U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR
DRUG EVALUATION AND RESEARCH

OFFICE OF COMPLIANCE

Annual Report
Fiscal Year 2022

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

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Office Organization

The Office of Compliance is considered a super office and comprises the following six component offices as well as a dedicated management staff:

- Office of Compounding Quality and Compliance (OCQC)
- Office of Drug Security, Integrity, and Response (ODSIR)
- Office of Manufacturing Quality (OMQ)
- Office of Program and Regulatory Operations (OPRO)
- Office of Scientific Investigations (OSI)
- Office of Unapproved Drugs and Labeling Compliance (OUDLC)
- Program Management and Analysis Staff (PMAS)

DIRECTOR'S MESSAGE

I am pleased to share the CDER Office of Compliance annual report for fiscal year 2022 (FY22). This report highlights key initiatives and actions during the year that have a direct impact on public safety. We took critical steps to reduce the impact of the overdose crisis, protect patients from poorly compounded drugs, alert the public about misleading and potentially dangerous products, implement the Drug Supply Chain Security Act, and enhance risk-based monitoring of clinical trials.

Jill P. Furman, JD
Director
Office of Compliance

The best way to minimize the risk of potentially harmful medicines reaching consumers and patients is to prevent violations of FDA's laws and regulations before they occur. Accordingly, the Office of Compliance focuses on proactively promoting compliance through communication with stakeholders, including publication of policy documents, regularly engaging with members of industry, and conducting training programs and conference presentations.

We used a risk-based approach to take compliance and enforcement actions that have the greatest impact on public health, including actions to ensure that drugs entering the U.S. supply chain are safe, effective, and produced according to established quality standards. In FY22, we issued 101 warning letters across our compliance programs, obtained two consent decrees of permanent injunction, and classified 343 recall events relating to more than 1,500 products.

I especially want to recognize the highly skilled, specialized, and dedicated staff in our office as well as our collaborators across CDER and the agency. Our relationships with our federal partners, including the Federal Trade Commission, Drug Enforcement Administration, and U.S. Customs and Border Protection, as well as our international partners, have resulted in immeasurable benefit to the public.

Our accomplishments in FY22 demonstrate our resolute determination to shield patients and consumers from poor-quality, unsafe, and ineffective drugs through proactive compliance strategies and risk-based enforcement actions. I look forward to continuing our mission in 2023.

STRATEGIC PRIORITIES

The Office of Compliance uses three strategic priorities to guide our decision-making in support of our mission to shield the American public from poor-quality, unsafe, and ineffective drugs. This annual report shares accomplishments related to each of these priorities and the work completed in response to public health emergencies.

Promote Compliance
Proactively promote compliance through clear communication and collaboration with all stakeholders.

Regulatory and Enforcement Actions
Pursue effective, risk-based regulatory and enforcement actions.

Organizational Excellence
Pursue organizational excellence in workplace culture, human resources, and business processes.

BY THE NUMBERS

Fiscal Year 2022: October 1, 2021, to September 30, 2022

Promote Compliance

2
proposed rules issued by the Office of Compliance

10
guidance documents, draft or final, published by, or in collaboration with, the Office of Compliance

80+
conference presentations

32
immediate public notifications issued regarding fraudulent health products

13
presentations shared on FDA's YouTube channel, developed in collaboration with Center for Drug Evaluation and Research (CDER's) Small Business and Industry Assistance Program

2,732
courses completed by stakeholders through the Compounding Quality Center of Excellence's training program in FY22, totaling 4,675 courses completed since training programs began

Regulatory and Enforcement Actions

101
warning letters issued by the Office of Compliance

50+
additional warning letters issued by the Office of Regulatory Affairs in collaboration with CDER

343
drug recall events classified, totaling 1,500+ recalled products

2
consent decrees of permanent injunction obtained for quality violations

50+
facilities added to FDA import alerts that aim to prevent potentially unsafe products from entering the U.S.

99+
percent 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)

Operational Excellence

183
drug manufacturing inspection classification letters issued

10,220+
Electronic Certificates of Pharmaceutical Product issued to provide documentation of facilities' compliance with FDA standards

21,440+
drug listings inactivated from FDA's Drug Listing and Registration System

212
deficiency letters issued to firms for inaccurate or incomplete drug registration and listing data

SPOTLIGHT: PUBLIC HEALTH EMERGENCY RESPONSE

Overdose Prevention

In 2017, the opioid crisis was declared to be a public health emergency and to this day is still in effect. In 2022, Commissioner Robert M. Califf introduced the U.S. Food and Drug Administration's Overdose Prevention Framework— our vision to undertake impactful, creative actions to prevent drug overdoses and reduce harm from controlled substances. This report shares examples of our efforts to support this framework.

Encouraging Harm Reduction Through Innovation and Education

In recognition of the importance of access to naloxone, a life-saving medication, FDA partnered with the Reagan-Udall Foundation to hold a virtual public meeting to engage stakeholders and explore effective approaches that could increase naloxone availability. In September, our office worked to help facilitate availability and expand access to naloxone by issuing a guidance. This guidance clarifies the applicability of a public health emergency exclusion and exemption from certain requirements under the Drug Supply Chain Security Act (DSCSA), in terms of the distribution of FDA-approved naloxone products to harm reduction programs and includes a related compliance policy. We believe that this guidance will help to address some of the obstacles to naloxone access and will facilitate the life-saving work of harm reduction programs by aiding their ability to obtain naloxone directly from manufacturers and distributors while expanding public availability of this critical medicine.

Protecting the Public from Unapproved, Diverted, or Counterfeit Drugs Presenting Overdose Risks

Cracking down on the market for prescription drugs illegally sold online and securing the supply chain for approved medications, including opioids and other controlled substances, remains a top priority.

Compliance Opioid Quality Survey

FDA further developed our surveillance and enforcement efforts to search for potential adulteration within the supply chain of FDA-regulated products.

Specifically, CDER's Office of Compliance developed a multi-year opioid product quality survey designed to uncover impurities or substitutions of illegal, unsafe substances in place of the intended active pharmaceutical ingredient (API) in certain products. During this survey, the agency tested FDA-regulated opioid drugs, ingredients used to make opioid drugs, products used to reverse opioid overdoses, and products used in the treatment of opioid use disorder. FDA found no evidence of illegal substitution in any of the ingredients and products tested.

The agency will continue to test additional products as part of ongoing regulatory oversight efforts.

Enforcement and Regulatory Actions

FDA has aggressively worked to address controlled substances illegally sold online and leveraged high-impact partnerships to curtail sales of these products. FDA continues to work with internet domain registries to help prevent the illegal sale of opioids and other controlled substances over the internet. In April 2022, we partnered with the Drug Enforcement Administration to issue joint warning letters to operators of two websites illegally selling Schedule II stimulants, including amphetamine drug products marketed as Adderall. In August, we issued another warning letter to an online network that included 25 websites. The letter cited unapproved and misbranded opioids (tramadol and oxymorphone) and misbranded benzodiazepines (alprazolam).

FDA issued more than 50 warning letters targeting more than 500 websites unlawfully selling opioids over the internet to U.S. consumers since 2017. Moving forward, we recognize the need to promote collaboration among federal agencies in response to growing online sales of illicit and highly dangerous controlled substances, including opioids.

Lastly, the agency issued warning letters to four companies promoting unapproved kratom products and one company selling essential oils for the treatment or cure of opioid use disorder and withdrawal symptoms. These letters were issued jointly with the Federal Trade Commission.

COVID-19 Public Health Emergency Response

The emergence of COVID-19 variants and subvariants continued to affect public health worldwide in 2022, and responding to the COVID-19 pandemic has been a top priority for our office. Our safety focus included helping increase access to critically needed medications in shortage, taking action against fraudulent unapproved products claiming to treat COVID-19, supporting critical drug development evaluations, and keeping the public informed. We continued to monitor hand sanitizer products for safety concerns, conducted surveillance testing to identify problems, and took action when potentially unsafe products were identified. We issued a reminder to all registered and listed hand sanitizer manufacturers that, after March 31, 2022, they should cease distribution of hand sanitizers that were permitted only under temporary COVID-19 pandemic policies.

While critically needed medications were in shortage during the pandemic, our office issued enforcement discretion decisions to increase supplies of dinutuximab, remdesivir, heparin, albuterol, etomidate, midazolam, propofol, contrast agents, cefotaxime, afamelanotide, and many other medically necessary medications.

To continue to meet our public health mission and amidst the pandemic inspection limitations, the agency used alternative tools, including exercising its authority under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), to request records or other information in advance of or in lieu of an inspection. We conducted voluntary remote regulatory assessments of clinical sites conducting biomedical research to verify the reliability of data submitted and to ensure the rights of subjects in FDA-regulated research were protected.

By the Numbers

Our COVID-19 work in FY22 included:

- 19 warning letters issued to companies marketing products claiming to treat COVID-19. Products included cannabidiol (CBD), hemp oil, and more. We jointly issued several of these warning letters with the Federal Trade Commission.
- 5 warning letters issued to operators of websites illegally offering unapproved and misbranded drugs purporting to treat COVID-19.
- 2 warning letters issued for violations associated with the conduct of a clinical investigation studying investigational products in patients with COVID-19.
- 22 bioresearch monitoring inspections completed to inform data reliability assessments for five marketing applications, including emergency use authorizations, for the treatment and prevention of COVID-19.
- 40+ drug quality regulatory actions completed with information from remote assessments, sampling, and testing efforts.
- 13 hand sanitizer firms placed on import alert.
- 33 warning letters issued to manufacturers for potentially dangerous hand sanitizer products.
- 105 products added to the FDA list of hand sanitizers consumers should not use.

KEY ACTIONS TO PROMOTE COMPLIANCE

Preventing violations of FDA laws and regulations is critical to minimizing the detrimental impact of potentially harmful products. Proactively promoting voluntary regulatory compliance through communication and collaboration includes establishing clear compliance standards, along with engaging industry members to clarify how to best meet these standards. It is also equally important to recognize that collaborating with our federal partners and external stakeholders maximizes our efforts to address public health risks.

Policy

Promoting compliance involves ensuring that regulated entities have a clear understanding of the required standards and expectations and that they know how to follow them. In FY22, CDER's Office of Compliance led or collaborated on the policy documents outlined below.

Proposed Rules, Guidance, and Federal Register Notices

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.

- Proposed Rule National Standards for the Licensure of Wholesale Drug Distributors and Third-Party Logistics Providers
- Draft Guidance DSCSA Standards for the Interoperable Exchange of Information for Tracing of Certain Human, Finished, Prescription Drugs
- Draft Guidance Identifying Trading Partners Under the Drug Supply Chain Security Act
- Draft Guidance Verification Systems Under the Drug Supply Chain Security Act for Certain Prescription Drugs
- Immediately-in-effect Guidance Exemption and Exclusion from Certain Requirements of the Drug Supply Chain Security Act (DSCSA) for the Distribution of FDA-Approved Naloxone Products During the Opioid Public Health Emergency

Proposed Rules, Guidance, and Federal Register Notices (Continued)

National Drug Code

The NDC is the FDA standard for uniquely identifying drugs marketed in the United States.

- Proposed Rule Revising the National Drug Code Format and Drug Label Barcode Requirements

Recalls

A drug recall is the most effective way to protect the public from a defective or potentially harmful product.

- Final Guidance Initiation of Voluntary Recalls Under 21 CFR Part 7, Subpart C

Importation

Imported drugs must meet FDA's standards for quality, safety, and effectiveness.

- Final Guidance Importation of Prescription Drugs Final Rule Questions and Answers; Small Entity Compliance Guide
- Final Guidance Pre-Launch Activities Importation Requests (PLAIR)

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.

- FDA added the first four bulk drug substances to the list of bulk drug substances that may be used in compounding by outsourcing facilities (503B Bulks List).
- Draft Guidance Hospital and Health System Compounding Guidance to Help Preserve Patient Access to Compounded Drugs

Drug Efficacy Study Implementation (DESI) Proceedings

DESI is FDA's administrative process to consider the effectiveness of drugs that were approved for safety between 1938 and 1962.

Completion of the DESI process helps ensure that drugs that are marketed in the US are safe, effective, and of proven quality. Two DESI proceedings that were closed in FY22 and announced via the Federal Register are:

- DESI 7663: Potassium Aminobenzoate Oral Preparations
- DESI 10837 Oral Prescription Drugs Containing an Anticholinergic or Antispasmodic in Combination with a Sedative, and Single-Entity Antispasmodic Drug Products, in Oral Dosage Form

Clinical Trial Oversight and Bioresearch Monitoring

The CDER Bioresearch Monitoring (BIMO) program is designed to monitor the conduct and reporting of regulated research.

- Draft Guidance Digital Health Technologies for Remote Data Acquisition in Clinical Investigations
- Final Guidance E8(R1) General Considerations for Clinical Studies
- Update to the Bioresearch Monitoring Technical Conformance Guide

Global Collaboration

FDA's current regulatory and enforcement strategies are enriched through collaborations with international regulatory agencies and industry organizations. FY22 global collaborations focusing on outreach, education, and harmonization include:

- Ongoing participation in the World Health Organization (WHO) Member State Mechanism and Asian-Pacific Economic Cooperation (APEC) to address sub-standard and falsified medical products. FDA serves as a committee chair directing the Asia Pacific Economic Cooperation (APEC) toolkit improvements for postmarketing surveillance and internet sales.
- Participation in the United Nations inter-regional stakeholder consultation on public-private partnerships for prevention of dangerous substance trafficking through the internet as well as the United Nations International Narcotics Control Board's Inter-regional Stakeholder Consultation on Public- Private Partnerships for Prevention of Dangerous Substance Trafficking Through the Internet.
- Presenting to the Pharmaceutical Inspection Co-operation Scheme expert circle.
- Jointly publishing two papers in the scientific journal Therapeutic Innovation and Regulatory Science. The papers compared FDA and the European Medicines Agency (EMA) Good Clinical Practice (GCP) inspection processes and findings, providing insights into similarities across our regulatory agencies.
- Contributing to the agency's efforts to harmonize the FDA export certificate format with the World Health Organization Certification Scheme.
- Contributing to the Pharmaceutical Inspection Co-Operation Scheme's revised Annex 1 (Manufacture of Sterile Medicinal Products) to Guide to Good Manufacturing Practice for Medicinal Products, a guidance harmonized across multiple foreign regulatory authorities.

"International good clinical practice (GCP) collaboration is a critical component to ensure adequate regulatory oversight and assessment of data integrity given the landscape of globalized clinical trials and growing numbers of clinical trial sites per study."

David Burrow, JD
Director
Office of Scientific Investigations,
Office of Compliance

Information Sharing and Collaboration

245+ total inspection documents shared with foreign regulatory counterparts

9 joint and/or observed bioresearch monitoring inspections were conducted with global regulatory counterparts, including observation of fully remote assessments

Stakeholder Education, Engagement, Outreach

Educating companies on policies and laws that apply to their industry is an essential component of promoting sustainable compliance, managing risks, and protecting the public from poor-quality drugs. Educational programs and courses for regulated industry, healthcare professionals, the public, and other stakeholders include the following items outlined below.

Training and Engagement

Webinars and Virtual Training Courses

- Advances in Drug Supply Chain Security — Focus on Distribution
- National Standards for the Licensure of Wholesale Drug Distributors and Third-Party Logistics Providers
- FDA Inspections of Outsourcing Facilities
- Proposed Rule on Revising the National Drug Code Format
- Registration and Listing Regulatory Background and Requirements
- CDER Bioresearch Monitoring (BIMO) Good Clinical Practices Compliance and Enforcement
- New Compounding Quality Center of Excellence trainings offered in FY22 include: Process Validation, Quality Management Systems, Supplier Contractor Qualification & Management, Personnel Gowning in Sterile Drug Production, Aseptic Process Simulations (Media Fills), and Sterility Testing. These courses augment the self-guided, online courses offered to the public and the instructor-led courses offered multiple times per year.

Conferences

- 31st Annual FDA and Parenteral Drug Association (PDA) Co-sponsored Joint Regulatory Conference
- Compounding Quality Center of Excellence Annual Conference: "The Shared Pursuit of Compounding Excellence"
- Electronic Drug Registration and Listing (eDRLS) Using CDER Direct
- FDA, Medicines and Healthcare products Regulatory Agency (MHRA), and Health Canada Good Clinical Practice Workshop: Global Clinical Trials — Considerations and Lessons Learned from the Changing Landscape

Engagement

- The Pharmacy Compounding Advisory Committee met to discuss four bulk drug substances nominated for inclusion on the 503A bulks list: ammonium tetrathiomolybdate, enclomiphene citrate, ferric subsulfate, and glutathione.

Training

80+ conference presentations

2,732 courses completed by stakeholders through the Compounding Quality Center of Excellence's training programs in FY22, totaling 4,675 courses completed since training programs were first offered

13 presentations posted to FDA's YouTube developed in collaboration with CDER's Small Business and Industry Assistance

Training and Engagement (Continued)

- In 2022, a new compounding cross-sector stakeholder group was created to engage on issues that affect compounding outsourcing facilities, health care providers that purchase and use their products, and other stakeholders in the ecosystem.
- To engage state representatives on drug compounding topics, our office holds annual intergovernmental meetings.
- To support ClinicalTrials.gov registration and results reporting process, representatives served on an externally-led project to identify and explore the key challenges in meeting U.S. ClinicalTrials.gov Reporting Requirements and to identify potential solutions.
- CDER bioresearch monitoring specialists participated on a cross-industry working group led by PHUSE, a not-for-profit organization, and contributed to development of a Bioresearch Monitoring Data Reviewers Guide.
- The Partnership for DSCSA Governance (PDG) is a collaborative forum and FDA public-private partnership dedicated to developing, advancing, and sustaining an efficient model for interoperable tracing and verification of prescription pharmaceuticals in the U.S. PDG held a workshop to discuss implementation. To provide opportunity for engagement and feedback, FDA held a public meeting Enhanced Drug Distribution Security at the Package Level Under the Drug Supply Chain Security Act (DSCSA).
- Subject matter experts met with representatives from several states, the National Academy for State Health Policy, and HHS to discuss the development of Section 804 importation program proposals. Additionally, an FDA delegation to the Secretary's Tribal Advisory Council provided proactive guidance and information on these programs.

Outreach to Industry

- The Office of Compliance sent 17,880 annual registration renewal reminders to FDA-registered firms.
- As DSCSA implementation continues, a new mailing list was developed to share updates about DSCSA guidances, meetings, and announcements.
- To expedite entry screening of medical drug products by the Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) system, importers and entry filers should provide accurate entry data to FDA. To assist in this process, FDA shared new information: Human Drug Common Import Entry Errors.
- To enhance transparency, FDA developed a chart explaining the top reasons FDA may return an application for an electronic certificate of pharmaceutical product.
- The compounding incidents program collaborated on development of a podcast and article describing how the agency examines adverse events associated with compounded drugs from outsourcing facilities.

"We are committed to proactively engaging with compounders and stakeholders through annual conferences, listening sessions, and meetings with regulatory associations."

Gail Bormel, RPh, JD
Director
Office of Compounding Quality and Compliance, Office of Compliance

Public Health Risk Alerts

FDA has a duty to inform the public about emerging risks and safety concerns, including about products that have not been evaluated by FDA for safety or effectiveness. In FY22, we collaborated across FDA to make the public aware of specific product risks that include:

- Products illegally marketed for removing moles and other skin lesions that can cause serious injuries and scarring.
- Over-the-counter skin lightening products containing hydroquinone that may cause rashes, facial swelling, and permanent skin discoloration (ochronosis). The warning was translated into several languages.
- Products that contain hidden drug ingredients and are promoted for weight loss, sexual enhancement, and pain management. We issued 32 immediate public notifications to alert consumers and retailers about FDA's testing results.
- Artri and Ortiga products that were associated with reports of serious unexpected injuries and contain the undeclared drug ingredients: dexamethasone (a corticosteroid), diclofenac sodium (an anti-inflammatory drug), and methocarbamol (a muscle relaxant).
- Potential risks associated with compounded ketamine nasal spray.
- Concerns about compounding of drug products by medical offices and clinics under insanitary conditions, such as intravenous (IV) infusion treatments that add vitamins to IV infusion bags.
- Hand sanitizers that consumers should not use due to harmful ingredients, contamination, or other risks.
- Vaping products with unproven health claims.
- Tianeptine that has been illegally promoted as an opioid alternative and is linked to serious harm, overdoses, and death.
- Risks of giving homeopathic cold and cough medicine to very young children.

"We are committed to notifying the public when we identify unapproved products that may pose risks to U.S. consumers."

Tina Smith, MS
Director (Acting)
Office of Unapproved Drugs and Labeling Compliance,
Office of Compliance
Captain
U.S. Public Health Service

REGULATORY AND ENFORCEMENT ACTIONS

Effective, risk-based regulatory and enforcement actions are foundational to the Office of Compliance's work. Timely regulatory and enforcement actions substantially decrease the public's risk of exposure to harmful products. Across all our compliance programs, we strategically prioritize regulatory and enforcement actions against the companies and products that pose the greatest risk to the public. Through such actions as recalls, warning letters, import alerts, seizures, injunctions, and other actions, we keep harmful drugs from reaching the public.

> ***"The integrity of our U.S. drug supply chain is critical to protecting patients. We will continue to use import alerts, recalls, and other surveillance and enforcement tools to deter, detect, and quickly remove threats."***
>
> **S. Leigh Verbois, PhD**
> *Director*
> Office of Drug Security, Integrity, and Response,
> Office of Compliance

Safeguarding the Supply Chain

The drug supply chain is a critical aspect of the healthcare system, as it involves moving pharmaceuticals from the manufacturer to the end-user and includes hospitals, pharmacies, and patients. The drug supply chain plays a vital role in ensuring that safe, effective, and high-quality medications are available to those who need them. Drug supply chain regulatory actions in FY22 include:

- Overseeing 343 recall event classifications for 1,500+ violative drug products, including 64 that were potentially life-threatening.
- Issuing nine warning letters to website operators illegally offering unapproved and misbranded drugs, including unapproved and misbranded controlled substances, for sale to U.S. consumers.

Drug Related Import Alerts in FY22

- An import alert aims to prevent potentially harmful or illegal products from entering the U.S. We collaborated with FDA's Office of Regulatory Affairs to add 50+ facilities to import alerts. Major categories of import alerts include:
  - » **Current Good Manufacturing Practice (CGMP).** Sixteen facilities were added to import alert 66-40 that do not appear to be operating in conformity with CGMP requirements.
  - » **Unapproved new drug.** Twenty companies were added to import alert 66-41 that lists products for which we have sufficient evidence to demonstrate that a product appears to be an unapproved new drug.
  - » **Inspection refusal.** Nine facilities were added to import alert 66- 79 that lists companies and their products that appear to be adulterated because the companies have refused to permit FDA to inspect the facility.
  - » **Adulteration.** Six facilities were added to import alert 66-78 that lists manufacturers of drugs at risk for adulteration based on FDA analytical sample results demonstrating violations of the FD&C Act.
  - » **Hidden ingredients**. Two products were added to import alert 54-16 that lists products marketed as dietary supplements that contained undeclared active pharmaceutical ingredients and were promoted for sexual enhancement, weight loss, and muscle building.

Drug Quality

Pharmaceutical manufacturers and compounders are responsible for complying with applicable regulations and ensuring that only high-quality products reach U.S. patients. When FDA uncovers violations, we take action to protect the public. Regulatory actions related to drug quality in FY22 include:

- Morton Grove Pharmaceuticals Inc. Consent Decree A federal court ordered the company to stop manufacturing and distributing drugs alleged to be adulterated in violation of the FD&C Act. Morton Grove Pharmaceuticals makes and distributes both prescription and over-the-counter drugs such as cough syrups and nasal sprays. The agency inspected the company's facility multiple times between 2011 and 2021; many of the violations were repeated and identified in earlier inspections.
- Prison Sentence for Former Pharmatech CEO A former owner and CEO of a drug manufacturing company who lied to FDA and allowed contaminated products to make their way to pediatric hospitals was sentenced to 37 months in federal prison. As part of a larger investigation into an outbreak of infections linked to the bacteria known as Burkholderia cepacia, FDA inspected Pharmatech's operations. The CEO pled guilty to conspiring to defraud the agency, falsifying records in an FDA investigation, obstructing proceedings before the agency, and distributing adulterated drugs.
- Edge Pharma Inc. Consent Decree A federal court permanently ordered a Colchester, Vermont, compounder from distributing drugs unless they are manufactured in compliance with the FD&C Act. FDA inspections revealed record-keeping violations, labeling inadequacies, improper airflow, structural disrepair, and the presence of mold species in cleanroom suites that can potentially cause diseases in humans or could be fatal for immunocompromised patients.
- Over-the-Counter (OTC) Drug Warning Letters FDA issued 72 drug CGMP warning letters to firms that manufactured OTC drug products in FY22.
- Compounding Warning Letters FDA issued 11 warning letters to firms that compound drug products.

"Failure to adhere to Current Good Manufacturing Practice requirements puts consumers at risk. We will continue to do everything in our power to ensure compliance, address violations of federal law, and protect the American public from unsafe drugs."

Francis Godwin
Director
Office of Manufacturing Quality, Office of Compliance

Misbranded and Unapproved Drugs

Certain products are considered unapproved drug products because they have not been reviewed by FDA for safety and effectiveness. These products may not meet the same standards as approved drugs and can pose serious risks to consumers. Our office took action to stop sales of the following products:

- Over-the-counter skin lightening products containing hydroquinone Our office issued 12 warning letters, 19 notification letters, and added two firms to import alert for selling, or being listed as selling, over-the-counter skin lightening products containing hydroquinone.
- Mole and skin tag removal products Companies were issued three warning letters for introducing into interstate commerce mole and skin tag removal products that are unapproved new drugs in violation of the law. There are no FDA-approved over-the-counter drug products for the removal of moles and skin tags, and FDA is aware of harm associated with these products.
- CBD and Delta-8 THC Companies were issued 13 warning letters for marketing CBD products and making false or misleading drug claims. FDA also issued the first warning letters to companies selling products labeled as containing Delta-8. Forty-three notification letters were sent to firms that had active drug listings of unapproved nonprescription drug products containing CBD or CBD oil as an ingredient.
- Vitamin Vape Companies were issued warning letters for selling "wellness" vaping products containing vitamins and/or essential oils. The products were illegally sold with unproven claims and could be harmful if used. No vaping products are approved by FDA as a treatment for any indication.
- Domperidone The operator of a website offering unapproved domperidone drug products for sale to U.S. consumers was issued a warning letter. Domperidone is not currently a legally marketed human drug and is not approved for sale in the U.S. There are serious risks associated with domperidone, including cardiac arrhythmias, cardiac arrest, and sudden death.

"These actions highlight our dedication to fighting medication health fraud and investigating companies that may harm unsuspecting consumers."

Michael Levy
Deputy Director
Office of Compliance

Clinical Trial Oversight and Bioresearch Monitoring

CDER's Bioresearch Monitoring (BIMO) program is a comprehensive program of on-site inspections, data audits, and remote regulatory assessments designed to monitor all aspects of the conduct and reporting of regulated research. Regulatory actions taken in FY22 include:

- Daniel C. Tarquinio, D.O. was issued a warning letter for violations associated with his conduct of a clinical investigation. The letter cites Dr. Tarquinio for failure to ensure that the investigation was conducted according to the investigational plan.
- Smitha C. Reddy, M.D. was issued a warning letter for violations associated with her conduct of clinical investigations. The letter cites Dr. Reddy for failure to ensure that the investigation was conducted according to the investigational plan. Specifically, the investigator failed to adhere to protocol required blinding of certain study staff to avoid bias in two clinical studies and failed to ensure that subjects randomized to a specific intervention group received the assigned investigational drug for that intervention group.
- Daniel Goodman, M.D. was issued a warning letter for failure to submit an Investigational New Drug Application prior to enrolling subjects in a clinical investigation and failure to obtain informed consent and assent of children.
- Sabine S. Hazan, M.D. was issued a warning letter for failure to ensure that an appropriate Institutional Review Board reviewed and approved the conduct of a clinical investigation. Specifically, the clinical investigator enrolled and randomized subjects during a lapse in Institutional Review Board approval.
- Vasyl Melnyk, M.D. was issued a warning letter for failing to retain required records such as copies of informed consent forms, case report forms, and other supporting documents for clinical investigations.
- Richard J. Obiso, Ph.D. was issued a warning letter for failure to submit an Investigational New Drug Application for the conduct of a clinical investigation with a failure to ensure that an Institutional Review Board reviewed and approved the conduct of a clinical investigation and failure to obtain informed consent.
- Joseph A. Zadra, M.D. was issued a warning letter for failure to ensure the investigation was conducted according to the investigational plan. Dr. Zadra enrolled subjects who did not meet eligibility criteria and failed to perform safety-related labs, tests, and procedures as required by the protocol.
- Yveline Villaman-Bencosme, M.D. was issued a Notice of Opportunity for Hearing letter for repeatedly or deliberately submitting false information to the FDA or to the sponsor in required reports. This is the second step in the process to disqualify a clinical investigator from conducting investigational research

99+ percent 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)

ORGANIZATIONAL EXCELLENCE

Our office is committed to pursuing organizational excellence in business processes and human resources. As we reflect on the past year, we are proud to report that we have made significant strides in streamlining many core processes. Through a focused effort on process improvement and a commitment to the mission, we achieved our goals in the following categories:

Export Certificate Modernization

In FY22, we continued to improve the export certification process for human drug products. Our team worked collaboratively to streamline process and reduce the time required to obtain and validate electronic Certificates of Pharmaceutical Product (eCPPs). Through our efforts, we were able to reduce processing time and add a Quick Response (QR) code that can be used by anyone to verify authenticity. The QR code directly links to the FDA Unified Registration and Listing System Export Certification Validator (FECV) page. This saves participants time and enhances our ability to meet the needs of our international stakeholders. In FY22, our office issued over 10,220 export certificates.

Drug Registration and Listing

Our office continually works to improve the data quality found in the FDA's Drug Registration and Listing System. We issue registration reminders to firms; inactivate outdated firm registrations, product listings, and labeler codes; and issue deficiency letters when necessary. In FY22, over 21,440 drug listings were inactivated due to either not being certified as active or associated with an unregistered manufacturing establishment. The office also inactivated 1,119

unused labeler codes and issued 212 deficiency letters to firms for inaccurate or incomplete registration and listing data.

Product Testing

To help ensure that high-quality drugs are sold in the U.S., CDER may initiate testing of certain types of products. In FY22, FDA testing identified homeopathic aqueous-based drug products containing objectionable microbial contamination, including Bacillus cereus. The testing identified three products that were subsequently recalled, as use of contaminated product by certain populations could potentially result in severe or life-threatening adverse events.

Notification Letters

To efficiently protect the public, we piloted a program to issue short email notifications to firms listing unapproved new drugs containing higher risk ingredients in the drug registration and listing system. For example, OTC drug products are not allowed to have silver as an active ingredient. After issuing notification letters, many companies ceased marketing their products.

Concept of Operations (ConOps)

ConOps aims to ensure consistency, efficiency, and transparency in facility evaluations, inspections, and regulatory decision- making between CDER and ORA. The commitments to streamline and standardize our core operational processes are outlined in a white paper: Integration of FDA Facility Evaluation and Inspection Program for Human Drugs: A Concept of Operations. CDER and ORA agreed to the responsibilities and workflow for pre-approval, post-approval, surveillance, and for-cause inspections at drug manufacturing facilities. In FY22, we issued 183 drug manufacturing inspection classification letters. Additionally, the 2022 reauthorization of GDUFA includes additional commitments to promote transparency and accountability and continue to streamline and standardize our processes. The commitments allow eligible firms to request post–warning letter meetings to receive feedback on their corrective actions and to request reinspection of their facilities.

Human Capital

We are pleased to report that over the past year, we have made significant progress in building a talented and diverse workforce. We implemented initiatives to attract professionals with specialized skillsets that include legal, medical, regulatory affairs, drug manufacturing, and project management. Through our efforts, we successfully ended the year with 91 percent of the office's positions filled. These new employees bring a wealth of experience, skills, and perspectives that will help drive our office growth and innovation. We believe that 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.

LOOKING AHEAD

Looking ahead, we are committed to continuing our focus on operational excellence as well as promoting compliance, enforcement, and regulatory actions. We will continue to identify areas for improvement and implement initiatives to enhance responsiveness, quality, and public health outcomes. We intend to shield patients from poor-quality, unsafe, and ineffective drugs by focusing on the following priorities:

- Advance FDA's response to emerging and existing public health threats, including supporting development of new therapies, ensuring availability of critical medications, and protecting the public from potentially harmful products.
- Take concrete steps to reduce the public health crisis posed by dangerous controlled substances, including opioids.
- Create and implement innovative and cross-cutting regulatory and enforcement actions targeting drugs with the greatest risk of causing harm, including emerging threats.
- Continue to build and strengthen the compounding program.
- Collaborate across the agency to improve the quality of non-application drugs, such as over-the-counter monograph and unapproved drugs.
- Fully implement and operationalize the Drug Supply Chain Security Act requirements.
- Streamline, standardize, innovate, and provide training on core operational processes.
- Conduct outreach and education to inform FDA stakeholders.

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