U.S. FOOD & DRUG ADMINISTRATION

Office of Generic Drugs

2022 Annual Report

Ensuring high-quality, affordable generic drugs are available to the American public

January 2023

Director's Message

Susan Rosencrance, Ph.D.
Acting Director,
Office of Generic Drugs

Welcome to the eighth 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).

In 2022, generic drugs remained a significant public health priority for the FDA. Competition from generic drug makers helped make drugs more widely available and generally less expensive, allowing millions of patients to access the medicines they need more easily. The approval of generics often means that there are multiple manufacturers for a drug product, which also stabilizes the supply of medicines and reduces the risk of drug shortages. It is estimated that 91% of all prescriptions in the United States are filled as generic drugs, with more than 32,000 generic drugs approved by the FDA to date.

Ultimately, generic drug competition generates billions of dollars in savings each year for consumers and our health care system over higher-priced brand-name drugs. For example, a recent FDA study showed the savings accrued during the first year after approval for new generic drugs approved in 2018, 2019, and 2020 to be approximately $53.3 billion. This means tens-of-billions of dollars were saved each of those years, economy-wide, from new generic approvals.[1] Generic drug competition offers tremendous public health benefits for the United States by helping to lower drug prices and improve access to needed medicines for American patients.

The Renewal of the Generic Drug User Fee Amendments

Congress enacted the Generic Drug User Fee Amendments (GDUFA) in 2012 to ensure patients have affordable access to safe, effective, high-quality generic drugs, and reauthorized the third iteration of GDUFA this year. Since its enactment, GDUFA implementation has supported the development of generic drugs, including complex generic drugs, which can raise unique scientific and regulatory considerations. GDUFA formalized funding for a regulatory science program that addresses scientific challenges that delay access to complex generics. Enhancements made to GDUFA over time have been specifically designed to foster the development, assessment, and approval of these complex products. Funding from GDUFA expands FDA capabilities to conduct robust assessments of generic drug applications, facilitating timely access to generic medicines. The enactment of GDUFA I and the first renewal with GDUFA II were each transformative for the generic drug program.

[1] Estimating Cost Savings from New Generic Drug Approvals in 2018, 2019, and 2020, available at https://www.fda.gov/media/161540/download, August 2022.

The implementation of FDA's commitments under GDUFA III, which went into effect on October 1st, 2022, are bringing the program to yet another level. It will build on the successes of the GDUFA I and GDUFA II programs, with a focus on reducing the number of assessment cycles to advance earlier approvals and promote the timely availability of generic medicines. In the 10 years since it was enacted, GDUFA has helped strengthen and diversify the pipeline of generic drug applications reviewed by FDA.

In 2022, we continued to help increase access to needed medications for all Americans.

Susan Rosencrance, Ph.D.
Acting Director,
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Scientific Research: Helping to Increase Access to Complex Generic Drugs

FDA and OGD again made significant progress on efforts to advance scientific research. This research helps to ensure that regulatory standards, recommendations, and decisions are based on the most current scientific evidence. The GDUFA Science and Research Program is particularly important for pharmaceutical products known as complex products, which are harder to develop as generics. Complex products often have few or no generics, and drugs without competition may be too expensive for some patients to afford.

Abbreviated New Drug Application (ANDA), First Generics, Drug Competition Actions

In 2022, we continued to help increase competition by approving or tentatively approving 914 ANDAs, including 106 first generics. In one first generic example, FDA approved the first generic cyclosporine ophthalmic emulsion, 0.05% (referencing Restasis), a drug which helps millions of patients in the United States who suffer from dry eyes.

Beyond directly approving generic drug applications, OGD continued its implementation of FDA's Drug Competition Action Plan (DCAP). Notable deliverables include the October 2022 publication of draft guidances and product-specific guidances that provided recommendations for physicochemical and structural characterization tests, in vitro release test (IVRT) studies, and in vitro permeation test (IVPT) studies for topical generic drug products.[2] Other publications included draft and final guidances and MAPPs that also help to ensure that current and prospective ANDA applicants have the information they need to successfully submit high-quality ANDAs and to take advantage of the newly implemented GDUFA III commitments, including increased opportunities for meetings and other interactions with applicants.

[2] Draft Guidance for Industry Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs (October 2022); Draft Guidance for Industry In Vitro Release Test (IVRT) Studies for Topical Drug Products Submitted in ANDAs (October 2022), and Draft Guidance for Industry In Vitro Permeation Test (IVPT) Studies for Topical Drug Products Submitted in ANDAs (October 2022).

OGD's efforts to encourage competition by removing barriers to generic drug development and market entry also directly support the President's Executive Order on Promoting Competition in the American Economy. These actions help FDA to continue promoting generic drug competition to lower the prices of and improve access to prescription drugs, and to continue to clarify and improve the approval framework for generic drugs to make generic drug approvals more transparent, efficient, and predictable.

International Collaboration

OGD's work also extended beyond our borders through our international harmonization efforts. As a global leader in generic drug regulation, OGD actively engaged in collaboration with other international regulatory authorities to harmonize global standards for the development of safe, effective, and high-quality generic medicines. These efforts to foster development of uniform, scientifically driven, international standards can help improve the efficiency of drug development and promote public health by, among other things, preventing unnecessary duplication of studies and testing. Through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), FDA has been leading and participating in the M13 expert working group to develop the first ICH guideline focusing on BE standards for generic drugs. In December 2022, the draft ICH guideline M13A, titled "Bioequivalence for Immediate-Release Solid Oral Dosage Forms," reached an important milestone with its publication for public consultation. Additionally, through the Generic Drug Cluster, a multi-country scientific forum for the world's leading regulatory agencies to better enable harmonization, FDA and other leading regulatory agencies spent the bulk of 2022 collaborating on important regulatory topics to achieve a common understanding of each member agency's generic drug regulatory requirements and to help increase scientific alignment.

OGD also continued its international work with the Parallel Scientific Advice pilot program in collaboration with the European Medicines Agency (EMA). Under this program, applicants who submit a parallel application to the FDA and EMA for a complex generic or hybrid product, respectively, can meet in real-time to receive concurrent scientific advice from both agencies. Successful collaboration under the Parallel Scientific Advice pilot program provides applicants with a deeper understanding of the basis of the regulatory decisions from both agencies, optimizes the applicant's global product development program, and helps applicants avoid unnecessary duplication of studies or unnecessary testing methodologies to satisfy both agencies, which may have prolonged the development of complex generic products.

Expanding Access to COVID-19 Drug Treatments

In 2022 we continued efforts to identify and accelerate the assessment of applications for generic drugs critical to the treatment of patients with COVID-19. Since the pandemic began, we have approved more than 1,850 COVID-19-related ANDA submissions, including applications for life-saving medications used to assist mechanically ventilated COVID-19 patients.

Even with a continued focus on addressing the COVID-19 public health emergency, the generic drug program completed assessments of hundreds of original approvals and thousands of supplements for products not related to COVID-19. We also continued to identify science and research priorities to address scientific challenges which created opportunities for scientific advancement in the devel - opment of generic drugs, while concurrently devoting significant time and effort to facilitate the reauthorization of the Generic Drug User Fee Amendments. Altogether in 2022, FDA's generic drug program was extremely busy with efforts to steadily improve generic drug access. The FDA's Office of Generic Drugs' 2022 Annual Report provides a comprehensive look at what we accomplished and illustrates how OGD is well-positioned to continue its critical work in 2023.

Susan Rosencrance, Ph.D.
Acting Director, Office of Generic Drugs

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2022 Generic Drugs Program At-A-Glance

FDA's Office of Generic Drugs (OGD) hailed many successes concurrent with the implementation of the second reauthorization of the Generic Drug User Fee Amendments (GDUFA III) including:

914

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

1,775

Complete response letters issued in 2022 detailing the deficiencies that applicants needed to resolve before FDA could approve an ANDA.

108

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

31

New policy documents published to support generic drug developers by clarifying FDA's scientific and regulatory expectations and by bringing greater transparency to the generic drug assessment process, including with respect to new GDUFA III enhancements.

2,069

Total number of product-specific guidances (PSGs), including those published in 2022, found on the FDA website here.

$20 million

In 2022 provided approximately $20 million in funding for generic drug science and research projects.

257

PSGs for industry and other stakeholders in 2022 including 119 new draft PSGs, and 138 revised PSGs including 59 PSGs (new and revised) that added an efficient in vitro bioequivalence option.

13,900

Generic drug stakeholders participated virtually in 13 public workshops and webinars and 1 public forum with a total of more than 13,900 participants worldwide.

2022 Highlights

FDA's generic drug program was created to enhance the availability of affordable, high-quality generic drugs in the United States. Since the program's creation, more than 32,000 generic drugs have been approved by the FDA, and approximately 9 out of every 10 prescriptions filled in the United States are filled with generic drugs. Generic drugs are essential to public health in the United States not only because having multiple manufacturers for a drug product stabilizes the drug supply and reduces the risk of drug shortages, but also because generic products are substantially more affordable than brand-name drugs, allowing millions of patients to more easily access the medicines they need.

2022 and the Renewal of the Generic Drug User Fees Amendments (GDUFA)

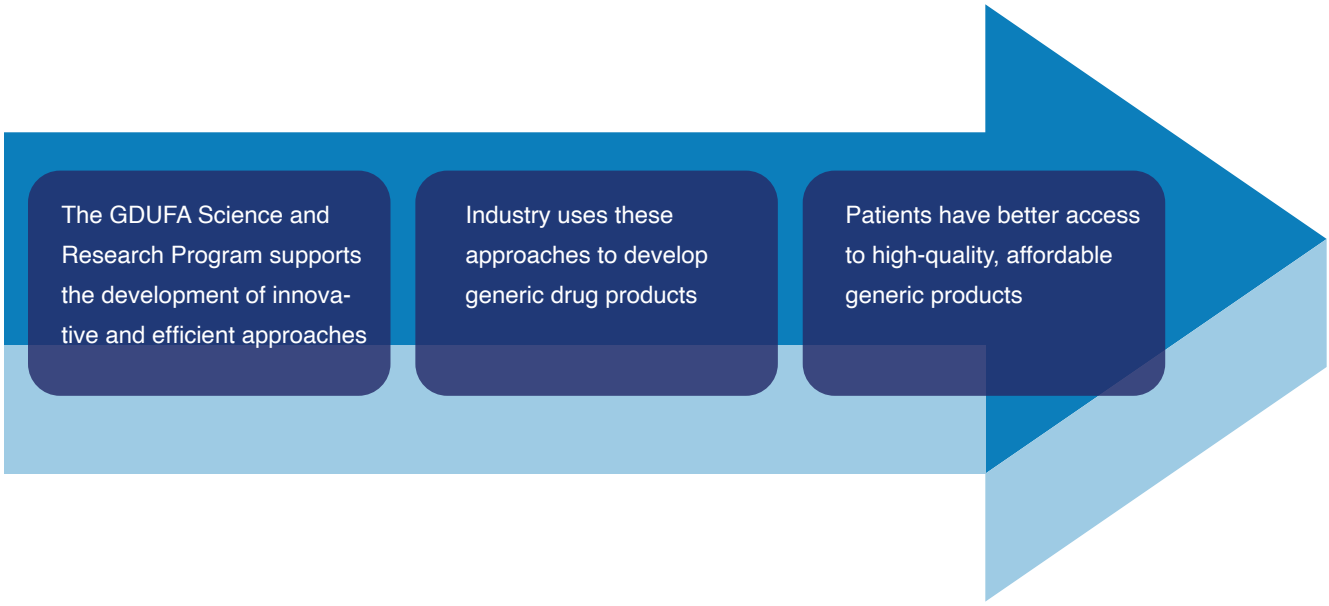
Congress enacted the Generic Drug User Fee Amendments (GDUFA) in 2012 to ensure patients have affordable access to safe, effective, high-quality generic drugs. GDUFA enables FDA to bring greater predictability and timeliness to the assessment of generic drug applications. The implementation of GDUFA III, which went into effect on October 1, 2022, brings the generic drug program to yet another level. It builds on the successes of GDUFA I and GDUFA II by providing enhancements to the program that focus on reducing the number of assessment cycles to reach approval and thereby avoiding delays in generic drug approval. Simultaneously, GDUFA III provides a solid financial foundation to support the evolving generic drug program and enables further regulatory science research around complex and other generic drug development. Through these types of enhancements, GDUFA III will continue to strengthen and diversify the pipeline of generic drug applications.

Scientific Research: Moving the Needle to Increase Access to Generic Drugs

OGD again made significant progress with efforts to advance scientific research on generic drugs in 2022. Our research helps to ensure that regulatory standards, recommendations, and decisions are based on the most current scientific evidence. The GDUFA Science and Research Program is particularly important for certain pharmaceutical products, known as complex products, which are harder to develop as generics. Complex products often have few or no generics. In the absence of market competition, these medicines can be so expensive that patients who need them may not be able to afford them.

The GDUFA Science and Research Program supports the development of innovative methodologies and more efficient tools to help establish drug equivalence standards that help in the development of safe, effective, and high-quality generic products. In 2022, OGD staff generated 72 peer-reviewed scholarly articles, 138 external talks, 13 public workshops and webinars, and 80 posters for exhibition at national and international scientific and medical conferences related to generic drugs.

The GDUFA Science and Research Program translates to better access to medicines



In 2022, OGD science and research outcomes supported new bioequivalence recommendations for developing generic products in both general guidances for industry and in new and revised Product-Specific Guidances (PSGs).

In addition to informing FDA guidances, GDUFA research outcomes also allowed FDA to clarify whether proposed bioequivalence approaches presented to FDA in pre-ANDA product development meetings were likely to be suitable. This allows FDA to provide prospective ANDA applicants with scientific and technical advice that helped them prepare submissions consistent with FDA's most current scientific thinking and regulatory requirements. In 2022, FDA facilitated 108 such product development and pre-submission pre-ANDA meetings.

International Collaborations

OGD's work in 2022 also extended beyond our borders through our international harmonization efforts as a global leader in generic drug regulation. FDA and other regulatory agencies collaborated in three areas in 2022 to create better harmonization around generic drug regulation:

- Through the multi-country forum, the Generic Drug Cluster, agencies collaborated on several important regulatory topics.
- With the Parallel Scientific Advice (PSA) pilot program, OGD continued its collaborative work with the European Medicines Agency (EMA). Under the PSA program, applicants who submit a parallel application to the FDA and EMA for a complex generic or a hybrid product, respectively, can meet in real-time to receive concurrent scientific advice from both agencies. Successful collaboration under the PSA pilot program provides applicants with a deeper understanding of the basis of regulatory decisions from both agencies, optimizes the applicant's global product development program, and helps applicants avoid unnecessary duplication of studies or unnecessary testing methodologies to satisfy both agencies.
- In December 2022, the draft ICH guideline M13A, titled "Bioequivalence for Immediate-Release Solid Oral Dosage Forms," reached an important milestone with its publication for public consultation.
- Additionally, with support from the Office of Global Policy and Strategy, OGD initiated an ORISE Fellowship project that reviewed global approaches to generic drug postmarketing safety surveillance. This opportunity to reach out to global partners enabled OGD to add global perspectives to our important work and demonstrated OGD's commitment to partnerships and information sharing.

Regulatory Science Education: Trainings to Enhance High-Standard Assessments

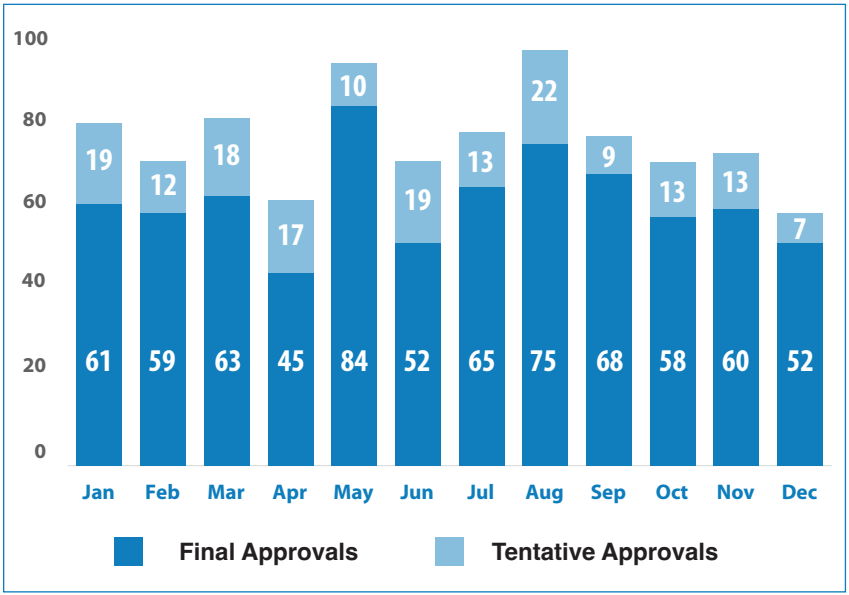
Relaying key educational information about new scientific tools, standards, and approaches to assess the safety, efficacy, quality, and performance of generic drug products was top of mind for OGD in 2022. OGD deployed several educational programs and courses for OGD staff, the generic drug industry, and other stakeholders of the generic drug program to communicate such new information. For example:

- In 2022, OGD provided training to OGD staff to assist with the implementation of GDUFA III. OGD provided general training about the GDUFA III commitment letter, as well as job-specific trainings to show how certain GDUFA III commitments will impact day-to-day job functions.
- In October 2022, OGD hosted an FDA-wide Scientific Rounds educational workshop to discuss data discrepancies identified during bioequivalence assessments (i.e., overlapping pharmacokinetic profiles and unusual pharmacokinetic trends) along with suspicious findings during inspections that led to data integrity and data quality issues.
- In addition to training FDA staff, OGD continued its robust educational programs for industry and other stakeholders. One of the greatest challenges to generic drug development, especially complex generics, as reported to FDA by industry and stakeholder feedback, is an uncertainty about how to implement scientific insights from 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 matters impacting generic drug applications. OGD hosted or co-hosted several public meetings focused on stakeholder use of innovative bioequivalence approaches to generic drug development using innovative bioequivalence approaches to generic drug development.
- In 2022, the generic drug program conducted 13 workshops and webinars for industry that helped advance 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.

Generic Drug Approvals

The impact of generic medicines on the consumer pocketbook is significant — saving consumers billions of dollars over the past decade.[3] In 2022, the generic drug program approved or tentatively approved 914 generic drug applications, known as Abbreviated New Drug Applications (ANDAs).

2022 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 generic competition previously existed. Because of their importance to public health, FDA prioritizes review of submissions for these products. In 2022, OGD approved 106 first generic drugs.

[3] https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers#q4

Significant First Generic Drug Approvals in 2022

Generic Name	Brand Name	Indication	Date Approved
Sofosbuvir Tablets	Sovaldi Tablets	Hepatitis C virus infection	1/27/2022
Brimonidine Tartrate Ophthalmic Solution	Alphagan P Ophthalmic Solution	Elevated intraocular pressure	1/31/2022
Cyclosporine Ophthalmic Emulsion	Restasis Ophthalmic Emulsion	Ocular inflammation associated with keratoconjunctivitis sicca	2/2/2022
Dapagliflozin Tablets	Farxiga Tablets	Glycemic control	2/22/2022
Apomorphine Hydrochloride Injection	Apokyn Injection	Parkinson's disease	2/23/2022
Lacosamide Tablets	Vimpat Tablets	Partial-onset seizures	3/17/2022
Bortezomib for Injection	Velcade for Injection	Multiple myeloma; Mantle cell lymphoma	5/2/2022
Pemetrexed for Injection	Alimta for Injection	Non-squamous non-small cell lung cancer and mesothelioma	5/25/2022
Empagliflozin Tablets	Jardiance Tablets	Type 2 Diabetes Mellitus	8/3/2022

One example of a noteworthy first generic approval in 2022 was for cyclosporine ophthalmic emulsion (referencing Restasis). The FDA assessment team extensively collaborated to resolve the scientific challenges underlying the approval of this complex generic ophthalmic drug product. This approval was, in large part, possible because FDA has been conducting research to address complex issues related to the assessment of a proposed generic product to Restasis as part of OGD's GDUFA Science and Research Program since 2012. The results of the findings from FDA's research program can be leveraged by the Agency to address challenges related to developing other similar complex locally acting drug products, paving the way for more first generics of complex generic products in the future.

Cost Savings from First Generics

*Example: Pregabalin capsules experienced a **95% price reduction** during the first 12 months of generic sales.*

Prior to ANDA approvals, a 30-day supply was about **$450.**

By July 2020 (when generics were on the market for a full year) this price fell to about **$23**.

Savings during the year following these approval amounted to more than **$6.6 billion.**

Information on this graphic can be found online at Generic Competition and Drug Prices | FDA

Communicating with Industry: Requests, Letters, and Controlled Correspondence

OGD communicated with industry through more than 4,260 information requests (IRs), more than 2,520 discipline review letters (DRLs), and 1,775 complete response letters (CRLs). These requests and letters identify issues that need to be addressed by applicants before 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 2022, OGD received more than 3,660 controlled correspondence inquiries submitted by industry.

Regulatory Science Research

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 the 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 2022, FDA funded approximately $20 million in science and research projects. FDA awarded funding for 8 new contracts and 7 new grants, as well as 26 ongoing grants and 25 ongoing contracts to conduct science and research. OGD had 77 ongoing external research collaborations in 2022, with many projects that had been awarded in previous years continuing into 2022. In keeping with FDA's commitment to promote high-quality and clinically relevant science, OGD staff and their external collaborators had 72 peer-reviewed scholarly articles published, presented 138 external talks, and presented 80 posters at national and international scientific and medical conferences.

On May 9th and 10th, FDA held the FY 2022 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 about priority areas for generic drug research during the next 5 years of the GDUFA science and research program. FDA considered information obtained during the public workshop, along with other input such as comments to the public docket, in developing the GDUFA Science and Research Priority Initiatives for Fiscal Year 2023.

During 2022, the GDUFA-funded Center for Research on Complex Generics (CRCG) expanded its scope of activities to enhance research collaborations between the generic industry, FDA, and academic institutions, and to further FDA's mission of increasing access to safe and effective generic products. The CRCG actively communicated with generic drug industry representatives to learn about current and emerging challenges that could impact the development of generic products. The CRCG did this through a series of meetings with individual companies involved in the generic drug industry, interactions with individual industry representatives at industry meetings such as the Association for Accessible Medicines annual GRx+Biosims conference, and multiple surveys that were used to focus the scope and content of FDA-CRCG workshops during 2022 on topics of greatest interest to generic industry representatives.

In September, FDA hosted a workshop on Advancing Generic Drug Development: Translating Science to Approval, which communicated how the outcomes of FDA's GDUFA Science and Research Program can help guide and facilitate generic drug development, regulatory assessment, and approval. The presentations and discussions during the workshop focused on common issues seen in ANDA submissions; mapped how GDUFA science and research outcomes supported the development of PSGs for complex products and prepared FDA to provide advice during pre-ANDA meeting discussions; and examined various areas of innovative science and cutting-edge methodologies that are available now to support generic drug development.

Research Program Is Bridging Key Knowledge Gaps in Generic Product Development

The GDUFA Science and Research Program buoys the development of innovative methodologies and more efficient tools to help establish drug equivalence standards that support the development of safe, effective, and high-quality generic drug products, including complex generics. To enhance patient access to complex generics, in 2022 FDA utilized its laboratories and computer systems to conduct more than 70 intramural GDUFA science and research projects focused on using our resources to improve generic product development and regulatory assessment. These research projects were aligned with the GDUFA Science and Research Priority Initiatives for 2022. These research outcomes also prepared FDA to assess ANDAs referencing complex products, which ultimately improved patient access to complex generics that were practically unfeasible to develop even just a few years ago.

For example, in February, FDA approved the first generic cyclosporine ophthalmic emulsion, 0.05% (referencing Restasis), which helps millions of patients in the United States who suffer from dry eyes. This is an immunomodulatory and anti-inflammatory complex product for which it was exceptionally challenging to demonstrate and assess BE. At the start of the GDUFA Science and Research Program, collaborative discussion between generic industry representatives and FDA established a research priority to develop more efficient BE approaches for locally acting ophthalmic products, and the resulting research across multiple years systematically advanced scientific insights and new tool

development. This included a series of research projects specifically related to cyclosporine ophthalmic emulsion that successfully addressed challenging product characterization issues, developed analytical measurement and statistical analysis tools, and supported updates to generic product development recommendations.

Collaboration to Enhance Engagement Between FDA and Generic Industry Stakeholders

As part of FDA's commitment to expanding its collaboration and communication with industry, during 2022, the CRCG continued to enhance communication and stimulate dialogue between generic industry stakeholders and FDA. In addition to ensuring that GDUFA research initiatives are focused on the most pressing scientific challenges, the CRCG helped generic industry stakeholders access and effectively utilize scientific insights, technical methods, study designs, data analyses, and other GDUFA Science and Research outcomes to develop complex generics.

Impact Stories on OGD Research

Formulating Drug Products for Optimized Absorption: Elucidating Amorphous Solid Dispersions

FDA scientists are seeking ways to improve the bioavailability of drugs that on their own do not dissolve well in water. Recent CDER research explored the potential for using amorphous solid dispersions to formulate generic drug products that may include ingredients that are poorly water-soluble. Amorphous solid dispersions (ASDs) are a popular mechanism for enhancing the solubility and bioavailability of drugs that are poorly soluble in water. Important drugs that treat cancer, cystic fibrosis, and organ transplant rejection, to name a few, use ASDs in their formulation to help overcome the solubility limitations of drugs when they are administered orally. OGD research explored the mechanistic understanding and prediction of in vivo performance of ASD drug products to better understand the prediction of in vivo performance of ASD drug products for test and reference drug products.[4]

Effects of Realistic In Vitro Test Factors on the Aerosol Properties of Metered-Dose Inhalers[5]

Metered dose inhalers (MDIs) are mainstays in the treatment of asthma, chronic obstructive pulmonary disease, and other respiratory diseases. FDA researchers investigated how the aerodynamic particle size distribution and droplet size distribution of commercial solution and suspension MDIs are affected by in vitro testing conditions. Development of generic inhalation products is challenging because the generic product should generally have the same delivery of small aerosol parti-

[4] *Available at: https://www.fda.gov/drugs/regulatory-science-action/formulating-drug-products-optimized-absorption-elucidating-amorphous-solid-dispersions*

[5] *Available at: https://www.fda.gov/drugs/regulatory-science-action/effects-realistic-in-vitro-test-factors-aerosol-properties-metered-dose-inhalers*

cles through the mouth and throat and into the lungs as the brand product. FDA scientists are helping develop more realistic laboratory models of the mouth-throat region that allow the generic industry to efficiently test their products and speed access to generic products.

Spotlight Story on CDER Science

A Spotlight on CDER Science[6] story on levothyroxine highlighted how FDA-sponsored researchers have meticulously culled through a national administrative claims database to assess the clinical management of thyroid function among patients undergoing treatment with approved levothyroxine products (either generic or brand-name). Robustly matched patient populations showed that patients who switched among different generic levothyroxine products maintained the same degree of thyroid health as patients who consistently used a single product. Despite medical guidelines that previously urged prescribers to avoid switching between levothyroxine products, the recent FDA analysis confirms that prescribers can regard FDA-approved generic drugs — even those with a narrow therapeutic index — as interchangeable.

Highlighted Significant 2022 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 were published in peer-reviewed scientific literature and presented and discussed at major medical and scientific meetings. These research outcomes contributed to guidance development, facilitated new pathways for generic product development, and supported the efficient review and timely approval of ANDAs. Significant 2022 GDUFA science and research accomplishments are highlighted below for each of 13 research program areas:

Abuse-Deterrent Opioid Drug Products

Among several research initiatives during CY 2022 related to abuse-deterrent formulations (ADFs) of opioid drug products, some notable outcomes related to the development of physiologically based pharmacokinetic (PBPK) models for morphine sulfate and naltrexone hydrochloride. The results of these PBPK models were validated against corresponding literature data for these drugs from a nasal insufflation clinical study with crushed extended-release capsules containing a fixed combination of morphine sulfate and naltrexone hydrochloride. The validated PBPK models were used to investigate the effect of different drug particle size distributions (PSDs) between 100 and 500 µm on in vivo systemic PK parameters,

[6] *A Real-World Case Study of Levothyroxine Use Addresses Institutional Concerns About Generic Product Interchangeability. Available at: https://www.fda.gov/drugs/news-events-human-drugs/real-world-case-study-levothyroxine-use-addresses-institutional-concerns-about-generic-product?utm_medium=email&utm_source=govdelivery*

and the models predicted that the PK would be dependent on the PSD of morphine sulfate, but not that of naltrexone hydrochloride. This research illustrated the value of in silico modeling tools during generic drug development, to inform the design of ADFs of opioid drug products.

Complex Injectables, Formulations, and Nanomaterials

GDUFA research with phytonadione injection established that potential differences in the source of a surfactant may not impact critical formulation characteristics and behavior during preparation, but the formulation composition or the manufacturing process parameters can produce products with a different initial dispersion state. These outcomes helped establish the types of characterizations, including relatively routine tests for appearance (turbidity) and PSD that can distinguish microemulsions from nanoemulsions, that may be appropriate to support a demonstration of BE for such products.

Complex Mixtures and Peptide Products

Research related to the characterization of complex mixtures and peptide products during 2022 focused on detecting, identifying, and quantifying impurities in peptide and oligonucleotide products. Even trace amounts of certain impurities have the potential to pose health risks to patients due to their potential carcinogenic or immunogenic effects. This research led to the development of a liquid chromatography-high resolution mass spectrometry (LC-HRMS) method to identify and quantify impurities in liraglutide products, which could arise from the manufacturing and purification processes utilized for a prospective generic product.

Data Analytics

Data analytics research contributed to advances in artificial intelligence (AI) technologies such as machine learning (ML) and natural language processing that can facilitate generic drug development and regulatory assessment. For example, a tool was recently developed to automate the collection and structured assembly of data submitted in ANDAs, which streamlines work during FDA's BE assessment process that is otherwise very labor-intensive. During 2022, OGD integrated this tool with other components of FDA's information technology infrastructure to facilitate efficient and high-quality regulatory assessments.

Drug-Device Combination Products

Research relating to drug-device combination products (DDCPs) during 2022 focused on understanding patient and caregiver perceptions, user interface considerations, and the development of in vitro techniques to assist in the development and evaluation of complex DDCPs. The outcomes from this research are elucidating how patients use generic vs. brand-name DDCPs, and thereby supporting the development of substitutable generic DDCPs that can enhance patient access to these critical medicines.

Inhalation and Nasal Drug Products

There were multiple notable research outcomes during 2022 that elucidated how in vitro tools such as mouth-throat models, in silico methods combining computational fluid dynamics (CFD) with physiologically based pharmacokinetic (PBPK) models, and in vivo systemic pharmacokinetics (PK) studies can be sensitive to performance differences for inhalation and nasal products. For example, two mometasone furoate nasal suspension formulations with different drug substance PSDs were developed and evaluated in vitro by dissolution testing and morphology directed Raman spectroscopy (MDRS), as well as in vivo, in a crossover PK study.

Locally Acting PBPK Modeling

Numerous research initiatives related to locally acting PBPK modeling produced outcomes that have the potential to support efficient bioequivalence approaches for orally inhaled and nasal products, ophthalmic products, and topical dermatological and vaginal products. For example, CFD and discrete element method approaches modeled how modifications could alter the average slip velocity between air and carrier particles to influence the quality of aerosolization. A notable outcome of multiple coordinated research projects on topical dermatological products was the development of in silico IVPT simulation tools that could accelerate IVPT method development and facilitate efficient optimization of IVPT study designs.

Long-Acting Injectable, Inserted and Implanted Products

Research related to long-acting injectable, inserted, and implanted products continued to evaluate novel methods to characterize complex polymeric excipients. The research outcomes elucidated the impact of processing parameters on the quality and performance of such products and provided a compelling demonstration of the power of AI-based imaging analysis to correlate formulation and manufacturing parameters with the resulting microstructure of polymeric microparticles, and with their drug release characteristics.

Ophthalmic Drug Products

FDA approved the first generic cyclosporine ophthalmic emulsion product as a direct outcome of several years of GDUFA-funded research that systematically advanced scientific thinking and developed new tools to support an efficient demonstration of BE for this complex generic ophthalmic product. In vitro, ex vivo, and in vivo (animal) research in this area continued during 2022, focusing on elucidating how the physicochemical properties of ophthalmic emulsion and suspension formulations affect the ocular tear film properties and local tissue in vivo absorption. The insights gleaned from this research are being used to develop and validate PBPK models that combine physics-based and compartmental approaches to predict bioavailability to eye tissues, and to establish relevant parameters based on which prospective generic products can support a demonstration of BE.

Oral Absorption Models and Bioequivalence

During 2022, research involving oral absorption models and BE investigated the clinical significance of in vitro results for biopharmaceutics classification system (BCS) Class II and Class III drugs and facilitated more opportunities for potential biowaiver approaches for these drug products. Insights from the research established a valuable foundation for understanding the impact of biologically relevant media on the solution phase behavior of poorly soluble drugs, which can facilitate the development of prospective generic drug products that use amorphous solid dispersions.

Patient Substitution of Generic Drugs

Recent research on the effects when patients transition from a brand-name levothyroxine product to a corresponding generic levothyroxine product showed that there was no significant difference, based on the proportion of patients with normal vs. markedly abnormal thyroid stimulating hormone (TSH) levels. Research during 2022 assessed the effects when patients switched from one generic levothyroxine product to another generic supplier of that levothyroxine product. Among 2,780 patients in the data set who switched between generic levothyroxine products, and 2,780 corresponding propensity-matched non-switcher patients, the proportion of patients with a markedly abnormal TSH concentration after the index date was 3.1% among non-switchers and 2.5% among switchers with a risk difference of 0.007. The outcomes of this research suggest that switching among different generic levothyroxine products was not associated with clinically significant changes in TSH levels, providing real-world evidence to support public confidence in the equivalence of these generic narrow therapeutic index drugs.

Quantitative Clinical Pharmacology

Research this year on innovative quantitative clinical pharmacology (QCP) approaches that may resolve fundamental study feasibility challenges that have otherwise hampered the development of generic ophthalmic drug products was conducted. The research optimized the design and assessment of challenging studies, such as those that necessitate relatively short durations, small sample sizes, or sparse sampling, and which may otherwise be unfeasible to conduct. A notable outcome of this research was the development of mechanistic models for dermatological and orally inhaled drug products that were made publicly available within the Open Systems Pharmacology Suite. This open-source platform integrates QCP modeling and simulation tools in one place to generate BE evidence in silico, which has the potential to reduce or replace in vivo BE studies for complex, locally acting drug products, ultimately improving the development efficiency of these generic products.

FDA continually advances scientific research to ensure that safe and effective generic drugs are available for people in the United States.

Topical Products

Research during 2022 expanded the development of in vitro tools to support efficient BE approaches for locally acting products administered topically via routes other than the skin, such as rectal suppositories or vaginal gels and creams. The resulting IVPT flux profiles for a commercially available 2% w/w clindamycin phosphate (CP) vaginal cream demonstrated good reproducibility and precision among tissue replicates and was able to differentiate the flux profiles from laboratory-made formulations of different strengths when compared in the same donor. These research outcomes suggest that it may be feasible to utilize efficient BE approaches like those developed for topical dermatological products to support the expansion of such characterization-based BE approaches to other locally acting semisolid drug products.

Consistently and Efficiently Evaluating Generic Drugs and Monitoring Generic Drug Safety

The FDA and its Office of Generic Drugs 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 also continues to monitor the safety of generic drugs after approval and then throughout the time the generic drug is available for sale in the United States. Effective postmarket surveillance is essential to making sure that FDA-approved generic drugs have the same clinical effect and safety profile as the brand-name drugs they reference.

Safety Surveillance for Generic Drugs

OGD leads many safety and surveillance activities to ensure generic drugs are therapeutically equivalent to their Reference Listed Drugs (RLDs), including review of excipient differences and impurities, and of pre-approval serious adverse event reports from

Bio-Investigational New Drugs (IND) and non-IND BE/BA studies intended to support ANDAs. In addition, clinical reviewers are responsible for assessing Health Hazard Evaluations for potential generic drug product recalls. A team of data analysts investigates generic drug quality and therapeutic equivalence adverse event reports and trends, follows generic drug distribution patterns, and identifies emerging safety issues.

Additionally, the OGD Risk Evaluation and Mitigation Strategies (REMS) Team assists in developing, implementing, managing, and evaluating REMS-related activities for ANDAs. A generic drug is subject to a REMS if the applicable listed drug has a REMS. The REMS Team members serve as experts on the statutory and regulatory requirements and recommendations in FDA guidance documents related to ANDAs subject to a REMS.

Safety and Surveillance in 2022

The following Drug Safety Alerts were issued in 2022:

- Updated the Drug Safety Alert related to *vinca alkaloid labeling for preparation in intravenous infusion bags only* was updated. (April 2022)
- A Drug Safety Alert for patients, caregivers, and health care providers regarding *cross-compatibility issues with autoinjector devices that are optional for use with glatiramer acetate injection* was developed and published. (August 2022)
- A Drug Safety Alert for health care professionals of compatibility issues with *prefilled glass syringes and certain Luer-activated valve (LAV) connectors was led and further developed through collaboration with CDER and CDRH and published.* (November 2022)

CDER's Drug Nitrosamine Impurities Task Force continued to address ongoing issues related to the presence of nitrosamine impurities in many prescription and over-the-counter drug products. CDER established acceptable intakes for several nitrosamine impurities and collaborated with FDA's National Center for Toxicologic Research and the Nitrosamine International Technical Working Group to optimize and harmonize principles of the safety assessment for nitrosamine impurities.

Generic Drug Risk Evaluation in 2022

Information on approved REMS for NDAs and ANDAs is available at REMS@FDA. Throughout 2022, OGD participated in CDER's cross-office efforts including:

- Evaluation of established REMS materials to aid in the approval of 27 new ANDAs subject to REMS
- Evaluation and approval of various Shared System REMS modifications, ultimately affecting 126 approved ANDAs
- Collaborating on Federal Register Notice regarding REMS

Communicating Safety and Surveillance Activities to Stakeholders in 2022

In 2022, OGD presented its scientific approach to conducting safety evaluations and postmarketing surveillance and engaged with several major stakeholder audiences including:

January

Presented *Updates and Opportunities for Generic Drug Postmarket Surveillance* at the DIA Global Pharmacovigilance and Risk Management Strategies Conference

February

Presented *Generic Pharmacovigilance — an FDA Regulator's Perspective* at the Medicines for Europe 21st Regulatory Affairs and Pharmacovigilance Virtual Conference

April

Presented and participated in panel discussions at the Generic Drugs Forum 2022: The Current State of Generic Drugs for the following sessions:

- *Review of Investigational New Drug Applications (Bio-INDs)* by the Office of Generic Drugs
- *Project Management of Premarket and Postmarket Generic Drug Safety*

May

Chaired session in Generic Drug Science and Research Initiatives Workshop and presented, *Research Opportunities for N-Nitrosamines in Pharmaceuticals: A Pharm/Tox Perspective*

June

Chaired a session FDA Updates on Ensuring Postmarket Safety and Surveillance of Generic Drugs and gave a presentation on the *FDA Perspective* at the Drug Information Association Global Annual Meeting

November

Joined a panel discussion on Complex Generics: An Inside look from the Agency as part of the Science and Regulatory Track at the GRx+Biosims Generics + Biosimilars Conference

Developed and gave a Division of Drug Information Webinar FDA Drug Topics: The Safety Evaluation and Surveillance of Generic Drugs

Advancing Bioequivalence and Generic Drug Assessments

Bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. 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.[7,8] OGD assesses the 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.

Noteworthy among the 2022 generic drug approvals for their use of new methodologies to demonstrate BE was a product on the drug shortage list, two that were COVID-19 priorities, and two that were complex generic drug approvals of phytonadione injectables. OGD scientists working on these applications were pivotal in resolving scientific and regulatory issues that could impact the determination of BE for these drug products. Principal among these was the conclusion that phytonadione injectable is a thermodynamically stable microemulsion and thus BE can be established without the need for in vivo BE studies for products that are qualitatively and quantitatively the same (Q1/Q2) as the RLD with respect to inactive ingredients. The validation of this conclusion reduced the regulatory burden on the applicant given that the PSG recommended in vivo studies to demonstrate BE.

[7] 21 CFR 314.3 "Bioequivalence" definition found online at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-D/part-314/subpart-A/section-314.3#p-314.3

[8] See preface of *Approved Drug Products With Therapeutic Equivalence Evaluations,* commonly known as the Orange Book, available at: https://www.fda.gov/drugs/development-approval-process-drugs/orange-book-preface.

Another noteworthy approval that utilized a BE approach was for dapsone gel, (referencing Aczone Gel, 7.5%), indicated for the topical treatment of acne vulgaris. This ANDA was the second dapsone gel, 7.5% product approved overall and the first utilizing the alternative approach outlined in the PSG in which the applicant may submit a combination of in vitro and in vivo studies, including one in vitro study evaluating local (cutaneous) pharmacokinetics (PK) and one in vivo study evaluating systemic (plasma) PK. The in vivo PK study for this ANDA demonstrated the feasibility of the alternative approach for this product, which significantly alleviates the burden on applicants by providing an alternative to conducting large comparative endpoint studies in patients, increasing the potential for more generic topical drug products to reach the market.

In another notable generic drug approval for a drug that is not quantitatively (Q2) the same as its RLD with respect to inactive ingredients, the applicant used an alternative BE approach to support their non-Q2 formulation when compared to the innovator product. The review of this application helped the Agency gain a better overall understanding of the complex scientific and regulatory challenges underlying the approval of non-Q2 drug products. This experience can be leveraged by the Agency in the approval of similar complex locally acting drug products in the future, paving the way for the availability of more complex generic drug products.

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

Assuring Integrity of BE Data in Support of Generic Drug Applications

OGD works diligently to ensure that the data on which approval decisions are based are accurate and valid. In September 2021, FDA requested applicants of upwards of 100 ANDAs submit data from repeat BE studies after uncovering a pattern of intentionally compromised data generated at the testing facilities of two Contract Research Organizations (CROs). These included both approved drugs as well as drugs under review. Keeping public health and patient safety as a top priority, OGD worked expeditiously in responding to a large number of controlled correspondences and multiple email inquiries from impacted applicants. OGD expended significant effort and resources throughout 2022 to assess large volumes of new data submitted by the impacted applicants and concurrently assure that any potential for shortage of impacted drugs on the market was addressed in a timely manner.

OGD made concerted efforts to raise the topic of data integrity in appropriate public forums. Through outreach, OGD continues to message the need to ensure the integrity of the data in generic drug applications, clarify the Agency's expectations related to data integrity and provide recommendations to the industry and CROs for decreasing incidences of compromised data integrity. In addition, OGD engaged in multi-lateral discussions with global regulatory partners to address data integrity topics. Also, in collaboration with other stakeholders in CDER, OGD established a framework for detecting and consistently addressing data integrity issues identified during ANDA assessments and supporting CDER's inspection program.

Policies that Support the Efficient Development of Safe, Effective, High-Quality, 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 public.

Guidances

We publish guidances that, when finalized, describe the Agency's current thinking, and make recommendations to industry on regulatory and scientific issues related to generic drugs. Guidances are available online in the FDA Guidance Documents database by choosing the "Generic Drugs" topic. Below are the guidances issued in 2022.

Final Guidances

- Good ANDA Submission Practices (January 2022)
- Failure to Respond to an ANDA Complete Response Letter Within the Regulatory Timeframe (July 2022)

- Orange Book Questions & Answers (July 2022)
- Information Requests and Discipline Review Letters Under GDUFA (January 2022, October 2022)
- Competitive Generic Therapies (October 2022)
- Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (October 2022)
- Post-Complete Response Letter Clarification Teleconferences Between FDA and ANDA Applicants Under GDUFA (October 2022)
- ANDA Submissions — Prior Approval Supplements under GDUFA (October 2022)

Draft Guidances[9]

- Revising ANDA Labeling Following Revision of the RLD Labeling (January 2022)
- Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use (April 2022)
- Evaluation of Therapeutic Equivalence (July 2022)
- Electronic Submission of Expedited Safety Reports from IND-Exempt BA/BE Studies (August 2022)
- Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs (October 2022)
- In Vitro Release Test Studies for Topical Drug Products Submitted in ANDAs (October 2022)
- In Vitro Permeation Test Studies for Topical Drug Products Submitted in ANDAs (October 2022)
- Topical Dermatologic Corticosteroids: In Vivo Bioequivalence (October 2022)
- Sameness Evaluations in an ANDA – Active Ingredients (November 2022)
- Statistical Approaches to Establishing Bioequivalence (December 2022)
- Controlled Correspondence Related to Generic Drug Development (December 2022)

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 2022, FDA issued the following MAPPs related to generic drugs:

- Issuance of Information Requests and/or Discipline Review Letters for Abbreviated New Drug Applications (January 2022, revised October 2022)

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

- Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs (April 2022)
- Classifying Approved New Drug Products and Drug-Device Combination Products as Complex Products for Generic Drug Development Purposes (April 2022)
- Assessment of the User Interface of a Drug-Device Combination Product Submitted in a Pre-ANDA Communication or an ANDA (June 2022)
- Communicating Abbreviated New Drug Application Review Status Updates with Industry (October 2022)
- Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings (October 2022)
- Prioritization of the Review of Original ANDAs, Amendments, and Supplements (October 2022)

Federal Register Notices (FRNs) and Other Policy Resources

Pursuant to its GDUFA III commitments, FDA also established a docket to solicit comments on the content of Appendix A in the July 2018 guidance for industry ANDA Submissions—Amendments to Abbreviated New Drug Applications Under GDUFA and continued to support the efficient development of safe, effective, high-quality, and more affordable generic drugs by regularly updating several websites with information for generic drug developers and other external stakeholders.

- Soliciting Public Comment on Appendix A of the Food and Drug Administration's July 2018 Guidance Entitled "Abbreviated New Drug Application Submissions—Amendments to Abbreviated New Drug Applications Under Generic Drug User Fee Amendments" (August 2022)
- Competitive Generic Therapy Approvals — website updated biweekly
- List of Off-Patent, Off-Exclusivity Drug Products without an Approved Generic —website updated in June 2022 and December 2022
- Paragraph IV Certifications List

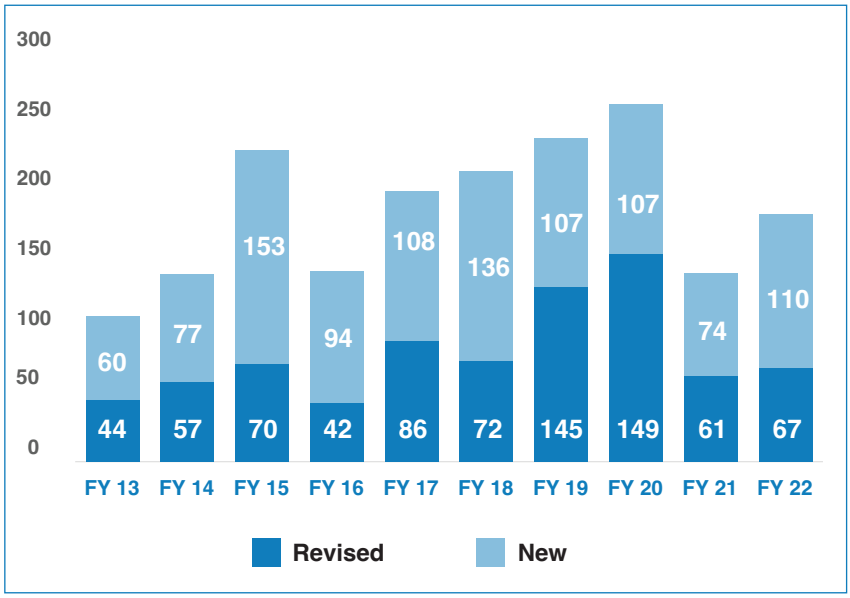
Revised Guidance for Controlled Correspondence

In December 2022, OGD revised the guidance for industry titled "Controlled Correspondence Related to Generic Drug Development." This guidance provides information on Agency communications related to controlled correspondence and how drug manufacturers and related industry can submit controlled correspondence to FDA requesting information related to generic drug development and requests to clarify ambiguities in FDA's controlled correspondence response. When finalized, the guidance will replace the December 2020 version. This guidance, Controlled Correspondence Related to Generic Drug Development, can be found online at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/controlled-correspondence-related-generic-drug-development.

Product-Specific Guidances (PSGs)

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. These PSGs 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. 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 to FDA with fewer deficiencies, 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 III commitments.

Total PSGs Published by Fiscal Year (2013–2022)



In 2022, FDA issued 119 new and 138 revised PSGs, which provided recommendations for developing generic products and generating the evidence needed to support ANDA approval. In FY 2022 FDA also created 59 PSGs (new and revised) that added an efficient in vitro BE option. Included among those is a PSG for medroxyprogesterone acetate injection, which was notable as the first PSG for a long-acting injectable suspension to recommend an efficient in vitro BE approach — the outcome of years of GDUFA-funded research that elucidated the role of key formulation characteristics on the performance of such products. Throughout 2022 PSGs helped prospective generic drug applicants focus their product development and prepare for ANDA submission, mitigated certain risks associated with generic drug development, and helped FDA expedite the assessment of ANDAs.

As of December 31, 2022, FDA had published 2,069 new and revised PSGs, which can be found on FDA's website at Product-Specific Guidances for Generic Drug Development. In November 2022, FDA also updated the "Upcoming Product-Specific Guidances for Generic Drug Product Development" web page to include new PSG revision categories (in vivo major revision and in vitro major revision) that will assist applicants in determining if a PSG revision may impact their generic drug development program and whether they should request any of the new PSG teleconferences or PSG meeting types as described in the GDUFA III Commitment Letter. The web page was also updated to provide information about the Agency's plans for issuing new or revised PSGs in the coming year along with anticipated publication information consistent with FDA's GDUFA III commitments.

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, assessment, 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 assessment and approval process and removing barriers to generic drug development and market entry supports patients' access to the medicines they need at more affordable prices.

In 2022, OGD undertook multiple actions to improve the efficiency of the generic drug development, assessment, and approval process and to maximize scientific and regulatory clarity with respect to complex generic drugs. Notable deliverables in this workstream include the October 2022 publication of 3 draft guidances and 80 product-specific guidances providing general recommendations for physicochemical and structural characterization tests, IVRT studies, and IVPT studies for topical

generic drug products and 10 final guidances and 8 MAPPs to ensure current and prospective ANDA applicants have the information they need to successfully submit high-quality ANDAs, taking into account the information reflected in the GDUFA III commitment letter. OGD's efforts to remove barriers to generic drug development and market entry to spur competition directly support the President's Executive Order on Promoting Competition in the American Economy, in which FDA is tasked with clarifying the approval framework to make generic drug approvals more transparent, efficient, and predictable.

Finally, as part of the continued implementation of the congressionally established Competitive Generic Therapy (CGT) pathway, we have approved more than 251 generic drug products with a CGT designation. Of these products, 83 were approved in 2022. Of the approved CGT-designated drugs eligible for CGT exclusivity, approximately 89% began commercial marketing within a median of 11 days from their approval.

Recommendations from FDA allow generic drug applicants to build the latest FDA information into their development programs, which helps them submit higher quality ANDAs.

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 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 2022 internal collaborators, especially the Office of Pharmaceutical Quality, who greatly contributed to our successes in 2022. We look forward to future collaborations that will help us further increase access to generic drugs for the American public.

Appendix

Conferences, Public Meetings, Webinars, Trainings, and Workshops

FDA-CRCG Webinar: Excipients and Formulation Assessments of Complex Generic Products — Best Practices and Lessons Learned (12/06/22)

This webinar provided an overview of the regulatory framework, scientific concepts, product-specific challenges, and best practices related to development of complex generic drug products that are either required or recommended to have the same formulation as their respective reference listed drugs. Presentations and discussions during the workshop clarified the formulation assessment practices for different types of drug products and identified the corresponding technical considerations for developing appropriate formulations in each case. The webinar also explored best practices for generic applicants to use when communicating with FDA about proposed formulations, to avoid information requests, and to accelerate generic product development.

FDA Drug Topics: The Safety Evaluation and Surveillance of Generic Drugs (11/29/22)

This webinar provided health care professionals with information on the evaluations performed and the methods and tools used by OGD's Office of Safety and Clinical Evaluation (OSCE) to assess the safety and effectiveness of generic drugs throughout the life-cycle of the product (e.g., pre-market and post-market setting).

4th International Symposium on BA/BE of Oral Drug Products (11/17 – 11/19/22)

Held in Otsu, Shiga, Japan and sponsored by the Drug Delivery Foundation and the Research Center for Drug Discovery and Pharmaceutical Development Science, the 4th International Symposium on BA/BE of Oral Drug Products welcomed the Director of OGD's Office of Bioequivalence to talk about areas of potential global harmonization to support BE assessment, including scientific and technical aspects of study design and data analysis. Also included in the presentation were critical insights on how to use alternative innovative BE approaches (e.g., modeling and simulation) to help establish BE for complex generic drug products that may help pave the way for timely access to high quality, affordable, safe, and effective generic medicines.

GRx+Biosims (11/07 – 11/09/22)

GRx+Biosims is a scientific and regulatory dialogue event for the U.S. generics and biosimilars industries sponsored by the Association for Accessible Medicines. The event featured timely programming relevant to technical, regulatory, and policy professionals. Top subject matter experts from OGD offices shared educational information and best

practices to enhance attendees' understanding of how to succeed in generic development and meet the rigorous standards of FDA's regulatory and approvals process.

FDA-CRGC Workshop: Formulation Characterization and Cutaneous Pharmacokinetics to Facilitate Generic Topical Product Development (11/03/22)

This virtual workshop discussed scientific considerations and potential BE approaches for topical generic products that are compositionally different compared to their reference standard. Presentations explained scientific challenges and practical issues related to characterizing the components or composition of reference standard products, including how sophisticated techniques to characterize physicochemical and structural (Q3) properties can mitigate the risk of failure modes for BE with prospective generic products, despite being compositionally different. The workshop also discussed the status of FDA's research collaborations to develop in vivo cutaneous PK approaches by which to evaluate the BE of topical products, and identified scientifically appropriate, practical, and efficient approaches for conducting and assessing such studies.

FDA Drug Topics: Understanding Generic Narrow Therapeutic Index Drugs (11/01/22)

This webinar provided health care providers with information and knowledge on how to answer questions that patients may have about narrow therapeutic index (NTI) generic drugs, such as how the FDA recognizes the importance of bioequivalence in NTI generic drugs and has stricter standards for bioequivalence of NTI drugs than for other generic drugs.

FDA-CRCG workshop: Best Practices for Utilizing Modeling Approaches to Support Generic Product Development (10/27 – 10/28/22)

This virtual workshop discussed how to modernize approaches for efficiently demonstrating BE; how to establish quantitative methods and modeling approaches in modern paradigms of generic drug development; and how to develop best practices for the use of modeling and simulation approaches in regulatory submissions and assessments. The workshop also clarified how a model master file may be leveraged to advance generic drug product development, to facilitate regulatory assessment, and to accelerate patient access to important generic medicines.

FDA, American Association of Pharmaceutical Scientists (AAPS), European Federation for Pharmaceutical Sciences (EUFEPS) 5th Annual Global Bioequivalence Harmonization Initiative (GBHI) Meeting (9/28 – 9/29/22)

The GBHI conference offers up-to-date information on the science and regulation of bioequivalence in global drug development. Workshop information for this event included statistical considerations for BE assessment, replicating design for BE of highly variable drugs, two-stage design, and pharmacokinetic modeling as supportive tools for BE assessment. The main goal of the event was to update participants on

the national and international initiatives affecting the development of safe and effective pharmaceutical drug products via global bioequivalence harmonization initiatives.

General Formulation Considerations in Bioequivalence Assessment for Generic Drug Approval Webinar (9/22/22)

This webinar presented for the American Association of Pharmaceutical Scientists (AAPS) provided case studies to demonstrate the role of formulation design in BE recommendations and during BE assessment for ANDAs. This information can help generic drug applicants understand factors that should be considered during product development to ensure the test product is bioequivalent to the RLD.

SBIA Workshop: Advancing Generic Drug Development — Translating Science to Approval (9/20 – 9/21/22)

This webinar public workshop communicated how the outcomes of FDA's GDUFA Science and Research Program guides and facilitates generic drug development, regulatory assessment, and approval. The presentations and discussions during the workshop focused on common issues seen in ANDA submissions; mapped how GDUFA science and research outcomes supported the development of PSGs for complex products and prepared FDA to provide advice during pre-ANDA meeting discussions; and examined various areas of innovative science and cutting-edge methodologies that are available to support generic drug development.

SBIA Webinar: Best Practices for Topical Generic Product Development and ANDA Submission (8/11/22)

This webinar provided an overview of comparative physicochemical and structural (Q3) product characterization tests, as well as in vitro release test and in vitro permeation test studies for topical generic drug product development, and addressed common deficiencies FDA has encountered with these studies submitted in ANDAs. The presentations and discussions during the webinar highlighted best practices and identified resources that FDA has developed and made publicly available to help generic drug applicants successfully implement efficient in vitro characterization-based BE approaches for topical generic products.

SBIA Webinar: Decoding the Guidance — Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use (8/10/22)

This webinar provided attendees a deeper look at FDA's draft guidance for industry on Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use(published April 2022), which is intended to assist ANDA applicants that reference an RLD intended for parenteral, ophthalmic, or otic use, and are seeking approval of a drug product that is qualitatively (Q1) or quantitatively (Q2) different from the RLD with respect to a pH adjuster.

FDA-CRCG Workshop: In Vitro Release Test and In Vitro-In Vivo Correlation of Complex Generic Ophthalmic, Injectable, Implantable, and Inserted Products (6/29/22)

This virtual workshop discussed the scientific principles and practical considerations that inform current FDA thinking for in vitro release test and in vitro — in vivo correlation studies to support the development and approval of complex generic ophthalmic, injectable, implantable, and inserted drug products.

FDA Webinar for Latin American Region Regulators (6/16 – 6/17/22)

The FDA Latin America Office, OGD's Global Affairs program, and the OGD Office of Bioequivalence (OB) collaborated with the Pan American Health Organization to host a two-day virtual webinar on generic drug regulations in the Latin American Region. More than 400 Latin American attendees from government and industry participated in this highly successful event.

FY 2022 Generic Drug Science and Research Initiatives Public Workshop (5/09 – 5/10/22)

This virtual public workshop presented an overview of the status of current science and research initiatives for generic drugs. It also provided multiple opportunities for public input on these initiatives through presentations and panel discussions, a docket for public comments, and an open microphone public comment session. Public feedback was sought to identify research areas that should be prioritized during the next 5 years of the GDUFA Science and Research Program, and to highlight research initiatives for FY 2023.

Generic Drugs Forum 2022: The Current State of Generic Drugs (4/26 – 4/27/22)

This virtual forum afforded attendees the opportunity to hear from FDA subject matter experts from every part of the generic drug assessment program. The goal of the forum is to provide information to aid potential and current applicants by offering practical advice, presenting case studies, and taking a deep dive into the ANDA assessment process.

SBIA Webinar: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (2/24/22)

This webinar provided attendees a deeper look at FDA's revised draft guidance for industry on Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, which was updated in August 2021 to clarify the Agency's recommendations regarding BE information submitted in an ANDA.

Resources

Links

- 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)
- GDUFA III Commitment Letter
- GDUFA III Reauthorization
- GDUFA Science and Research
- Guidances and MAPPs Related to the Generic Drug User Fee Amendments
- Off-Patent, Off Exclusivity List
- Orange Book
- Paragraph IV (PIV) Patent Certifications
- Points of Contact for Questions Related to Generic Drugs
- Product-Specific Guidances
- Upcoming Complex PSGs

Helpful Acronyms and Abbreviations

Acronym/ Abbreviation	What it means
ANDA	Abbreviated New Drug Application
AE	Adverse Events
BA	Bioavailability
BE	Bioequivalence
CDER	Center for Drug Evaluation and Research
CGT	Competitive Generic Therapy
CRL	Complete Response Letter
DCAP	Drug Competition Action Plan
DRL	Discipline Review Letter
FDA	Food and Drug Administration
FR Notice	Federal Register Notice
GDUFA	Generic Drug User Fee Amendments
IR	Information Request
IVPT	In Vitro Permeation Test
IVRT	In Vitro Release Test
MAPP	Manual of Policies and Procedures
NDA	New Drug Application
OGD	Office of Generic Drugs
OND	Office of New Drugs
Orange Book	Approved Drug Products with Therapeutic Equivalence Evaluations
ORISE	Oak Ridge Institute for Science and Education
PBPK	Physiologically Based Pharmacokinetic
PK	Pharmacokinetic
PSG	Product-Specific Guidance
REMS	Risk Evaluation and Mitigation Strategy
RLD	Reference Listed Drug
SBIA	Small Business & Industry Assistance

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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 III and DCAP goals.

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