U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research

OFFICE OF COMPLIANCE

Annual Report

Fiscal Year 2023

Shielding the public from poor-quality, unsafe, and ineffective drugs through proactive compliance strategies and risk-based enforcement actions.

January 2024

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Director's Message

On the heels of our crucial pandemic-related initiatives, new public health challenges emerged in 2023, requiring careful attention and swift action to protect consumers. We pivoted to preventing and addressing contamination from diethylene glycol and ethylene glycol (DEG/EG), harmful and potentially harmful eye products, and mitigating risks from drug shortages while ensuring the safety our drug supply.

Jill P. Furman, JD
Director
Office of Compliance

Our highest priority remains protecting public health through preventing unsafe products from reaching American consumers. In keeping with that goal, in 2023, as hundreds of children's deaths were reported abroad and worldwide alarms about contamination of certain liquid dosage products from DEG/EG reappeared, we quickly worked to alert manufacturers and ensure the safety of products within the U.S. We issued 170 requests for information designed to determine if manufacturers were able to provide adequate documentation about required testing. We issued warning letters to firms that failed to respond or provided inadequate responses to the FDA's requests for information about required testing and manufacturing processes designed to detect and prevent DEG/EG contamination. To promote voluntary compliance, we further clarified testing requirements in an immediately-in-effect guidance.

In addition to our work to prevent DEG contaminated products from entering the U.S. market, we undertook an initiative to curb distribution of potentially dangerous ophthalmic products in 2023. Ophthalmic drug products are especially concerning from a public health perspective because products intended for use in the eyes generally pose a greater risk of harm due to the route of administration that bypasses some of the body's natural defenses. Over the past year we recommeded recalls, warned companies after the agency's inspections identified insanitary conditions and current good manufacturing practice (CGMP) violations, and warned the public regarding unapproved eye products and potentially contaminated eye drops.

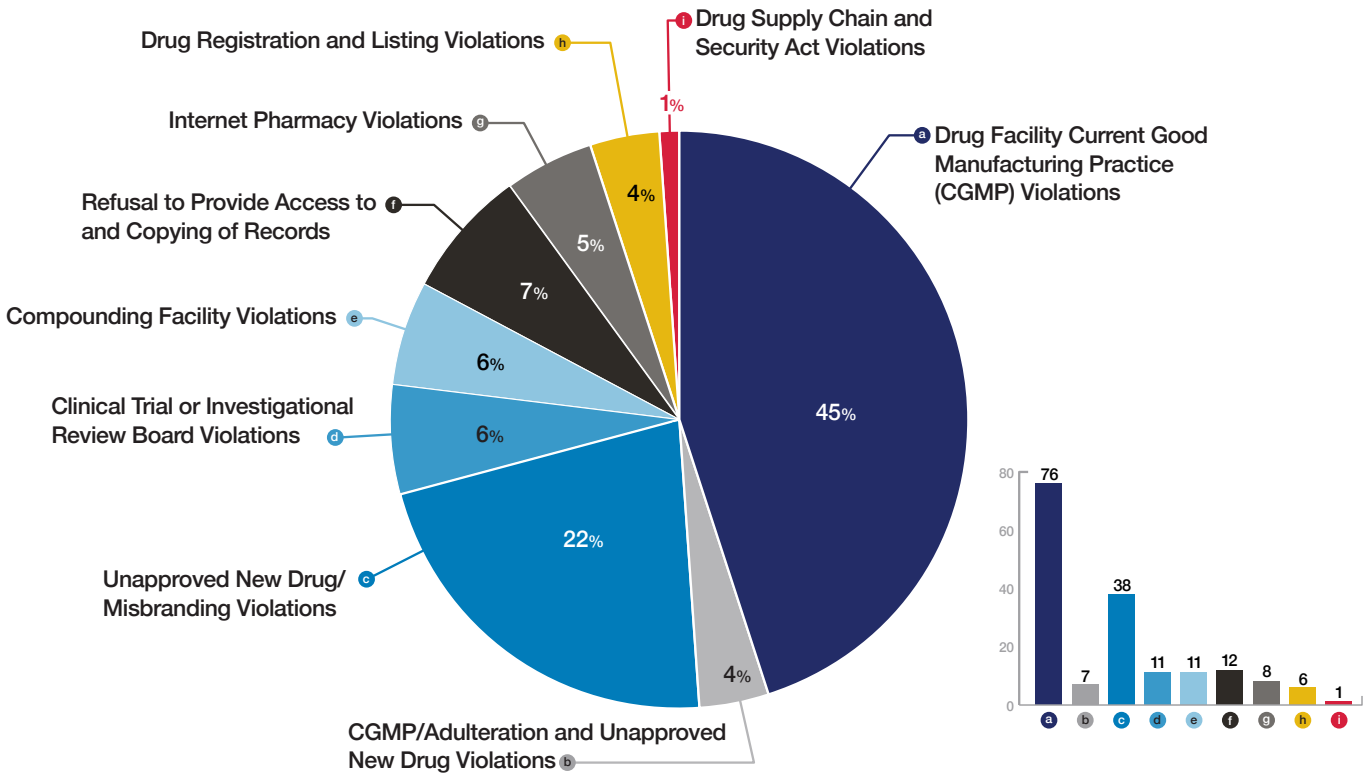
As our work continues to safeguard public health, stakeholder input is a critical aspect in our policy development. We heard concerns about supply chain readiness related to implementation of the Drug Safety Supply Chain Act (DSCSA) and we believe that some flexibility will support successful implementation and lead to a stronger and safer drug supply chain. FDA compliance policies issued in August 2023 accommodated an additional year for implementing the enhanced drug distribution security requirements under the Federal Food, Drug, and Cosmetic Act (FD&C Act). This stabilization period allows trading partners additional time to implement, troubleshoot and mature their systems and processes while supporting the continued availability of products to patients.

We also sought to balance efforts to keep unsafe products out of the U.S. market with the crucial need to ensure access critical drugs. Our work to help keep medically necessary drugs available continues, with an increased level of

innovation required as the complexity of supply chains increase. We collaborated closely with CDER's drug shortages staff to develop strategies to mitigate shortage risks to the public when quality issues arise. Our immediately-in-effect compounding guidance documents were a high priority for our office to help mitigate reports of challenges in obtaining important drugs.

As these initiatives demonstrate, risk-based compliance and enforcement actions form the foundation of our work. As an example, two consent decrees of permanent injunction for human drug companies were entered by federal courts this year after FDA inspections identified significant violations of CGMP requirements in both facilities. One involved a compounder with repeat CGMP requirement violations, and another involved an importer and exporter of active pharmaceutical ingredients (APIs) who failed to adequately qualify foreign manufacturers of API used in compounding.

Human Drug Warning Letters and Violations, FY23[1]



The majority of drug warning letters issued in FY23 cited current good manufacturing practice (CGMP) requirement violations. Compared to last year, we saw an increase in warning letters citing a failure to respond to FDA-issued requests for records and other information pursuant to section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

This report highlights our work[2] to protect the public, which would not be possible without close collaboration with our many partner offices across CDER, ORA and the agency. As new challenges emerge in 2024, we will continue to remain vigilant to quickly detect and remove dangerous drugs from the supply chain and always keep the consumer at the forefront of our work.

[1] Includes human drug warning letters issued by CDER and the Office of Regulatory Affairs.
[2] See Appendix A for a list of offices that comprise the Office of Compliance super office.

By the Numbers

Fiscal Year 2023: October 1, 2022, to September 30, 2023

Policy and Outreach

13
guidance documents published by Center for Drug Evaluation and Research (CDER) Office of Compliance[3]

110+
presentations given to external stakeholders

44
immediate public notifications issued regarding fraudulent health products

10+
presentations shared on FDA's YouTube channel, developed in collaboration with CDER's Small Business and Industry Assistance Program

4,232
stakeholders completed compounding training courses

Compliance Actions

170
human drug warning letters issued by CDER's Office of Compliance or by the Office of Regulatory Affairs

264
drug recall events classified, totaling 1,178 recalled drugs

2
consent decrees of permanent injunctions obtained for quality violations

19,265
drug listings inactivated from FDA's Drug Registration and Listing System

95
new companies or facilities added import alerts to help stop drugs from entering the U.S.

Compliance Reviews

300+
compliance documents shared with foreign regulatory counterparts

32
pre-notice of noncompliance letters issued for ClinicalTrials.gov violations

100%
of clinical inspection summaries issued by agreed-upon goal dates for new drug applications and biologics license applications under the Prescription Drug User Fee Amendments (PDUFA) and Biosimilar User Fee Amendments (BSUFA)

218
drug manufacturing inspection classification letters issued

9,778
Electronic Certificates of Pharmaceutical Product issued to provide documentation of facilities' compliance with FDA standards

[3] See Appendix B for a list of guidance documents issued and contributed to by CDER's Office of Compliance.

SPOTLIGHT:

Key Initiatives

Safeguarding the Nation's Drug Supply from Contamination

Focusing on microbial and other types of contamination

FDA actively monitors drug products sold without a prescription by conducting surveillance, including sampling and testing products on the market[4], and monitoring side effects; however, facility inspections of manufacturing facilities for OTCs may not occur prior to the product being marketed. The agency may recommend voluntary recalls to remove products from the market and issue warning letters. FDA laboratory testing identified significant microbial contamination in a nasal spray product, resulting in a recall and warning letter. The letter noted the manufacturer released finished drugs without adequate testing for critical microbial attributes. We warned the public not to use two methylsulfonylmethane (MSM) eye drop products after FDA testing identified bacterial contamination, fungal contamination or both. One of the two companies agreed to a voluntary recall. A homeopathic earache ear drop also was recalled for microbial contamination identified by FDA testing.

[4] Unlike application-based drugs associated with a new or abbreviated drug application, when a drug does not fall under an application there is not a requirement for FDA review or inspection prior to marketing and sale.

After an inspection, we issued a warning letter to a company making products for young children. The warning letter noted multiple foul odor complaints to the company that were determined to be *Staphylococcus epidermis*, that company investigations were inadequate, and that the company failed to take action to protect consumers from harm. In a second example, after an inspection, a contract testing laboratory received a warning letter describing a failure to have adequate microbiological testing methods that should have been able to reliably detect objectional microorganisms.

Lastly, we continue to notify the public about hand sanitizers consumers should not use due to harmful ingredients, contamination or other risks.

Preventing diethylene glycol/ethylene glycol contamination

One of FDA's top priorities is ensuring the safety, quality, and effectiveness of the drugs available to the American public. There have been repeated instances of diethylene glycol (DEG) poisonings around the world, including in the U.S. in 1937. Each outbreak resulted in numerous deaths, many among children. In 2022 and 2023, numerous countries abroad reported incidents of oral liquid drugs, primarily indicated for children, with confirmed or suspected contamination with high levels of DEG and ethylene glycol (EG). The cases of contamination were associated with more than 300 deaths outside of the U.S., primarily among children under the age of five years.

After the initial World Health Organization reports, FDA notified registered manufacturers about the incidents and began to closely scrutinize multiple liquid dosage drugs in the supply chain. To proactively assess whether drug manufacturers were conducting required testing to detect and prevent DEG contamination, FDA issued more than 170 requests to companies for records and other information under section 704(a)(4) of the FD&C Act. The agency issued warning letters to the companies that failed to respond or provided inadequate responses to FDA's requests for information about required testing and manufacturing processes designed to detect and prevent DEG/EG contamination. We placed companies' facilities and their products on either import alert 66-40 or import alert 66-79 to help stop potentially contaminated drugs from entering the U.S. supply chain.

In May 2023, we issued an immediately-in-effect guidance for industry that outlines recommendations to help pharmaceutical manufacturers, repackers and other suppliers of high-risk drug components and compounders prevent the use of drug components contaminated with DEG or EG.

The agency has not identified any drugs contaminated with DEG connected to the recent international incidents in the U.S. market. We will continue to enforce U.S. safeguards designed to prevent DEG-contaminated drugs from reaching consumers.

Implementing the Drug Quality and Security Act (DQSA)

As we approach the 10-year anniversary of the Drug Quality and Security Act (DQSA), we continue to focus on implementation and operationalization. This law contains provisions for human drug compounding and securing the drug supply chain from illegitimate products, such as those that are counterfeit or otherwise harmful.

Human Drug Compounding

FDA's compounding program protects patients from unsafe, ineffective, and poor-quality compounded drugs while preserving access to lawfully marketed compounded drugs for patients who have a medical need for them.

Over the past decade, FDA's policy development efforts have helped to clarify applicable regulatory requirements that are in place to protect patients. We have released more than 60 policy documents, including 27 final guidance documents and three final rules. We established the Compounding Quality Center of Excellence to assist compounders in meeting FDA's requirements. FDA's inspections and regulatory actions resulted in compounders implementing corrective actions to address unsafe practices that could lead to quality problems. FDA continues to investigate reports of serious adverse events associated with contaminated or otherwise poor-quality compounded drugs and has issued 11 compounding risk alerts since 2017.

POLICY

In FY23, to address shortage concerns and reports to the agency about challenges with accessing oral suspension products for pain and fever, we developed two immediately-in-effect guidance documents:

Compounding Certain Ibuprofen Oral Suspension Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act and Compounding Certain Beta-Lactam Products in Shortage Under Section 503A of the Federal Food, Drug, and Cosmetic Act.

Additionally, we published three *Federal Register* notices[5] to update the list of bulk drug substances for which there is a clinical need under section 503B of the FD&C Act and provided safety information on use of quinacrine.

A new draft guidance describes our interpretation of, and policies concerning, the prohibition on wholesaling in section 503B of the FD&C Act. This guidance also describes examples of how we intend to apply section 503B's wholesaling provision.

OUTREACH

The Compounding Quality Center of Excellence continues to provide training to compounders and conducts stakeholder engagement and research. The

[5] See Appendix B for a full list.

Compounding Quality Center of Excellence Annual Conference convened stakeholders from across the compounding industry to discuss emerging trends and best practices, CGMP-related topics, progress in the outsourcing facility industry over the past 10 years and how to address other challenges. More than 4,200 courses were completed by stakeholders through the Compounding Quality Center of Excellence's training programs in FY23, a significant increase of participants over the previous year and a total of 8,914 courses completed since training programs were first offered.

We hosted a webinar What to Expect after a Compounding Inspection: 483s, Responses and Beyond and updated our compounding inspections and oversight frequently asked questions to clarify our expectations around inspections. We also held a webinar for health care professionals: Regulatory Framework For Human Drug Compounding. We continue to have cross-sector stakeholder meetings to obtain perspectives on issues that affect compounders, outsourcing facilities, health care providers that purchase and use their compounded drugs and other stakeholders.

We also hosted our annual intergovernmental meeting to engage with the states and U.S. territory representatives on a variety of compounding topics.

4,200 courses were completed by stakeholders through the Compounding Quality Center of Excellence's training programs in FY23, a significant increase of participants over the previous year and a total of 8,914 courses completed since training programs were first offered

COMPLIANCE ACTIONS

In FY23, FDA issued 11 warning letters to compounders. We also worked with the Department of Justice on an injunction action against Qualgen, an Oklahoma-based outsourcing facility with a history of federal law violations. The lawsuit was settled by a consent decree that prohibits the company from directly or indirectly distributing adulterated drugs in interstate commerce. There were allegations that the defendants violated the FD&C Act, including failing to follow written procedures applicable to the quality control unit, failing to reject drug products that did not meet specifications and failing to follow appropriate procedures in handling complaints about its drug products. FDA inspected the company's facilities five times from 2015 to 2022, and many of the violations were repeat violations FDA had identified in earlier inspections.

Drug Supply Chain Security Act (DSCSA)

The Drug Supply Chain Security Act (DSCSA) provides FDA with tools to protect consumers from exposure to drugs that may be counterfeit, stolen, contaminated or otherwise harmful. These requirements improve detection and removal of potentially dangerous drugs from the drug supply chain. Over the past decade, we have successfully implemented various provisions of DSCSA, issuing 22 final and draft guidance documents and two proposed rules, holding public meetings and establishing FDA's DSCSA pilot project program.

POLICY

We are actively monitoring industry readiness and are committed to supporting the efforts of industry to achieve enhanced drug distribution security while also supporting the continued availability of drugs to patients. In FY23, we finalized

six critical guidance documents required for successful DSCSA implementation. This includes two compliance policy guidances that established a one-year stabilization period to accommodate additional time that trading partners in the drug supply chain may need to adhere to DSCSA requirements for electronic drug tracing at the package level. The stabilization period will accommodate an additional year, until November 27, 2024, to allow trading partners to implement, troubleshoot and mature their electronic interoperable systems. FDA expects trading partners to use this stabilization period to build and validate interoperable systems and processes, manage products and data, and ensure continuity of the supply chain and product availability to patients. The other final guidances provide agency recommendations and clarifications to help trading partners to understand terms and requirements to support DSCSA implementation, including standards for interoperable data exchange and enhanced drug distribution security.

We are working to complete the national licensure standards for wholesale drug distributors and third-party logistics providers, as well as a small dispenser assessment to determine if alternative methods of compliance are warranted.

OUTREACH

FDA's DSCSA Pilot Project Program summarized the results of 20 industry-led pilot project that explored methods to enhance the safety and security of the drug supply chain. The DSCSA Pilot Project Program final report was made available to the public so that all supply chain stakeholders can benefit from the information gathered and lessons learned as they develop electronic, interoperable capabilities.

Additionally, our outreach and engagement includes a public meeting to discuss DSCSA readiness efforts for 2023 and provide an opportunity for stakeholders to share their perspectives. We continue to engage with the Partnership for DSCSA Governance through a public-private partnership. We also published a *Federal Register* notice requesting comments on proposed topics and questions that FDA plans to include in the small dispensers assessment.

Safeguarding the Drug Supply Chain

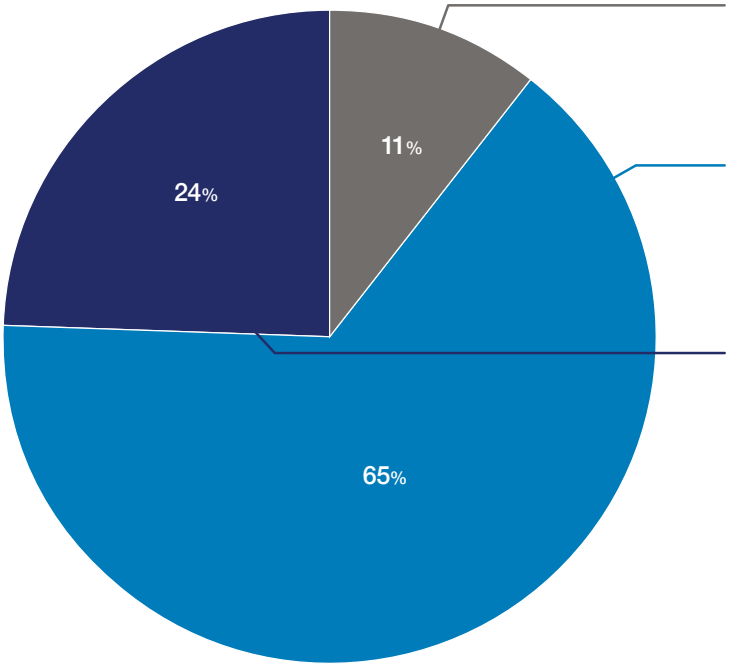
The drug supply chain involves the movement of pharmaceuticals from the manufacturer to the consumer, and we play a vital role in ensuring that safe, effective and high-quality medications are available.

Recalls

Recalls are actions taken by a company to remove a product from the market or warn consumers and patients about potential harm. Recalls may be conducted voluntarily on a company's own initiative, by FDA request or by FDA order under statutory authority in certain circumstances. In FY23, we classified 264 recall events totaling 1,178 violative drug products, including 28 events that were potentially life-threatening. In 2023, the top three reasons for recall were CGMP deviations, lack of assurance of sterility and failed impurities/degradation specifications.

Our presentation on best practices for drug recalls was posted to FDA's YouTube channel, and we participated in the public listening session on modernizing recalls of FDA-regulated commodities. To help increase public awareness of potentially harmful products, two recalls were amplified via alerts: G-Supress DX Pediatric Cough Drops that may have incorrect drug in packaging and Tydemy, a prescription oral contraceptive, may have reduced effectiveness.

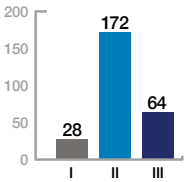
Recall Events by Classification[6]



Class I Recall Events: a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death.

Class II Recall Events: a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

Class III Recall Events: a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.



Online Pharmacies

We issued eight warning letters to website operators illegally offering unapproved and misbranded drugs, including controlled substances, for sale to U.S. consumers. A recent podcast, Navigating the World of Online Pharmacies, for health care professionals provides information they can use to help their patients identify unsafe online pharmacies.

We also issued a warning letter to an entity unlawfully causing the introduction of unapproved and misbranded drugs from foreign sources into interstate commerce in violation of the FD&C Act. The entity contracts with public and private sector employers throughout the U.S. to provide select prescription drugs to employees and acts as a broker between foreign pharmacies and the employee-sponsored health insurance plans to provide enrolled employees with prescription drugs. This is concerning as the drugs offered on the entity's formularies include drugs for which the FDA-approved version is subject to a risk evaluation and mitigation strategy (REMS) program, has a narrow therapeutic index (NTI), is a controlled substance and/or is indicated to treat serious conditions such as HIV, cancer or hepatitis, as well as maintenance medications. The substitution of FDA-approved prescription drugs with unapproved drugs poses significant health risks to U.S. consumers.

Drug-related import alerts

We collaborated with FDA's Office of Regulatory Affairs to add facilities or products to the following import alerts to help stop products from entering the U.S. supply chain. The table below lists CDER additions to drug-related import alerts in FY23.

[6] See the FDA Data Dashboard for detailed recall information.

Human Drug Import Alert Additions in FY23

Import Alert Number	Import Alert Description	Drug-related Facility or Product Additions to Import Alerts in FY23
66-40	Lists manufacturing facilities that have not met CGMP requirements.	41
66-41	Lists companies and products for which FDA has sufficient evidence to demonstrate that a product appears to be an unapproved new drug.	13
66-78	Lists drug manufacturers at risk for adulteration based on FDA analytical sample results demonstrating violations of the FD&C Act.	1
66-79	Lists companies and their products because the facility refused an FDA inspection.	38
54-16	Lists companies and products that are marketed as dietary supplements but contain active pharmaceutical ingredients.	1
55-05	Lists companies and products due to potentially hazardous microbiological contamination.	1

Outreach

We hosted our fourth online controlled substances summit as part of the agency's overall efforts to protect patients and consumers, including youth, from harm associated with drugs that have abuse potential. Summit attendees from the public and private sector, including those from the internet ecosystem, academia and regulatory organizations, gathered to discuss these challenges and develop strategic and effective solutions.

Our regulatory and enforcement strategies are enriched through collaborations with international regulatory agencies and industry organizations. FY23 global collaborations focusing on outreach and education include co-sponsoring the Asia-Pacific Economic Cooperation (APEC) Medical Product Supply Chain Dialogue, which focused on global supply chain integrity as part of the 2023 U.S. host year for APEC. We integrated corresponding updates to the APEC toolkit, which is designed to cover the entire supply chain and lifecycle of medical products and develop processes, procedures and tools directed at enhancing global medical product quality and supply chain security.

We also participated in the World Health Organization Member State Mechanism, and the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Expert Circle. PIC/S published two good distribution practices documents for medicinal products: AIDE-Memoire Inspection of Good Distribution Practice (GDP) for Medicinal Products in the Supply Chain and Questions & Answer document regarding PIC/S GDP Guide (PE 011-1).

Drug Manufacturing Compliance

Drug manufacturers and compounders are responsible for complying with applicable regulations and ensuring that high-quality products reach U.S. patients. When the agency uncovers violations that put patients and consumers at risk, we take action.

Outreach

We recently released a webinar *Understanding FDA Inspections and Data* which discussed drug manufacturing inspections, CGMP requirements and how to locate inspection data online.

We co-sponsored the annual Parenteral Drug Association/FDA Joint Regulatory Conference, which focused on the role of effective quality systems in ensuring an ongoing state of control related to drug manufacturing and quality. We discussed the role of effective quality systems in ensuring an ongoing state of control related to drug manufacturing and quality.

Policy

Our recently published draft guidance Post-Warning Letter Meetings Under GDUFA describes the process an eligible facility may use to request a post-

warning letter meeting with FDA. We also developed the immediately-in-effect guidance: Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol.

We served as a key member in a working group that revised the FDA compliance program that provides risk-based strategies for inspectional coverage on post-approval inspections: post-approval inspection.

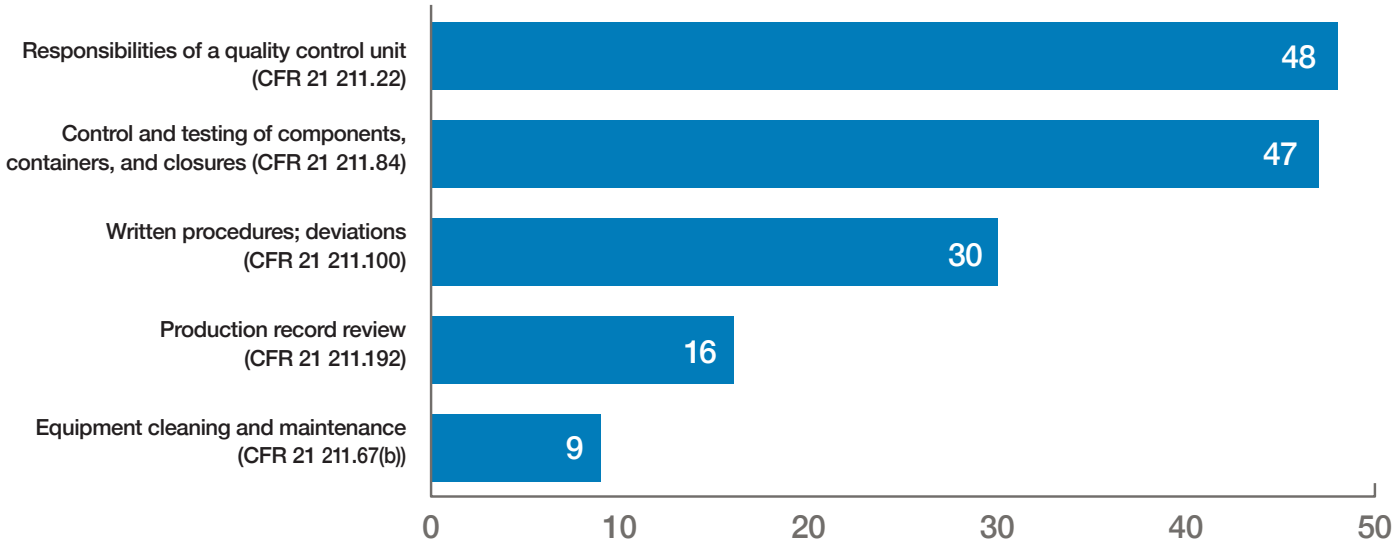
Compliance Actions

We worked with the Department of Justice to bring an injunction action against a Florida-based drug importer and distributor. The company imported and exported active pharmaceutical ingredients (APIs) used to manufacture or compound finished drugs. FDA inspections identified significant violations of CGMP requirements, including the company's failure to perform adequate investigations of quality-related customer complaints involving out-of-specification APIs that it distributed, failure to adequately qualify foreign manufacturers, and failures to establish adequate procedures after an API supplier was disqualified by the company. The company agreed to enter into a consent decree and is thereby required to undertake detailed quality-related compliance actions to ensure it is in compliance with the law.

After an inspection identified serious violations, we issued the first CGMP-related warning letter to an excipient manufacturer whose product is extensively used as a major component in a wide variety of drug products.

The following metrics provide a snapshot of drug manufacturing facility compliance actions. Visit FDA's Data Dashboard for more information.

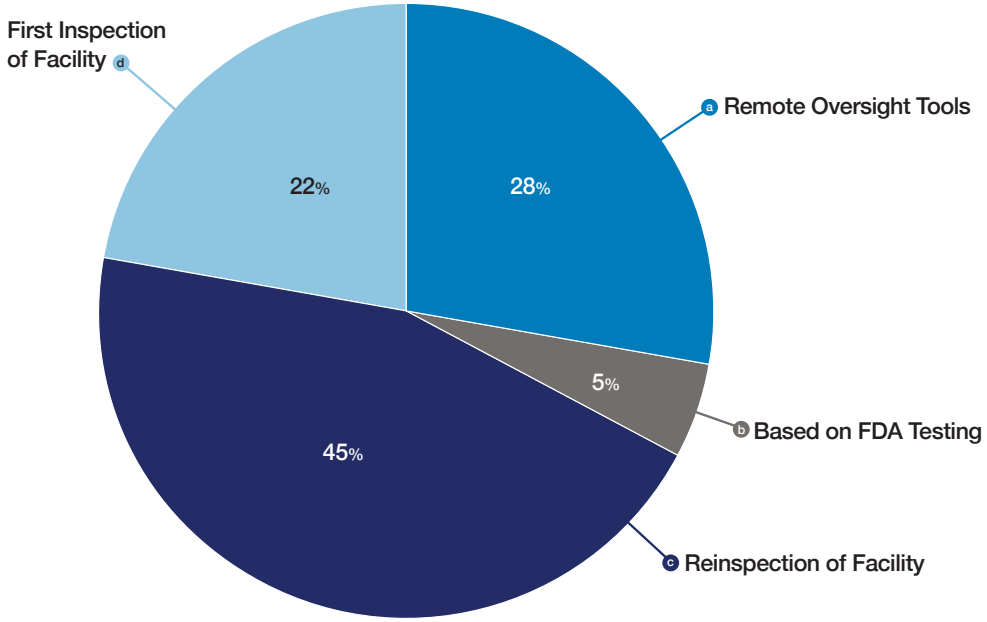
Most Common Citations in Warning Letters with CGMP-related Violations for Finished Product Manufacturers, FY23[7]

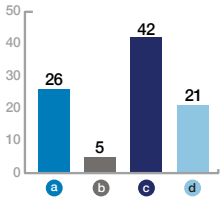


[7] Excludes compounding facilities

The most common CGMP citation in FY23 warning letters to drug manufacturing facilitites involved quality units (21 CFR 211.22) followed closely by control and testing citations (21 CFR 211.84). In the top five citations of the year were written procedures and deviations (21 CFR 211.100), production record review, (21 CFR 211.192) and equipment cleaning and maintenance (21 CFR 211.67(b)).

Basis for Warning Letters with CGMP or Adulteration Citations, FY23[8]





The majority of drug CGMP or adulteration warning letters were issued after an on-site inspection, either a facility's first inspection or a reinspection. In FY23, we issued 28 percent of our CGMP warning letters while utilizing FDA's remote oversight tools.

Operational Efficiency

We are continually refining our processes and cross-office coordination on cases to maximize our resources. One ongoing area of focus is the concept of operations agreement. ConOps enables FDA to more effectively provide oversight of pharmaceutical manufacturing by:

- Ensuring consistency, efficiency and transparency in facility evaluations, inspections and regulatory decision-making for marketing applications across FDA;
- Enhancing collaboration between various CDER and ORA offices;
- Enhancing the quality of and increasing access to facility and regulatory decisional information across FDA; and
- Meeting user fee commitments and improving the timelines for regulatory, advisory and enforcement actions to protect public health and promote drug quality, safety and effectiveness.

In FY23, we issued 218 drug manufacturing inspection final classification letters.

[8] Excludes compounding facilities

Clinical Trial Oversight and Bioresearch Monitoring

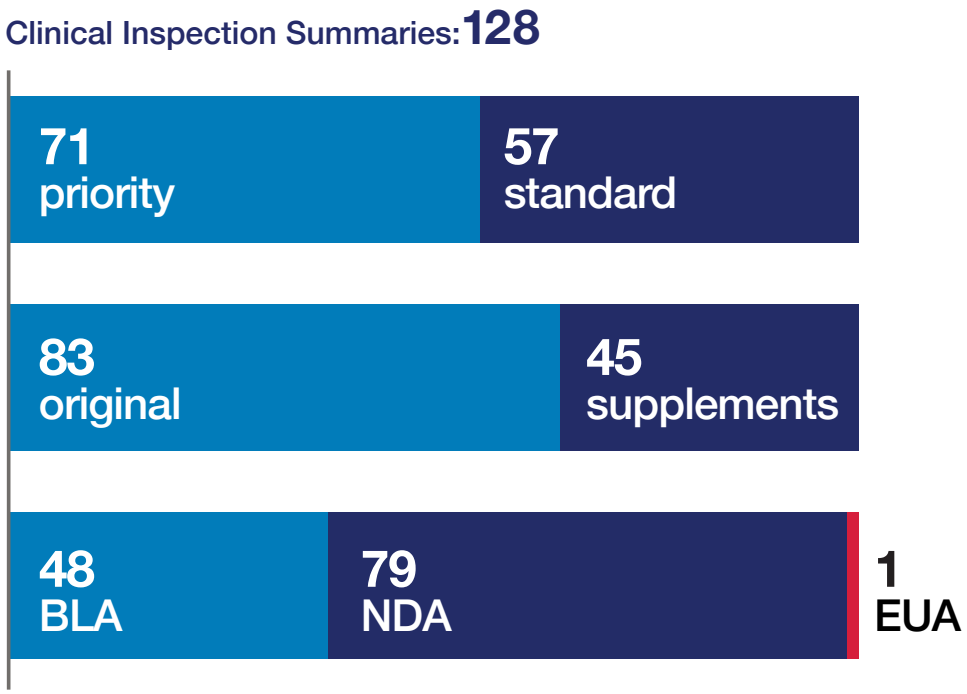
The bioresearch monitoring (BIMO) program is an agency-wide comprehensive program of onsite inspections, data audits and remote regulatory assessments (RRAs) designed to monitor all aspects of the conduct and reporting of clinical and non-clinical research and to oversee a company's compliance with postmarketing requirements. We continue to manage the agency BIMO program for CDER.

Eight joint and/or observed good clinical practice inspections were conducted with global regulatory counterparts

Inspections, Compliance Review and Compliance Actions

We directed more than 600 BIMO inspections and RRAs in support of FDA and CDER's public health mission, including over 400 inspections to assess the reliability of data submitted in support of marketing applications. We provided 128 clinical inspection summaries to support the review of marketing applications.

Clinical Trial Oversight and Bioresearch Monitoring Inspections, FY23



We issued eleven warning letters – six to clinical investigators, four to sponsor-investigators, and one to an Institutional Review Board.

We advanced the use of novel tools for the effective assessment of bioresearch monitoring establishments by developing and implementing RRA pilot programs in advance of PADE and REMS inspections and in lieu of IRB inspections, to rigorously evaluate the use of RRAs and determine how they can be used most effectively.

Policy

We contributed to the development of more than 10 policy documents relevant to the conduct of FDA-regulated research and postmarketing activities published in FY23, including:

- International Council on Harmonization (ICH) E6(R3) Guideline for Good Clinical Practice draft guidance, which encourages innovation, focuses on quality and establishes proportionate and risk-based approaches for conducting clinical trials, while minimizing unnecessary complexities.
- Decentralized Clinical Trials for Drugs, Biological Products, and Devices draft guidance that provides recommendations for sponsors, investigators and other stakeholders regarding the implementation of decentralized clinical trials to facilitate the development of drugs including in areas of medical need, resulting in more treatment options and improved patient outcomes.
- Postmarketing Studies and Clinical Trials: Determining Good Cause for Noncompliance with Section 505(o)(3)(E)(ii) of the Federal Food, Drug, and

Cosmetic Act draft guidance, describing the factors FDA considers when determining whether an applicant has demonstrated good cause for failure to comply with the timetable for completion of required postmarketing studies or clinical trials and describing actions FDA may take for noncompliance with the requirements.

ClinicalTrials.gov

We continue to support clinical trial transparency by ensuring that responsible parties submit registration and results information to the ClinicalTrials.gov data bank for applicable clinical trials of CDER-regulated products. In FY23, we issued 32 preliminary notice of noncompliance letters to responsible parties for potential violations or noncompliance with ClinicalTrials.gov requirements meeting risk criteria. Additionally, we developed a three-part webinar series to provide a general overview of ClinicalTrials.gov and relevant definitions, laws, and regulations for complying with ClinicalTrials.gov registration and results information submission requirements.

Outreach

To proactively promote compliance and clarify expectations with external stakeholders, we participated in more than 25 conferences and outreach events and delivered more than 35 individual presentations. Highlights include:

- Participating in the FDA Clinical Investigator Training Course to clarify expectations for international clinical trials and associated regulatory requirements.
- Presenting at the Drug Information Association conference on real world data and quality briefs and a conference hosted by the Society of Clinical Research Associates (SOCRA) designed to aid sponsor-investigator's understanding of their responsibilities in the conduct of clinical trials.

We also published an article in the *Journal of the Society for Clinical Data Management* quantitatively and qualitatively describing FDA's experience using alternative tools to evaluate good clinical practice during the COVID-19 public health emergency.

We co-led the PIC/S pharmacovigilance expert circle and led pharmacovigilance sub-groups focused on best practices and on artificial intelligence and machine learning in pharmacovigilance.

Unapproved Drugs

An unapproved drug can include the marketing of medication products with unproven, false or misleading claims about the products' ability to diagnose, cure, treat or prevent diseases or conditions. Use of medication products marketed with unproven claims could cause serious health problems.

Policy

In FY23, FDA issued a final guidance, Homeopathic Drug Products, which describes the agency's approach to prioritizing regulatory actions for homeopathic products posing the greatest risk to patients. Since homeopathic products have not been approved by FDA for any use, they may not meet modern standards for safety, effectiveness and quality. Many homeopathic products fall outside the risk-based categories described in the guidance.

Compliance Actions and Public Notifications

Medication health fraud can occur anywhere products are offered for sale, including online and at physical sales locations like stores, salons or gas stations. We issued five letters to various online marketplaces, including to Amazon, Walmart.com and Latin Foods Market, for distributing unapproved drugs marketed on their platforms.

We issued warning letters to eight companies for manufacturing or marketing unapproved eye products in violation of federal law. Eye products addressed in the eight warning letters are illegally marketed to treat conditions such as conjunctivitis ("pink eye"), cataracts, glaucoma and others.

Products marketed to change the physique through weight loss or body building were a continued area of focus, particularly if they could put patient's health at risk. We warned teens and young adults about the dangers of using selective androgen receptor modulators (SARMs), chemical substances that mimic the effects of testosterone and anabolic steroids. Online vendors and social media influencers are using social media to make SARMs seem safe and effective, but they are not FDA approved and have caused serious adverse events. Consumers are also warned not to use Apetamin, which is a potentially dangerous product promoted and sold through social media, targeting people seeking to gain weight and achieve a certain physique.

We issued 44 immediate public notifications to alert consumers and retailers about hidden drug ingredients found by FDA testing. Products containing hidden drug ingredients were promoted for pain relief, weight loss, sexual enhancement and energy. This year we identified a trend of products marketed for energy that contained hidden drug ingredients for Viagra and Cialis, used to treat erectile dysfunction.

Following a 2022 warning to consumers regarding the availability of products marketed with variations of the names "Artri" or "Ortiga." We issued warning letters to Amazon, Walmart, and Latin Foods Market for distributing various "Artri" and/or "Ortiga" unapproved and misbranded drug products. Walmart and Latin Foods Market issued voluntary recalls.

Unapproved drugs marketed for use in vulnerable populations, such as children, are another area of concern. We developed a warning to parents and issued warning letters to six companies selling unapproved drugs marketed to treat molluscum, a common skin condition. Health care providers were warned about use of an unapproved potassium phosphates drug in children due to risk for aluminum toxicity.

We also warned consumers not to use Nose Slap and Soul Slap, which are inhalants and primarily contain ammonia; the company later received a warning letter.

We warned consumers about heavy metal poisoning associated with certain unapproved ayurvedic products.

Drug Registration and Listing

The accuracy and integrity of establishment registration and drug listing data are essential to FDA's mission. Owners or operators of drug manufacturing establishments are required to register their establishments with FDA.

We offer continual assistance with the registration and listing process, send annual registration reminders, and provide stakeholder outreach and training. To clarify our expectations, we held the Drug Registration and Listing (eDRLS) Using CDER Direct Conference designed to provide basic instruction in the registration and listing policy and process. This training includes case studies and a demonstration for submissions.

We continually work to improve the data quality found in the FDA's drug registration and listing system (DRLS). While FDA employs automated validation rules in order to prevent inaccurate and incomplete data submission, not all the data screening can be automated. Our compliance program is designed to monitor the data, have manufacturers correct inaccuracies, and remove inaccurate data if corrections are not completed. In FY23, more than 19,265 drug listings were inactivated due to either not being certified as active or being associated with an unregistered manufacturing establishment. The office also inactivated 435 unused labeler codes and issued 104 deficiency letters to companies for inaccurate or incomplete registration and listing data. We issued warning letters to six companies.

In 2023, FDA updated the marketing category and application number fields[9] for over-the-counter (OTC) monograph drugs in DRLS. For the marketing category field, FDA replaced "OTC monograph final" and "OTC monograph not final" with the single term "OTC monograph drug" for nonprescription drug products marketed without an approved new drug application under section 505G of the FD&C Act. For the application number field, users will now provide an OTC monograph reference in the drug listing, using the number of the applicable OTC monograph found on the OTC Monographs@FDA portal. For example, they would include "M014" as the application number for an otic drug product marketed under OTC Monograph M014: Topical Otic Drug Products for OTC Human Use.). In the case of a drug currently marketed under 505G(a)(3), they would include the term "505G(a)(3)" in the application number field.

[9] The Coronavirus Aid, Relief, and Economic Security Act (CARES Act) (Public Law No. 116-136, 134 Stat. 281, 457) was signed into law on March 27, 2020. The CARES Act added section 505G to the Federal Food, Drug and Cosmetic Act (FD&C Act) (21 U.S.C. 355g). Section 505G reforms and modernizes the over-the-counter (OTC) drug review process.

As part of these reforms, under section 505G(b)(8) of the FD&C Act, a final monograph or tentative final monograph (TFM) that establishes conditions of use for a drug described in section 505G(a)(1) or (2) of the FD&C Act and that represents the most recently issued version of the conditions of use, including as modified, in whole or in part, by any proposed or final rule, is deemed to be a final order (deemed final order).

FDA has made available all such deemed final orders. The current OTC monographs are posted in the OTC Monographs@FDA portal. FDA also intends to issue a notice to withdraw the pre-CARES regulations establishing final OTC monographs in title 21 of the Code of Federal Regulations (CFR), which no longer govern the marketing of OTC monograph drugs. A drug that complies with the OTC monograph conditions embodied by a final order and other applicable requirements, including general requirements for OTC drugs, can be legally marketed without an approved new drug application.

In addition to drugs that are subject to final orders, currently, an OTC drug that was categorized in category III for safety or effectiveness in the preamble of a tentative final monograph (TFM) that is the most recently applicable proposal or determination for such drug issued under 21 CFR part 330 (prior to enactment of the CARES Act) and that was not deemed to be a new drug under section 505G(a)(4) of the FD&C Act, may be legally marketed without an approved new drug application if the drug conforms to the provisions of section 505G(a)(3)(A) of the FD&C Act, even though a determination of whether there are conditions under which the drug is generally recognized as safe and effective (GRASE) has not yet been made. When a final order issued by FDA under section 505G(b)(1)(A) regarding such a drug takes effect, that order will govern subsequent marketing.

Human Capital

We recognize our talented and dedicated staff as our greatest asset, and we continue focus on attracting, retaining and engaging highly qualified candidates who foster a work environment dedicated to excellence. Addressing the needs of our workforce, and providing the tools needed for success, is intrinsically linked to our organizational culture and ability to meet our mission. We publicly post open Title 21 job opportunities focused on scientific, technical or professional positions. We actively promote positions via job announcement boards, through FDA's LinkedIn, and at hiring events. We successfully ended the year with 92% of the office's positions filled and have made progress in building a specialized and diverse workforce. Diversity and inclusion are critical to our success as an office, and we are committed to creating a workplace where everyone feels valued and supported. Ultimately, a critical aspect of our strategic goal is to identify highly qualified individuals who can contribute their talent and energy towards a lasting commitment to the FDA mission.

Appendix A: Office of Compliance Organization

The **Immediate Office (IO)** provides leadership and overall direction to all Compliance activities to ensure that the mission of the office is accomplished. The IO includes the Program Management and Analysis Staff, who provide administrative services that support Office of Compliance employees.

The **Office of Compounding Quality and Compliance (OCQC**) aims to protect patients from unsafe, ineffective and poor-quality compounded drugs while preserving access to lawfully marketed compounded drugs for patients who have a medical need for them.

The **Office of Drug Security, Integrity, and Response (ODSIR)** protects the integrity of the legitimate drug supply chain. ODSIR uses a risk-based approach to minimize consumer exposure to dangerous products marketed outside the legitimate supply chain.

The **Office of Manufacturing Quality (OMQ)** evaluates compliance with manufacturing requirements for drugs based on inspection reports and evidence gathered by FDA investigators. OMQ develops and implements compliance policy and takes risk-based actions to protect the public from adulterated drugs in the U.S. market.

The **Office of Program and Regulatory Operations (OPRO)** leads and manages operational infrastructure for the Office of Compliance relating to project management and process management.

The **Office of Scientific Investigations (OSI)** ensures that CDER-regulated drugs and biologics are safe and effective for the life of the product, through oversight and enforcement activities involving: the reliability of safety and efficacy data submitted to FDA, the application of human subject protection in clinical trials and certain post market safety requirements.

The **Office of Unapproved Drugs and Labeling Compliance (OUDLC)** develops and implements surveillance activities, compliance strategies and policies related to unapproved prescription and over-the-counter (OTC) drugs, fraudulent drugs and drug registration and listing. OUDLC engages in strategic, risk-based, compliance and enforcement activities to minimize consumer exposure to unsafe and unapproved new drugs.

Appendix B: Compliance-related Policies Published in FY23

This appendix lists compliance-related policies published in FY23. Documents marked with an asterisk (*) were initiated by CDER's Office of Compliance. Documents marked with a circumflex (^) were not initiated by CDER's Office of Compliance, but included review and input by CDER's Office of Compliance. Documents may have been initiated by the Office of Regulatory Affairs, Office of Pharmaceutical Quality, Office of Clinical Policy, Office of Medical Policy, the International Council on Harmonization, or other FDA offices.

Drug Supply Chain Security Act (DSCSA)

DSCSA significantly strengthens FDA's ability to protect consumers from exposure to counterfeit, stolen, intentionally adulterated or otherwise harmful drugs.

- Final Guidance: DSCSA Standards for the Interoperable Exchange of Information for Tracing of Certain Human, Finished, Prescription Drugs*
- Final Guidance: Wholesale Distributor Verification Requirement for Saleable Returned Drug Product and Dispenser Verification Requirements When Investigating a Suspect or Illegitimate Product — Compliance Policies*
- Final Guidance: Enhanced Drug Distribution Security at the Package Level Under the Drug Supply Chain Security Act*
- Final Guidance: Enhanced Drug Distribution Security Requirements Under Section 582(g)(1) of the Federal Food, Drug, and Cosmetic Act — Compliance Policies*
- Final Guidance: Waivers, Exceptions, and Exemptions from the Requirements of Section 582 of the Federal Food, Drug, and Cosmetic Act*
- Final Guidance: Definitions of Suspect Product and Illegitimate Product for Verification Obligations Under the Drug Supply Chain Security Act Guidance for Industry*
- Federal Register Notice: Development of Small Dispensers Assessment Under the Drug Supply Chain Security Act; Request for Comments*

Human Drug Compounding

FDA's compounding program aims to protect patients from unsafe, ineffective and poor-quality compounded drugs, while preserving access to lawfully marketed compounded drugs for patients who have a medical need for them.

- Federal Register Notice: List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B the Federal Food, Drug, and Cosmetic Act*

- Draft Guidance: Prohibition on Wholesaling Under Section 503B of the Federal Food, Drug, and Cosmetic Act*
- Federal Register Notice: List of Bulk Drug Substances for Which There Is a Clinical Need Under Section 503B of the Federal Food, Drug, and Cosmetic Act*
- Immediately-in-Effect Guidance: Compounding Certain Ibuprofen Oral Suspension Products Under Section 503B of the Federal Food, Drug, and Cosmetic Act*
- Federal Register Notice: List of Bulk Drug Substances for Which There is a Clinical Need Under Section 503B the Federal Food, Drug, and Cosmetic Act*
- Immediately-in-Effect Guidance: Compounding Certain Beta-Lactam Products in Shortage Under Section 503A of the Federal Food, Drug, and Cosmetic Act*
- Federal Register Notice: Extension of the Period Before the Food and Drug Administration Intends To Begin Enforcing the Statutory 5 Percent Limit on Out-of-State Distribution of Compounded Human Drug Products*

Unapproved Drugs

Unapproved drug products have not been reviewed by FDA for safety, effectiveness or quality.

- Final Guidance: Homeopathic Drug Products*

Human Drug Manufacturing Compliance

All drugs manufactured for the U.S. market must comply with CGMP requirements.

- Immediately-in-Effect Guidance: Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol*
- Draft Guidance: Post-Warning Letter Meetings Under GDUFA*
- Draft Guidance: Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug or Device Inspection^
- Question and Answers on CGMP Requirements: Records and Reports: Can a firm demonstrate compliance with current good manufacturing practice (CGMP) by relying on records not accessible to FDA?^
- Question and Answers on CGMP Requirements: Production and Process Controls: Is parametric release an appropriate control strategy for sterile drug products that are not terminally sterilized?^
- Final Guidance: Q9(R1) Quality Risk Management^
- Compliance Program 7356.002: Drug Manufacturing Inspections^
- Compliance Program 7346.832: Preapproval Inspections^

- Proposed Rule: Current Good Manufacturing Practice for Medical Gases^
- Final Guidance: Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs)^

Clinical Trial Oversight and Bioresearch Monitoring

The CDER BIMO program is designed to monitor the conduct and reporting of regulated research and to oversee a company's compliance with postmarketing requirements. We contributed to the development of the following policies:

- Proposed Rule: Investigational New Drug Applications; Exemptions for Clinical Investigations to Evaluate a Drug Use of a Product Lawfully Marketed as a Conventional Food, Dietary Supplement, or Cosmetic^
- Final Guidance: Considerations for the Use of Real World Data and Real World Evidence to Support Regulatory Decision Making for Drugs and Biological Products^
- Final Guidance: A Risk-Based Approach to Monitoring of Clinical Investigations—Questions and Answers^
- Final Guidance: Considerations for the Conduct of Clinical Trials of Medical Products During Major Disruptions Due to Disasters and Public Health Emergencies^
- Final Guidance: Use of Whole Slide Imaging in Nonclinical Toxicology Studies: Questions and Answers^
- Draft Guidance: Postmarketing Studies and Clinical Trials: Determining Good Cause for Noncompliance with Section 505(o)(3)(E)(ii) of the Federal Food, Drug, and Cosmetic Act^
- Draft Guidance: Electronic Systems, Electronic Records and Electronic Signatures on Clinical Investigations Questions and Answers^
- Draft Guidance: Decentralized Clinical Trials for Drugs, Biological Products, and Devices^
- Draft Guidance: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products^
- Compliance Policy: Postmarketing Adverse Drug Experience (PADE) Inspections Compliance Program, Compliance Policy 7353.001^
- International Council on Harmonization (ICH) guideline: ICH draft guideline ICH M11 Clinical electronic Structure Harmonize Protocol (CeSHarP)^
- International Council on Harmonization (ICH) guideline: ICH draft guideline E6(R3) Good Clinical Practice^

U.S. FOOD & DRUG ADMINISTRATION

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