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Internal research has also been initiated to evaluate the application of pharmacogenomic (PGx) information for BE purposes. PGx information can be applied in BE studies for generic drug development to further enhance subject safety and BE study design. The ongoing research will help determine when PGx information should be used to identify subjects vulnerable to serious adverse events, minimize carryover effects in a crossover study, and ensure balanced groups in a parallel study.

Significant 2021 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 presented and discussed at major medical and scientific meetings to contribute to and facilitate generic drug product development, and to support the efficient review and timely approval of ANDAs. OGD's GDUFA Science and Research Program included the following 13 research areas, each highlighted with a key outcome in 2021.

- **Abuse-Deterrent Opioid Drug Products**
  In vitro and in vivo studies were performed which provided mechanistic, clinically meaningful insights about the role of excipients in products that may be abused. In vivo studies in guinea pigs identified that one such excipient, high molecular weight polyethylene oxide, was associated with a risk of kidney damage. Subsequent in vitro studies were initiated to develop efficient tools that could test excipient formulations and reproduce the mechanistic effects that may correlate with kidney damage in vivo.

- **Complex Injectables and Formulations**
  In vitro studies were performed that systematically characterized the influence of manufacturing conditions on the arrangement of matter in liposomal Amphotericin B. This research revealed how the manufacturing process changed the molecular state of the drug and its association with the lipid shell of the liposome and illustrated how this affected drug release.

- **Complex Mixtures and Peptide Products**
  In vitro and in silico studies were performed to develop efficient ways to anticipate or characterize impurities that can arise in oligonucleotide or peptide drug products. This research will help inform product-specific guidances for these products to facilitate the development and approval of generics in this evolving class of therapeutics.

- **Data Analytics**
  Research exploring artificial intelligence methods resulted in the successful development of a novel tool that can assist FDA scientists who collect and organize large amounts of detailed scientific information to be reviewed, so that they can assess whether the information supports specific regulatory decisions.

- **Drug-Device Combination Products**
  In vivo studies involving patients with asthma and chronic obstructive pulmonary disease provided new insights into patient perceptions about generic dry powder inhalers, which can help identify and characterize potential differences in the user interface of generic drug-device combination products, and to evaluate how such differences may affect the risk of user medication errors when a patient switches from using the brand name product to a generic.

- **Inhalation and Nasal Drug Products**
  In vitro and in vivo studies were performed to clarify whether differences in the characteristics of dry powders (drugs) that are inhaled into the lung (which causes orally inhaled drug particles to deposit in different regions of the lung) can be differentiated by efficient plasma or serum pharmacokinetic studies. The result of these studies indicated that pharmacokinetic parameters can be sensitive to differences in regional lung deposition and this sensitivity may be dependent on specific parameters for dry powder inhalers.

- **Locally Acting Physiologically Based Pharmacokinetic (PBPK) Modeling**
  An extensive literature search was performed to characterize the differences in anatomy and physiology between animals (like rabbits) and humans, as well as to identify scientific issues that may otherwise limit the extrapolation of animal data to humans. These anatomical and physiological parameters were incorporated into PBPK models that have the potential to help predict human ocular pharmacokinetics and pharmacodynamics through interspecies extrapolation by PBPK modeling, and thereby, support the development of locally acting ophthalmic generics which are very challenging to study in humans.

- **Long-Acting Injectables and Implanted Products**
  In vitro studies were performed that revealed injectable suspensions can be very sensitive to the shear forces produced when such formulations get injected; the reversable flocculation or deflocculation of drug particles was highly dependent upon the differences in shear. Since deflocculated particles may dissolve up to six times faster than the flocculated particles, these studies suggested that differences in shear forces during the administration of injections may have the potential to substantially alter bioavailability, and may increase variability in product performance, if not controlled.

- **Ophthalmic Drug Products**
  A novel in vitro release test (IVRT) method involving adaptive perfusion was developed based upon tangential flow filtration principles; it provided size-based separation of particulates with a simultaneous analysis of the released drug as well as the remaining drug. Using this novel IVRT method, discriminatory drug release profiles were obtained in solutions, micelles, and nanoemulsions of small, medium, and large size globules.

- **Oral Absorption Models and Bioequivalence**
  A review of relevant literature describing differences in relative bioavailability between adult and pediatric populations indicated that particular care is needed for Biopharmaceutics Classification System (BCS) Class II drugs and narrow therapeutic index drugs, when assessing the bioequivalence of products used in a pediatric population. Biorelevant dissolution methods were explored for several drugs that have been studied in both adults and children, and their dissolution profiles are being integrated into PBPK modelling to determine whether these methods provide suitably discriminatory tools to better predict bioequivalence for children based upon studies performed in adults.

- **Patient Substitution of Generic Drugs**
  The rising cost in recent decades of inhaled corticosteroid and long acting β agonist combination products has led to concerns about equitable patient access to these products. The availability of generic alternatives for such products can improve patient access to more affordable, high quality, safe, and effective medicines. To understand the potential impact of generics for such products on patient access, an analysis of pharmacoeconomic data was performed.

- **Quantitative Clinical Pharmacology**
  Research into the development of model-integrated strategies for generic long-acting injectable and implantable drug products indicated that one of the advantages of using the model-integrated approach is that it can increase statistical power while handling differences in the rate and extent of drug absorption with an adequately controlled Type 1 error.

- **Topical Dermatological Products**
  In vitro studies were performed to understand the impact of differences in manufacturing processes, and corresponding differences in the physicochemical and structural properties of topical gels, on the release and bioavailability of tretinoin from topical gels with nanotechnology microparticles. The results indicated that it is essential to understand the manufacturing processes of a topical microparticle gel, because manufacturing differences may alter the quality and performance of such products.

Consistently and Efficiently Evaluating Generic Drugs and Monitoring Generic Drug Safety

OGD follows a rigorous assessment process to ensure that, compared to the brand-name drug, a generic drug has the same:

- Active ingredients (the ingredients that treat a condition or symptoms)
- Strength
- Dosage form (for example: tablet, capsule, cream, patch, or liquid)
- Route of administration (for example: oral, topical, inhalation, or injection)
- Conditions of use
- Labeling (with certain exceptions)

OGD continues to maintain a robust drug lifecycle management program for evaluating generic drugs and monitoring their safety once marketed. In 2021, OGD reorganized several divisions to create the Office of Safety and Clinical Evaluation (OSCE) and to continue to improve the efficiency and consistency of our assessments and approvals of applications of novel and complex generic drug products. The realignment of these sub-organizations placed scientists and other

staff with expertise in clinical assessment, such as clinical endpoint bioequivalence studies and comparative analyses review, and drug safety under one office within OGD to create better resource efficiency. This has maximized operational effectiveness and the ability of subject matter experts to collaborate on clinical and pharmacologic/toxicologic scientific analyses, and on the surveillance of pre-market and post-market drug safety data.

OGD safety staff review Bio-Investigational New Drug Applications (Bio-INDs) and pre-approval serious adverse events from both Bio-IND studies and other bioequivalence/bioavailability studies that support ANDAs. OGD safety staff also review adverse event reports and trends, initiate GDUFA-related post market safety research and support CDER's Postmarket Safety Modernization efforts, including through identifying, evaluating, and resolving newly identified safety signals consistent with CDER's MAPP 4121.3 Collaborative Identification, Evaluation and Resolution of a Newly Identified Safety Signa . Staff perform generic drug safety and surveillance outreach through presentations and publications to generic drug stakeholders including patients, healthcare providers, pharmacists, and drug safety focused organizations.

In 2021, OGD's key safety evaluation and assessment contributions included 30 responses to COVID-related inquiries and 166 assessments for drug-device combination products. OGD safety staff also conducted outreach to stakeholders on data integrity issues, Drug Master Files, impurity safety assessments, flavors in oral dosage forms, extractables and leachables assessments, novel excipients, and excipient safety reviews.

Safety/Surveillance Highlights

OGD evaluates generic drug safety before the product is approved and continues monitoring and evaluating the safety of the product after approval and throughout the time it is available for sale in the United States. Effective postmarket surveillance is essential to making sure that FDA-approved generic drugs provide the same therapeutic effect and safety as their brand-name counterparts.

Highlights of OGD's safety and surveillance work in 2021 include:

JANUARY

Publication of the FDA Drug Safety and Availability communication "FDA updates vinca alkaloid labeling for preparation in intravenous infusion bags only." Continued efforts to have all ANDA holders of vincristine sulfate, vinblastine sulfate, and vinorelbine tartrate drug products remove instructions for use with a syringe and add use with minibags to address the risk of fatal neurologic injury or death related to accidental spinal, rather than intravenous, administration of these chemotherapies.

JUNE

Collaborated with CDER's Office of Medical Policy in updating the "Safety Reporting Requirements for BA and BE Studies" portion of the draft guidance for industry "Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies."

JULY

Collaborated with other CDER offices in the publication of a Consumer Update which provided important safety precautions in the storage, use, and disposal of fentanyl patches (predominantly generic drug products) in order to prevent accidental exposure and poisoning in children.

SEPTEMBER

Contributed to the investigation that supported FDA's communication to the public regarding data integrity concerns with clinical and bioanalytical studies conducted by Synchron Research Services and Panexcell Clinical Lab in support of certain ANDAs and NDAs.

Collaborated with CDER's Office of Medical Policy in updating the draft guidance for industry "Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices."

Risk Evaluation and Mitigation Strategies (REMS) Highlights

FDA can require a REMS for a drug if the Agency determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks. OGD's REMS Team assists with developing, implementing, managing, and evaluating REMS-related activities for ANDAs. If a generic drug's reference listed drug is subject to a REMS, the generic drug is subject to certain elements of the REMS. REMS Team members serve as experts on the statutory and regulatory requirements and recommendations in FDA guidance documents related to ANDAs subject to REMS requirements and they assist generic drug applicants in developing and maintaining REMS for these ANDAs. For example, in 2021 OGD's REMS Team:

- Supported the first generic approval of Macitentan Tablets, which led to the first Shared System REMS for Macitentan.
- Supported the first generic approval of Lenalidomide Capsules, which contained the first Shared System REMS for Lenalidomide.

Communicating Safety Surveillance Activities to Stakeholders

OGD's staff led or participated in public workshops on nitrosamine impurities and their safety and completed 73 projects for CDER COVID-19 priority drugs. They also collaborated with FDA's National Center for Toxicological Research for upgrades to FDA Label, FDA's web database application that allows users to perform customizable searches of the more than 140,000 label entries, resulting in FDA Label version 2.6.

Additionally, FDA staff presented OGD's scientific approach to conducting safety evaluations and postmarket surveillance and engaged with major stakeholder audiences:

JANUARY

Presented *Update on Safety Surveillance for Generic Drugs* at the Drug Information Association Pharmacovigilance and Risk Management Strategies Conference: FDA Updates in Pharmacovigilance session.

APRIL

Presented and participated in panel discussions at the CDER Small Business and Industry Assistance (SBIA)Generic Drugs Forum 2021: Lifecycle of a Generic Drug

SEPTEMBER

Presented *Comparative Analyses for Generic Oral Inhalers* in Session 5: Complex Generics: Nasal and Inhalation Products at the CDER Small Business and Industry Assistance Advancing Generic Drug Development: Translating Science to Approval.

Advancing Bioequivalence and Generic Drug Assessments

A brand-name drug product and a generic drug product are considered bioequivalent when there is not a significant difference in the rate and extent to which the active pharmaceutical ingredient becomes available at the site of the drug action when they are administered at the same dose under similar conditions in an appropriately designed study.[4] OGD assesses the bioequivalence (BE) of ANDAs, including through evaluation of studies that use pharmacokinetic, pharmacodynamic, and comparative clinical BE endpoints. OGD also assesses new methodologies to demonstrate BE, especially for generic drugs with complex dosage forms which pose challenges to the use of traditional approaches for demonstrating BE.

In 2021, OGD performed more than 1,700 BE assessments related to ANDA originals, amendments, and supplements. This number also included 550 clinical assessments, 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).

Throughout 2021, OGD worked with CDER's Drug Nitrosamine Impurities Task Force addressing ongoing issues related to the presence of nitrosamine impurities in ranitidine, metformin, rifampin, rifapentine, and varenicline drug products. OGD provided expert review to develop new highly sensitive methods for detecting and limiting nitrosamine impurities which are probable human carcinogens. OGD worked with

4 Bioequivalence definition in the preface of the FDA's Orange Book online at www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.

OGD assesses the bioequivalence (BE) of ANDAs, including through evaluation of studies that use pharmacokinetic, pharmacodynamic, and comparative clinical BE endpoints.

international stakeholders to evaluate the extent and severity of the concerns and take steps to mitigate the risks associated with these impurities. OGD made assessments and set thresholds for 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 and to ensuring that generic drug products were not approved with unacceptable levels.

Of all the assessments conducted in 2021, more than 166 were comparative analyses assessments. A comparative analysis helps to support findings of sameness of the generic product to its RLD, and to support therapeutic equivalence, which is a determination that the generic product will have the same clinical effect and safety profile as its RLD when administered to patients under the conditions specified in the labeling.

OGD also assessed an increased number of topical products that demonstrated BE using an in vitro approach, leading to "first generic" approvals such as clindamycin gel. The in vitro option eliminates the burden on applicants to conduct typically large (e.g., 1000+ subjects) comparative endpoint studies for such products, increasing the potential for more generic topical drug products to reach the market.

Another noteworthy approval that required an innovative BE assessment approach was for hydrocodone bitartrate extended-release tablets which are indicated for the management of severe pain. The reference listed drug formulation has abuse-deterrent properties per its labelling and therefore the generic product was expected to demonstrate that it was no less abuse deterrent for all potential routes of abuse as compared to the reference listed drug product. OGD assessors worked on guidance development and data analysis over several assessment cycles, which ultimately resulted in the approval of this first generic product with demonstrated abuse-deterrent properties.

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

As part of OGD's efforts to improve patient access to generic drugs, we take steps to maximize scientific and regulatory clarity for generic drug developers regarding how they can meet the requirements for approval. Timely recommendations from FDA allow generic drug applicants to build that information into their research and development programs and helps them submit higher quality ANDAs. As further described below, there are a variety of ways OGD makes its current thinking on regulatory and scientific issues known to applicants and the general public. For example, in 2021, FDA issued four final and two draft guidances for industry related to generic drugs (not including the product-specific guidances discussed below), two Federal Register Notices, and one MAPP.

OGD publishes guidances that, when finalized, describe the Agency's current thinking and recommendations to industry on regulatory and scientific issues related to generic drugs. Guidances are available on-line in the FDA Guidance Documents database by choosing the "Generic Drugs" topic. Below are the guidances issued in 2021.

Final Guidances

- Protecting Healthy Patients in Bioequivalence Studies for Abbreviated New Drug Applications During the COVID-19 Public Health Emergency
- Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers

- M9 Biopharmaceutics Classification System-Based Biowaivers Final Guidance
- ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin

Draft Guidances[5]

- Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA
- Cover Letter Attachments for Controlled Correspondences and Abbreviated New Drug Application Submissions

Manual of Policies and Procedures (MAPP)

CDER's Manual of Policies and Procedures (MAPP) describes internal Agency policies and procedures and is accessible to the public to help make the Agency's operations more transparent. In 2021, FDA issued the following MAPP related to generic drugs:

- Generic Drug Labeling Revisions Under Section 505(j)(10) of the Federal Food, Drug, and Cosmetic Act (5230.3)

Federal Register (FR) Notices

- Listing of Patent Information in the Orange Book
- Drug Products Approved Under ANDAs Before the Enactment of the Hatch-Waxman Amendments

Other Policy Resources

- Competitive Generic Therapy Approvals — updated biweekly
- List of Off-Patent, Off-Exclusivity Drug Products without an Approved Generic — updated June and December
- Paragraph IV Certifications List – updated biweekly

Product-Specific Guidances (PSGs)

To further facilitate generic drug product availability and assist generic drug developers with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA publishes PSGs, which describe the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs. In 2021, OGD also published a new infographic, a PSG Snapshot that provides highlights of FDA's PSG program. This infographic explains what a PSG is, what the PSG development timeline is for newly approved drugs, and more.

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

PSGs help the generic drug industry make more efficient and cost-effective research and development decisions and advance the opportunity for discussion of new or alternative generic drug development strategies — especially for complex generic drug products. PSGs also help applicants submit ANDAs with fewer deficiencies to FDA, which helps lead to more first-cycle approvals. OGD develops PSGs based on public health priorities, requests from industry, and current and anticipated patient and industry needs, and consistent with OGD's GDUFA II commitments.

In 2021, OGD developed 54 new PSGs for complex products — an OGD priority. Some of those PSGs included in vitro BE options for assisting generic drug development, such as the PSGs for Trelegy Ellipta (fluticasone furoate; umeclidinium bromide; vilanterol trifenatate powder for inhalation), Nayzilam (midazolam nasal spray), Gimoti (metoclopramide metered nasal spray), and Anjeso (meloxicam solution for intravenous use).

Some PSGs for complex drug-device combination products such as Alvesco (ciclesonide inhalation aerosol, metered), and Atrovent HFA (ipratropium bromide inhalation aerosol, metered) were revised in 2021 to include recommendations for using additional in vitro, in vivo, and in silico studies as an alternative approach to conducting the recommended comparative clinical endpoint BE studies, incorporated in the recommended weight-of-evidence approach to facilitate greater access to affordable generics.

In total, FDA issued 149 PSGs in 2021, of which 88 were new draft PSGs, and 61 were revised draft PSGs (revisions to existing PGSs are generated, for example, as new information or scientific methodologies become available). Fifty-four of the new PSGs were for complex products. As of December 31, 2021, FDA had published 1,949 PSGs, which can be found on FDA's website at the Product-Specific Guidances for Generic Drug Development section.

Additionally, OGD held a webinar titled "FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs" in May 2021 that highlighted how PSGs are developed and revised and their role in facilitating generic drug development and generic drug application assessment. OGD discussed ways prospective and current generic drug applicants can use PSGs, including those for complex products, to improve the efficiency of generic drug development.

In 2021, in collaboration with CDER Small Business and Industry Assistance (SBIA), OGD published an eNewsletter (SBIA Chronicles) article and an accompanying Audio Podcast on *"The ABCs of Product-Specific Guidances"* as an added resources for stakeholders to learn more about the FDA's PSG program.

Timely recommendations from FDA allows generic drug applicants to build FDA science and research information into their development programs, and helps applicants submit higher quality ANDAs.

Orange Book Enhancements

In 2021, FDA established a public docket to solicit comments on several issues related to FDA's regulation of certain drug products approved under abbreviated new drug applications before the enactment of the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. As explained in the Federal Register Notice, FDA also began adding RLD designations for Pre-Hatch-Waxman ANDAs (PANDAs) to the Orange Book and will continue making these designations as expeditiously as resources permit. Designation of PANDA products as RLDs provides clarity both to prospective 505(j) ANDA applicants seeking to make generics of these products, and to applicants of 505(b)(2) NDAs that FDA's finding of safety and effectiveness for these drugs may be relied upon for approval. In addition, it is aligned with FDA's efforts to help advance competition and increase patient access to more affordable medicines. To aid stakeholders in identifying PANDAs, OGD also posted a list of the products currently included in the Orange Book and identified as being approved under an ANDA that were approved for safety and effectiveness under section 505(c) of the FD&C Act in a PANDA prior to the enactment of the Hatch-Waxman Amendments. This list is available under "Additional Resources" on FDA's Orange Book web page.

OGD also began providing certain updates to the Orange Book on a semi-monthly rather than monthly schedule. Increasing the frequency of these updates provides information pertaining to market status and therapeutic equivalence on an even more timely schedule.

Other Initiatives to Support Generic Drug Competition

FDA is committed to addressing the high cost of medicines by encouraging robust and timely market competition for generic drugs through various initiatives, one of which is FDA's Drug Competition Action Plan (DCAP). Through this plan, FDA continues 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. Bringing greater transparency to the generic drug review and approval process and removing barriers to generic drug development and market entry, supports patients' access to the medicines they need at affordable prices. A number of the policy actions that OGD took in 2021 were DCAP deliverables.

Among OGD's initiatives to increase access to affordable medicines is our work to implement the law widely known as CREATES, which was enacted in December 2019 as part of the Further Consolidated Appropriations Act of 2020, and which provides an important new pathway for developers interested in developing generic, 505(b)(2), and biosimilar products to obtain access to the samples of brand-name products that they need to support their applications. In 2021 OGD issued 21 *Covered Product Authorization Letters* for generic drug developers to obtain samples of brand products that they needed to support their ANDAs.

OGD also maintains the List of Off-Patent, Off-Exclusivity Drug Products without an Approved Generic (OPOE list) to improve transparency and encourage the development and submission of generic applications for drugs with limited competition. The list is updated by OGD 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. Starting with the December 2021 update to the list, FDA is now publishing two versions of the OPOE list, one for prescription drug products and one for over-the-counter drug products that are approved and marketed under an NDA.

In support of FDA's DCAP and using FDA developed tools, the U.S. Pharmacopeia (USP), an independent, scientific nonprofit organization focused on building trust in the supply of safe, quality medicines, prioritized the development of monographs associated with drug products on the OPOE list. USP successfully developed 14 monographs (associated with 13 drug products on the OPOE list), including treatments for chronic Hepatitis B, major depressive disorder, and short-term intravenous sedation. USP is continuing these efforts using FDA developed tools to help support the development of new generic drugs to foster a more competitive marketplace for medicines.

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

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

National Center for Toxicological Research

Office of the Chief Counsel

Office of the Commissioner

Office of Executive Programs

Office of Regulatory Affairs

We would like to thank our 2021 internal collaborators, especially the Office of Pharmaceutical Quality, who greatly contributed to our successes in 2021. We look forward to future collaborations that will help us further increase access to generic drugs for the American public.

Appendix

Public Workshops, Webinars, and Forums

Non-clinical Immunogenicity Assessment of Generic Peptide Products
(January 26, 2021)
FDA's Office of Generic Drugs, in collaboration with the Office of Pharmaceutical Quality and Office of Translational Sciences, and the Center of Biologics Evaluation and Research, hosted this virtual workshop. The workshop brought together global experts from industry, academia, and FDA to discuss the current regulatory thinking and challenges on non-clinical assays for comparative immunogenicity risk assessment for certain generic peptide products outlined in FDA's guidance *ANDAs for Certain Highly Purified Synthetic Peptide Drug Products That Refer to Listed Drugs of rDNA Origin*. This virtual event attracted over 900 attendees globally.

Generic Drugs Forum 2021: Lifecycle of a Generic Drug
(April 28–29, 2021)
FDA held its annual Generic Drugs Forum in April 2021 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. The information was intended 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 had more than 2,250 attendees from 101 countries.

Webinar: FDA Product-Specific Guidances (PSGs): Lighting the Development Pathway for Generic Drugs
(May 5, 2021)
In this webinar, FDA provided an overview of PSGs, including how they are developed and revised, and of their role in facilitating generic drug development and generic drug application review. Also discussed were ways prospective and current generic drug applicants can use PSGs, including those for complex products, to improve the efficiency of generic drug development. More than 1,000 people attended the webinar globally.

Webinar: Common Labeling Deficiencies/Tips for Generic Drug Applications
(May 7, 2021)
In this webinar, FDA discussed the most common labeling mistakes found in ANDAs and how to avoid them and other labeling tips. FDA also provided answers to common labeling questions asked by generic drug applicants. More than 800 people attended the webinar from more than 75 countries.

FY 2021 Generic Drug Science and Research Initiatives Public Workshop
(June 23, 2021)
FDA held the annual Generic Drug Science and Research Initiatives Public Workshop in June. This science-focused public workshop provided an overview of ongoing work and outcomes from research advanced under the FY2021 GDUFA Science and Research Priorities. During the plenary session, the Center for Research on Complex Generics (CRCG) coordinated feedback from numerous generic drug industry stakeholders. The event included breakout sessions on 1) model-integrated evidence for generic drug development, 2) complex product characterization/ analysis, and 3) in vitro and in vivo bioequivalence approaches. This virtual workshop had more than 1,300 attendees from more than 100 countries.

FDA/CRCG Public Workshop: In Vitro Release Test (IVRT) and In Vitro Permeation Test (IVPT) Methods: Best Practices and Scientific Considerations for ANDA Submissions
(August 18-20, 2021)
FDA and the CRCG co-hosted this 3-day workshop to provide a forum for discussion of the scientific principles and practical considerations that inform current FDA thinking and USP recommendations for IVRT and IVPT studies. The scope of the workshop included discussions on several challenging issues, the identification of areas needing further research, and the examination of opportunities for coordination and collaboration between the FDA, USP, academic institutions, product manufacturers, diffusion cell equipment manufacturers, contract research organizations, consultants, and other stakeholders. More than 2,300 attendees joined the workshop virtually.

Regulatory Education for Industry Conference — Advancing Generic Drug Development: Translating Science to Approval
(September 21-22, 2021)
FDA held a 2-day workshop in September focused on common issues seen in ANDAs. The workshop included discussion of scientific issues to PSG development and examined various areas of the science and cutting-edge methodologies behind generic drug development. Topics also included COVID-19's impact on generic drug regulation and cutting-edge science in complex generics. The virtual workshop had approximately 1,600 attendees from more than 90 countries. More than 5,000 people joined the YouTube Live Stream during the event.

FDA/CRCG Public Workshop: Regulatory Utility of Mechanistic Modeling to Support Alternative Bioequivalence Approaches
(September 30–October 1, 2021)
FDA and the CRCG co-hosted this 2-day workshop to engage the generic drug industry and other stakeholders on how mechanistic modeling and simulation can support their product development and regulatory submissions. It also provided a forum in which to share the current state of mechanistic modeling for bioequivalence assessments (through case studies) and helped to establish a consensus on best practices for using physiologically based pharmacokinetic (PBPK) and computational fluid dynamic (CFD) modeling to support bioequivalence assessments. Approximately 700 people virtually attended the workshop.

FDA/CRCG Public Workshop: Establishing the Suitability of Model-Integrated Evidence to Demonstrate Bioequivalence for Long-Acting Injectable and Implantable Drug Products
(November 30, 2021)
FDA and the CRCG co-hosted this workshop to engage experts in the generic and new drug industries, academia, and relevant stakeholders to explore, identify, and recommend best practices for the development and assessment of model-integrated approaches for BE assessment of long-acting injectables and implants. The workshop focused on how model-integrated approaches support innovative study designs and data analyses and how they can be validated and verified. More than 600 people virtually attended the workshop.

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 (DCAP)
- First Generic Drug Approvals
- First Generic Drug Approvals Previous Years
- Generic Drugs Web Pages
- Generic Drug User Fee Amendments (GDUFA)
- GDUFA II Commitment Letter
- GDUFA II Videos and Resources
- GDUFA III Commitment Letter
- GDUFA Science and Research
- GDUFA Guidances and MAPPs
- Off-Patent, Off-Exclusivity List
- 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 and DCAP goals.

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