Compliance Approaches to Emerging Threats

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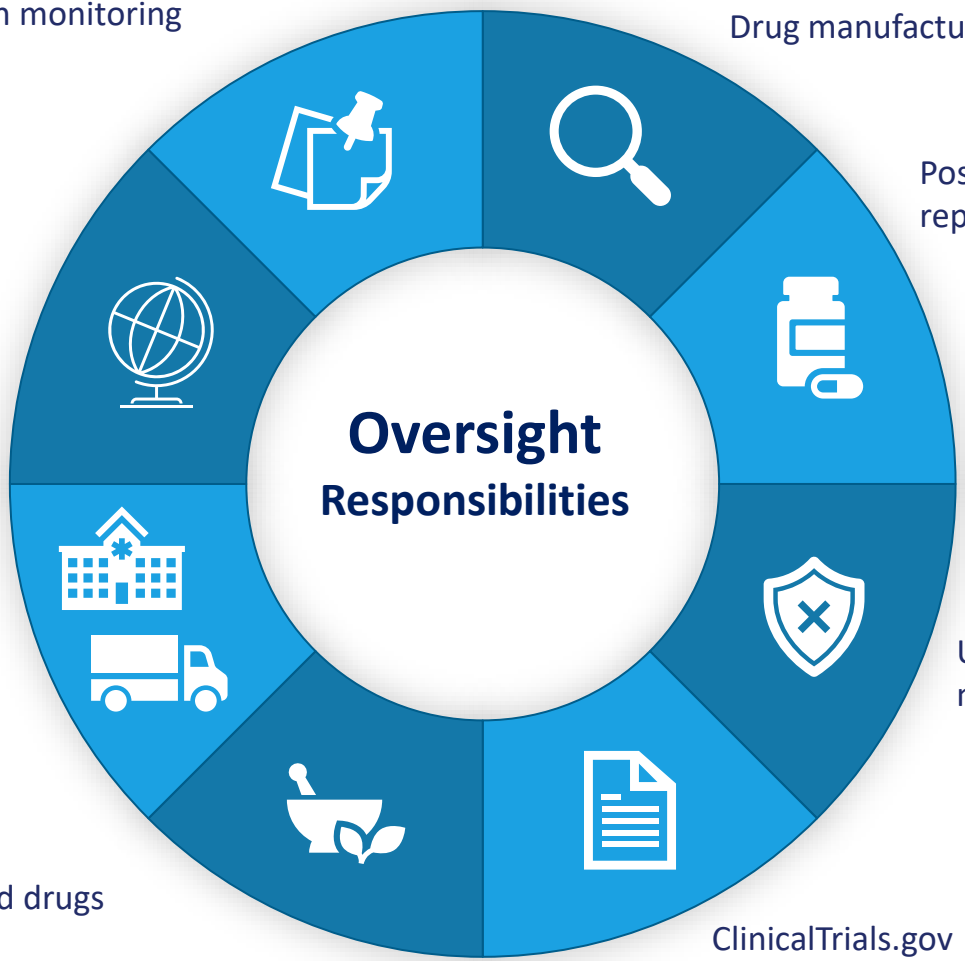
Director, Office of Compliance,
CDER | US FDA

CDER SBIA REdI – May 30, 2024

Learning Objectives

- Describe CDER's compliance program
- Discuss recent CDER compliance cases
- Describe how the public can access FDA pharmaceutical inspection and compliance data



Bioresearch monitoring

Drug manufacturing facilities

Drug supply chain: imports and exports

Post-market reporting

Unsafe online pharmacies

Drug registration and listing

Recalls and incident response

Unapproved and misbranded drugs

Compounded drugs

ClinicalTrials.gov

fda.gov/cdersbia

Mission

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

Compliance Tools

Stakeholder Engagement

Guidance
Training
Public Meetings
Transparency

Detect

Inspection reivew
Remote tools
Testing
Supply chain monitoring
Import surveillance
Safety signal monitoring

Advise

Warning and untitled letters
Inspection classification
Regulatory meetings
Public warnings
Import alerts

Mitigate

Recalls
Administrative detention
Seizures
Injuction actions

Compliance Activities

Data from fiscal year 2023

Compliance Actions

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

264
drug recall events classified totaling

1,178 recalled products

95
new import alerts added to help stop certain drug products from entering the U.S.

Compliance Reviews

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

9,778
Electronic certificates of pharmaceutical product issued to provide documentation of facilities' compliance with FDA standards

Policy and Outreach

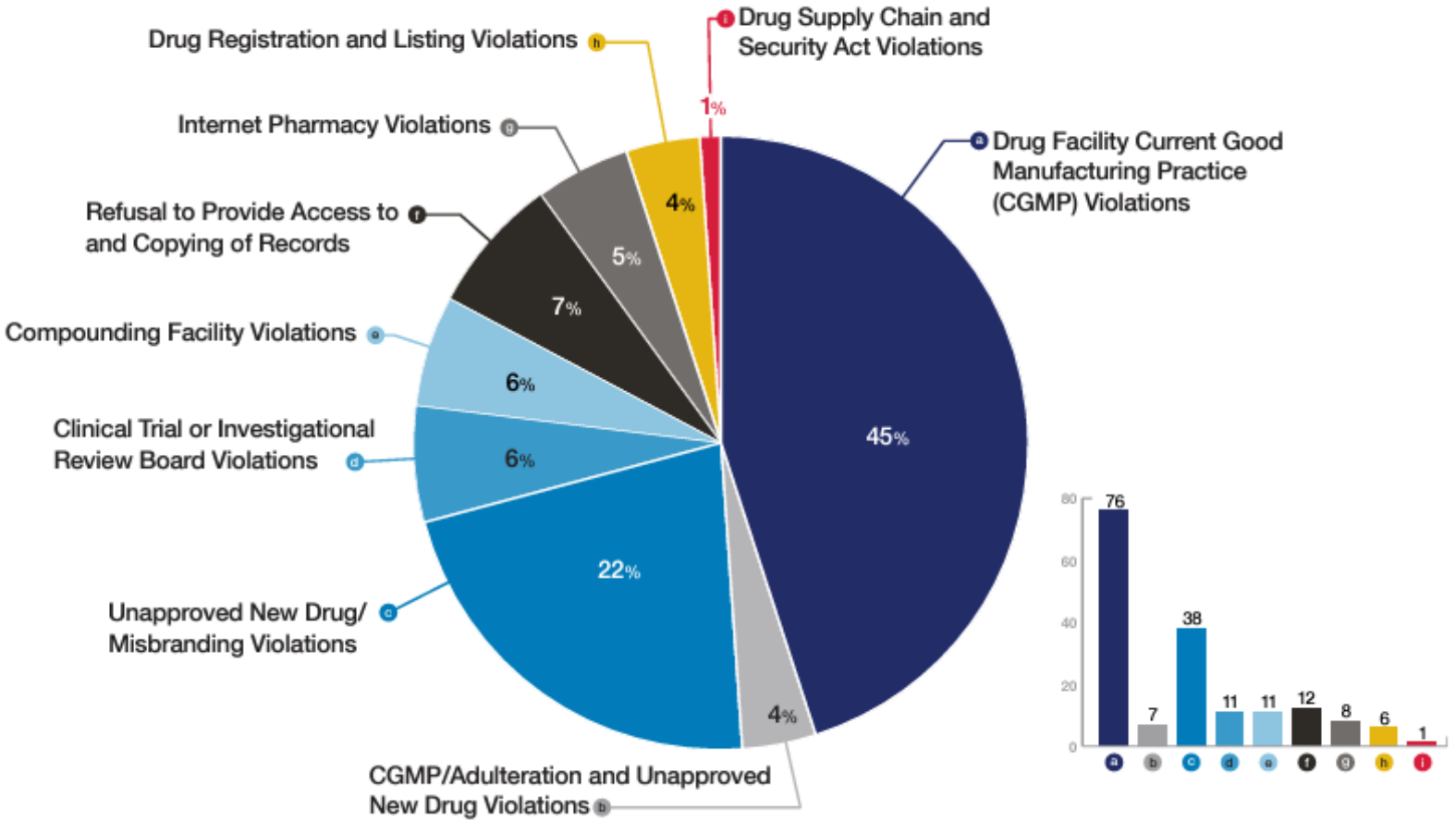
13
guidance documents issued

300+
compliance documents shared with foreign regulatory counterparts

10+
Presentations on FDA's YouTube channel

4,232
stakeholders who completed compounding training courses

Human Drug Warning Letters and Violations, FY23[1]



Risk-Based Compliance Actions

Emerging and evolving threats require dynamic compliance strategies.

Safeguarding the Drug Supply Chain

Compliance Activities

- Foreign authority communication
- Industry outreach
- Updated DEG guidance published
- 170 Records requests issued
- Sampling
- Warning letters sent for CGMP violations and failure to respond to mandatory records requests
- Import alerts for appearance of CGMP violations and failure to respond to mandatory records

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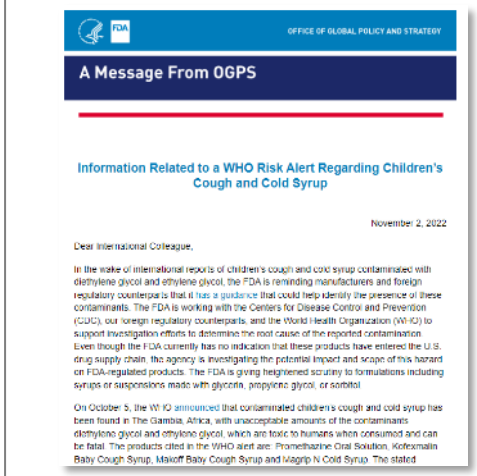

OFFICE OF GLOBAL POLICY AND STRATEGY

A Message From OGPS

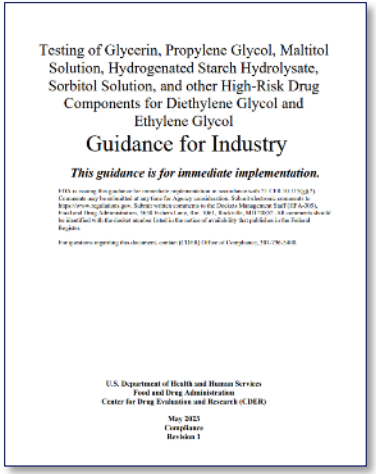
Information Related to a WHO Risk Alert Regarding Children's Cough and Cold Syrup

November 2, 2022

Dear International Colleague,

In the wake of international reports of children's cough and cold syrup contaminated with diethylene glycol and ethylene glycol, the FDA is reminding manufacturers and foreign regulatory counterparts that it has a guidance that could help identify the presence of these contaminants. The FDA is working with the Centers for Disease Control and Prevention (CDC), our foreign regulatory counterparts, and the World Health Organization (WHO) to support investigation efforts to determine the root cause of the reported contamination. Even though the FDA currently has no indication that these products have entered the U.S. drug supply chain, the agency is investigating the potential impact and scope of this hazard on FDA-regulated products. The FDA is giving heightened scrutiny to formulations including syrups or suspensions made with glycerin, propylene glycol, or sorbitol.

On October 5, the WHO announced that contaminated children's cough and cold syrup has been found in The Gambia, Africa, with unacceptable amounts of the contaminants diethylene glycol and ethylene glycol, which are toxic to humans when consumed and can be fatal. The products cited in the WHO alert are: Promethazine Oral Solution, Kofexmalin Baby Cough Syrup, Makoff Baby Cough Syrup and Magrip N Cold Syrup. The stated


Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and other High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol

Guidance for Industry

This guidance is for immediate implementation.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2023
Compliance
Revision 1

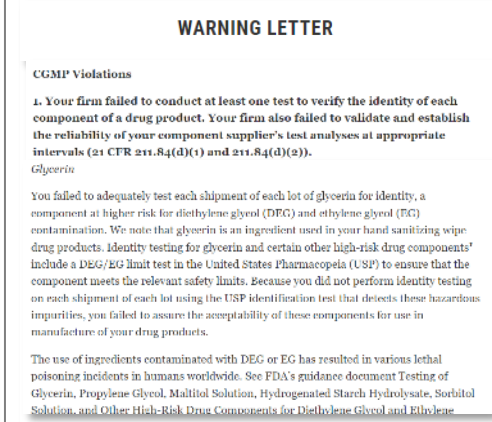

FDA Acts to Ensure the Safety of the Nation's Drug Supply

Patricia Cavazzoni, M.D.

Although we have no indication that any products described in the 2022 and 2023 WHO alerts have come into the U.S. drug supply chain, we are investigating the potential impact on FDA-regulated drug products. We are making every effort to prevent contaminated drug products from entering the U.S. market.

We have implemented strict safeguards to prevent DEG/EG adulterated products, including those listed in the WHO alerts, from being imported into the U.S., and we are also working with the Centers for Disease Control and Prevention (CDC), regulatory authorities in other countries, and the WHO to support investigation efforts to determine the root cause of the reported contamination. We are closely scrutinizing multiple liquid formulations of FDA-regulated drug products, including syrups, solutions, and suspensions, made with glycerin, propylene glycol, polyethylene glycol, maltitol solution, hydrogenated starch hydrolysate, or sorbitol solution.

FDA has also contacted drug product manufacturers and foreign regulatory counterparts to remind them that products intended for sale within the U.S. must meet CGMP requirements and appropriate quality specifications. This includes testing raw materials and finished product batches before release to ensure that a product is safe for use, and that it has the ingredients and strength it claims to have. We have also previously published a guidance document, Testing of Glycerin for Diethylene Glycol, [Updated Guidance as of May 2023] intended to inform stakeholders, including pharmaceutical


WARNING LETTER

CGMP Violations

1. Your firm failed to conduct at least one test to verify the identity of each component of a drug product. Your firm also failed to validate and establish the reliability of your component supplier's test analyses at appropriate intervals (21 CFR 211.84(d)(1) and 211.84(d)(2)).

Glycerin

You failed to adequately test each shipment of each lot of glycerin for identity, a component at higher risk for diethylene glycol (DEG) and ethylene glycol (EG) contamination. We note that glycerin is an ingredient used in your hand sanitizing wipe drug products. Identity testing for glycerin and certain other high-risk drug components' include a DEG/EG limit test in the United States Pharmacopeia (USP) to ensure that the component meets the relevant safety limits. Because you did not perform identity testing on each shipment of each lot using the USP identification test that detects these hazardous impurities, you failed to assure the acceptability of these components for use in manufacture of your drug products.

The use of ingredients contaminated with DEG or EG has resulted in various lethal poisoning incidents in humans worldwide. See FDA's guidance document Testing of Glycerin, Propylene Glycol, Maltitol Solution, Hydrogenated Starch Hydrolysate, Sorbitol Solution, and Other High-Risk Drug Components for Diethylene Glycol and Ethylene

Challenge Question

What is the purpose of an FDA import alert?

A. Help stop products from being distributed in the U.S.

B. Free-up FDA resources to examine other shipments

C. Alert FDA staff about the appearance of a violation

D. All of the above

Challenge Question

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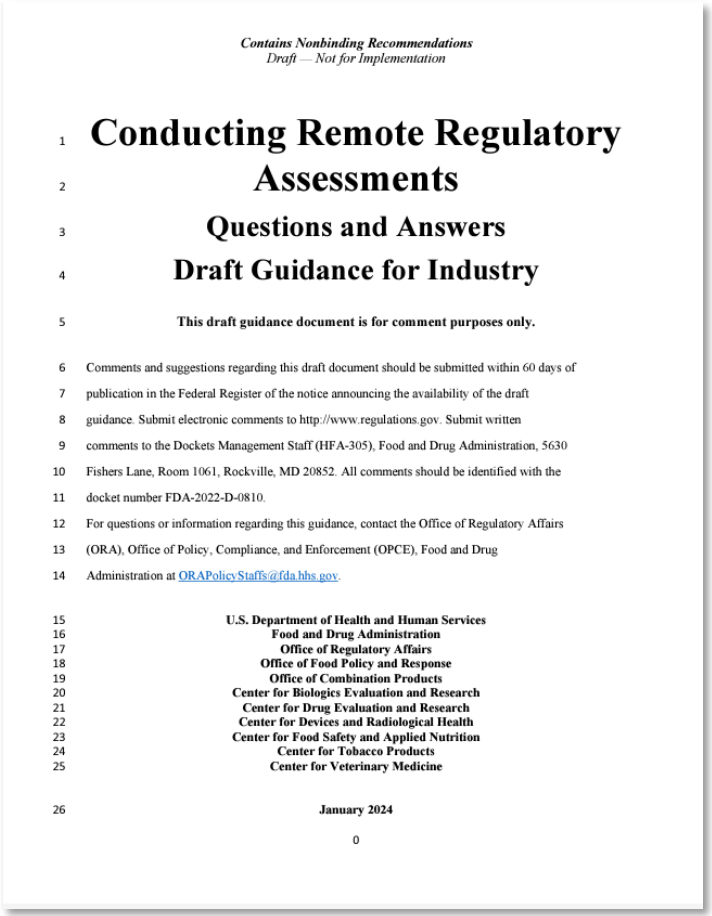
Remote Tools

FDA may utilize remote oversight tools such as remote interactive evaluations (RIEs) and requests for records or other information in advance of (or in lieu of) an inspection. Such remote tools are collectively referred to as "Remote Regulatory Assessments."



Contains Nonbinding Recommendations
Draft — Not for Implementation

Conducting Remote Regulatory Assessments

Questions and Answers

Draft Guidance for Industry

This draft guidance document is for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the docket number FDA-2022-D-0810.

For questions or information regarding this guidance, contact the Office of Regulatory Affairs (ORA), Office of Policy, Compliance, and Enforcement (OPCE), Food and Drug Administration at ORAPolicyStaffs@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Regulatory Affairs
Office of Food Policy and Response
Office of Combination Products
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Devices and Radiological Health
Center for Food Safety and Applied Nutrition
Center for Tobacco Products
Center for Veterinary Medicine

January 2024

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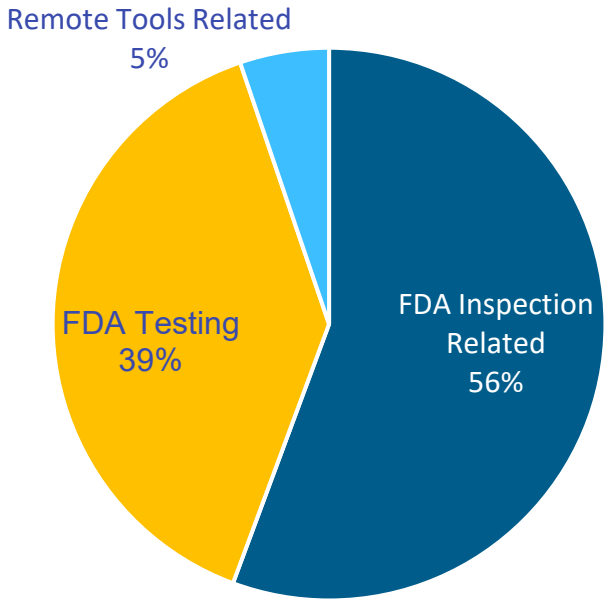
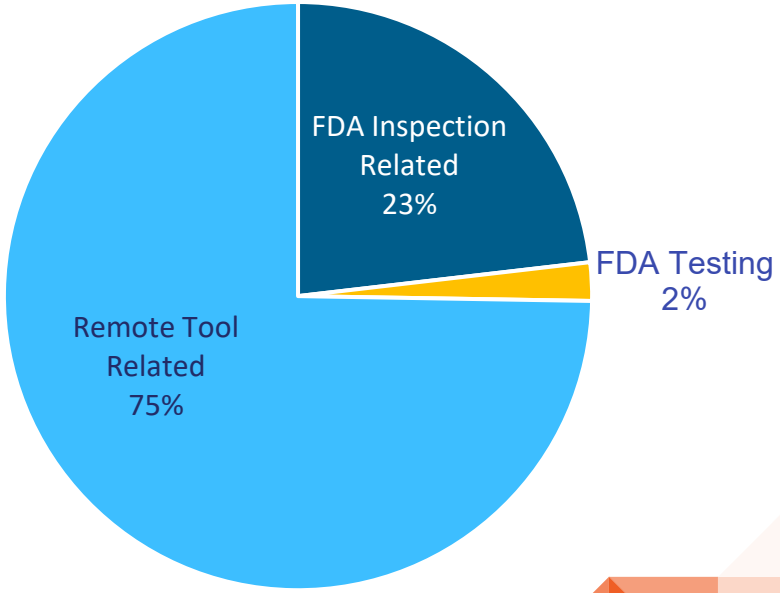
Import Alerts

Approach used to identify basis for addition to drug adulteration import alert

FY20

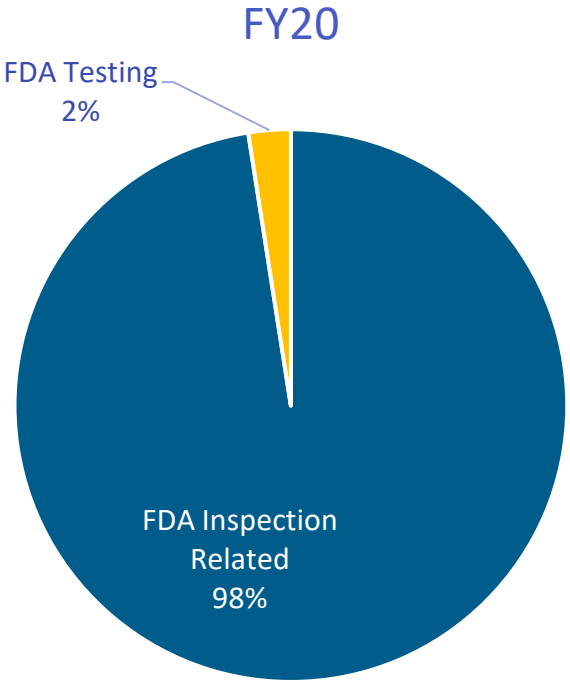


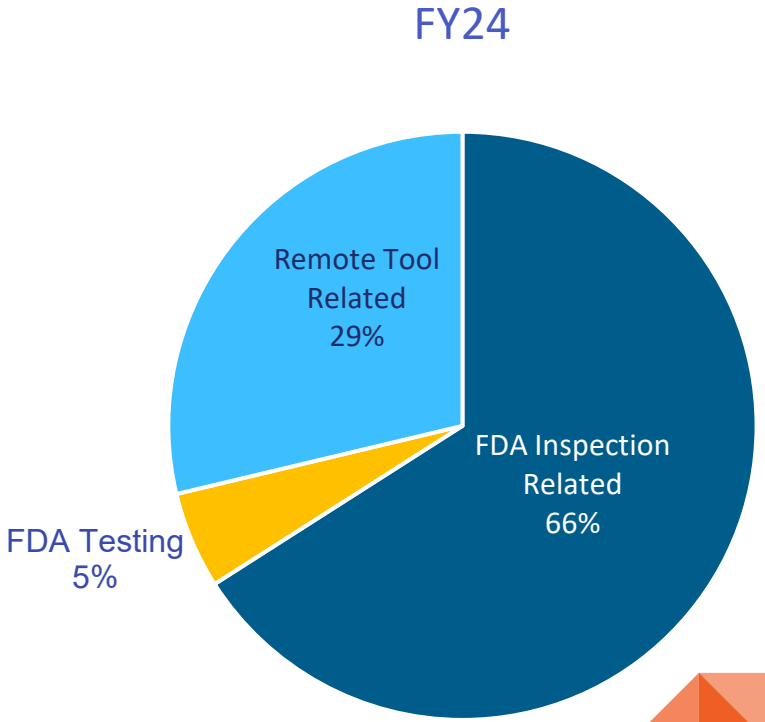
FY24



Drug Manufacturing Facility Warning Letters

Approach used to identify basis for addition to drug adulteration import alert, excluding compounders





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21 U.S. Code § 331 - Prohibited Acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.

(c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344, 350d, 355, or 360bbb–3 of this title.

Ophthalmic Products

Ophthalmic drug products pose a potential heightened risk of harm to users because drugs applied to the eyes bypass some of the body's natural defenses.

Ophthalmic Compliance Activities

- Guidance
- Labeling review
- Consumer advisories
- Recall oversight
- Inspections
- Warning letters
- Import alerts

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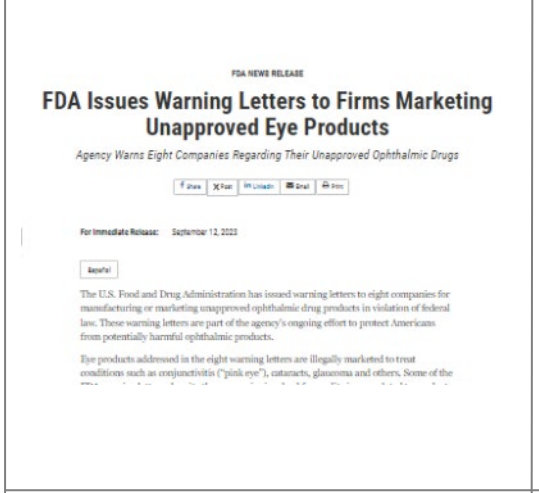


FDA NEWS RELEASE

FDA Issues Warning Letters to Firms Marketing Unapproved Eye Products

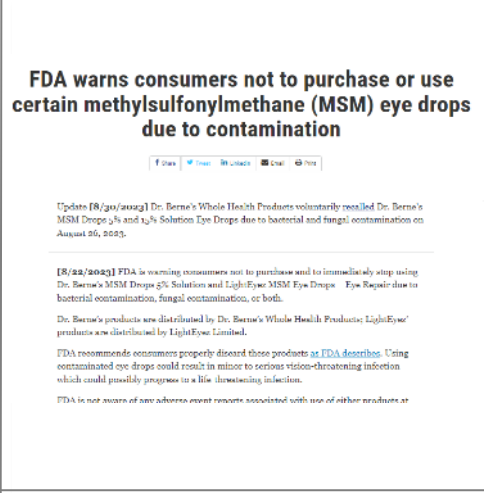
Agency Warns Eight Companies Regarding Their Unapproved Ophthalmic Drugs

For Immediate Release: September 12, 2023

Español

The U.S. Food and Drug Administration has issued warning letters to eight companies for manufacturing or marketing unapproved ophthalmic drug products in violation of federal law. These warning letters are part of the agency's ongoing effort to protect Americans from potentially harmful ophthalmic products.

Eye products addressed in the eight warning letters are illegally marketed to treat conditions such as conjunctivitis ("pink eye"), cataracts, glaucoma and others. Some of the



FDA warns consumers not to purchase or use certain methylsulfonylmethane (MSM) eye drops due to contamination

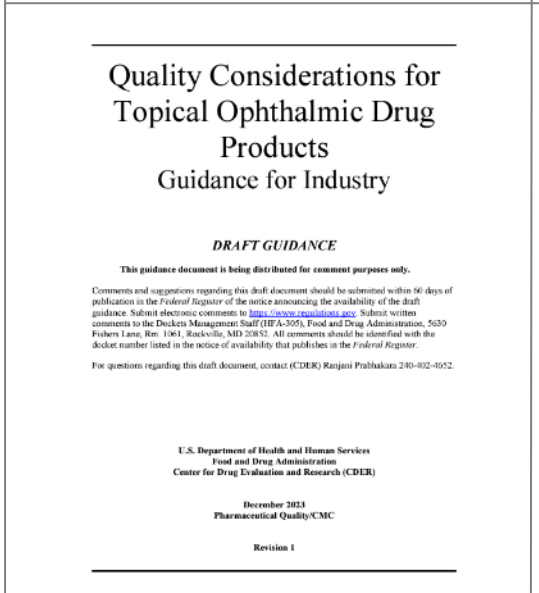
Update [8/30/2023] Dr. Berne's Whole Health Products voluntarily recalled Dr. Berne's MSM Drops 5% and 13% Solution Eye Drops due to bacterial and fungal contamination on August 26, 2023.

[8/22/2023] FDA is warning consumers not to purchase and to immediately stop using Dr. Berne's MSM Drops 5% Solution and LightEyes MSM Eye Drops™ Eye Repair due to bacterial contamination, fungal contamination, or both.

Dr. Berne's products are distributed by Dr. Berne's Whole Health Products; LightEyes' products are distributed by LightEyes Limited.

FDA recommends consumers properly discard these products at FDA describes. Using contaminated eye drops could result in minor to serious vision-threatening infection which could possibly progress to a life threatening infection.

FDA is not aware of any adverse event reports associated with use of either products at



Quality Considerations for Topical Ophthalmic Drug Products

Guidance for Industry

DRAFT GUIDANCE

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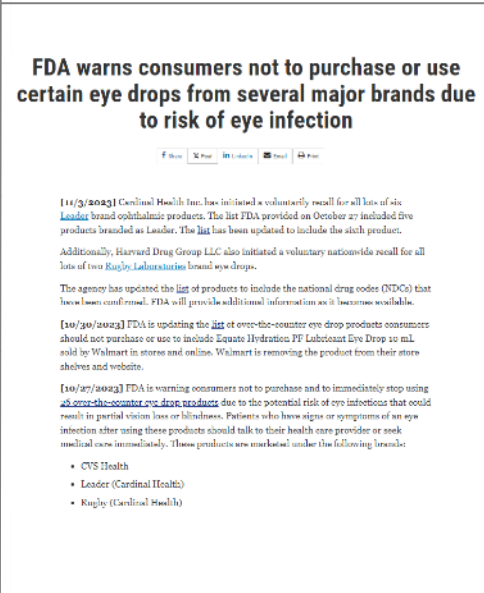
For questions regarding this draft document, contact (CDER) Ranjani Prabhakara 240-402-4952.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2023
Pharmaceutical Quality/CMC

Revision 1



FDA warns consumers not to purchase or use certain eye drops from several major brands due to risk of eye infection

[11/3/2023] Cardinal Health Inc. has initiated a voluntarily recall for all lots of six Leader brand ophthalmic products. The list FDA provided on October 27 included five products branded as Leader. The list has been updated to include the sixth product.

Additionally, Harvard Drug Group LLC also initiated a voluntary nationwide recall for all lots of two Rugby Laboratories brand eye drops.

The agency has updated the list of products to include the national drug codes (NDCs) that have been confirmed. FDA will provide additional information as it becomes available.

[10/30/2023] FDA is updating the list of over-the-counter eye drop products consumers should not purchase or use to include Equate Hydration PF Lubricant Eye Drop 10 mL sold by Walmart in stores and online. Walmart is removing the product from their store shelves and website.

[10/27/2023] FDA is warning consumers not to purchase and to immediately stop using 26 over-the-counter eye drop products due to the potential risk of eye infections that could result in partial vision loss or blindness. Patients who have signs or symptoms of an eye infection after using these products should talk to their health care provider or seek medical care immediately. These products are marketed under the following brands:

- CVS Health
- Leader (Cardinal Health)
- Rugby (Cardinal Health)

Unapproved Drugs

Online Marketplaces

Warning Letters Issued

Outreach and Communication

Public Alerts

Pharmaceutical Inspections and Compliance

Webpage: *fda.gov/drugs/guidance-compliance-regulatory-information/pharmaceutical-inspections-and-compliance*
CDER SBIA Webinar: *fda.gov/drugs/news-events-human-drugs/understanding-fda-inspections-and-data-09062023*

How FDA Evaluates and Ensures Compliance

- CGMP Inspections
- FDA's Compliance Review
- Inspection Classifications
- FDA's Tools and Actions

More Information

ORA Frequently Requested or Proactively Posted Compliance Records: Search publicly available Form FDA 483 inspection findings and other correspondence to FDA-regulated companies located within the U.S.

CDER Frequently Requested or Proactively Posted Compliance Records: Search for publicly available Form FDA 483 inspection findings, untitled letters and other correspondence to FDA-regulated companies located within or outside of the U.S.

fda.g

FDA Data Dashboard

https://datadashboard.fda.gov/ora/index.htm

Inspections

U.S. domestic and foreign inspections by fiscal year, classification, product type, etc.

Compliance Actions

Warning letters, injunctions and seizures by fiscal year, product type, etc.

Recalls

Recalls by fiscal year, classification, product type, status, etc.

Imports Summary

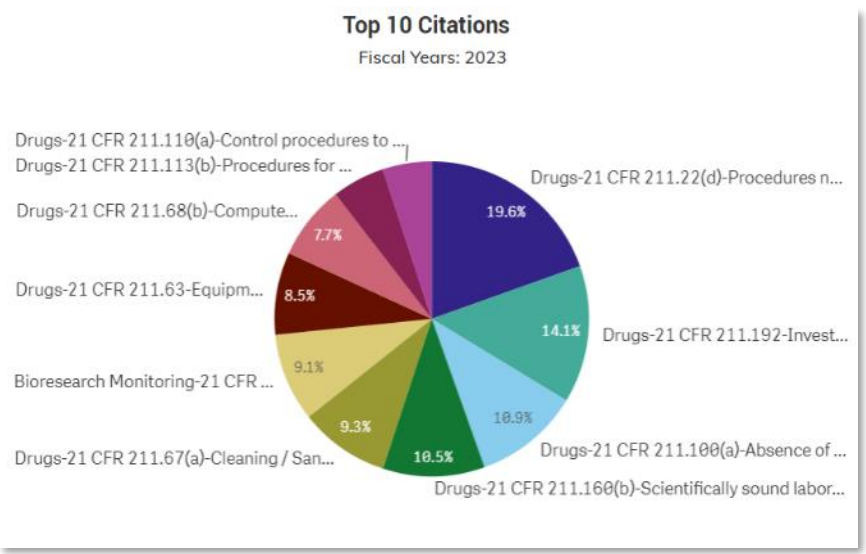
Imports summary data by fiscal year, import lines, product categories, countries, etc.

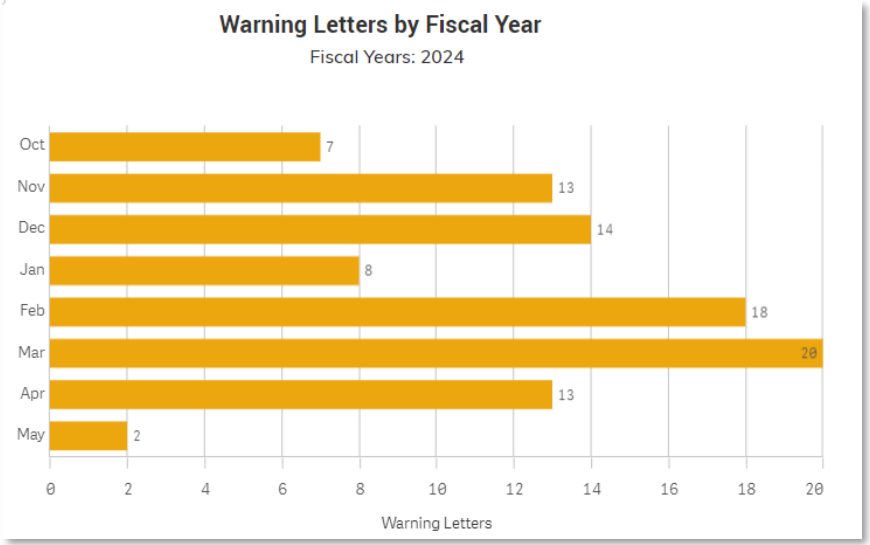
Import Refusals

Import refusals by fiscal year, product categories, country, divisions, etc.

Imports Entry

Imports entry data by fiscal year, country of origin, port of entry district, etc.





Act/CFR Number	Short Description	Long Description
FDCA 505-1(f)(4)	Failure to comply with REMS Implementation System	An application holder did not maintain the drug distribution and dispensing records to ensure restricted distribution, as required by your approved REMS Implementation System.
21 CFR 211.192	Written record of investigation incomplete	Written records of investigations into unexplained discrepancies do not include the conclusions and follow-up.
21 CFR 314.81(b)(1)(ii)	Failure to meet specifications	An NDA-Field Alert Report was not submitted within three working days of receipt of information concerning a failure of one or more distributed batches of a drug to meet the specifications established for it in the application.
21 CFR 211.110(a)	Control procedures to monitor and validate performance	Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Public Events

Upcoming

- Jun. 17-18: DSCSA Stabilization Period Midway Checkpoint
- Jul. 25-26: FDA Online Controlled Substances Summit
- Aug. 21-23: Compounding Center of Excellence Annual Conference
- Sep. 9-11: FDA/PDA Joint Regulatory Conference
- Drug Registration and Listing Annual Conference

Past

- See CDER SBIA online training listings

UNIFIED COMPLIANCE

Summary

- We are dedicated to addressing persistent and emerging threats
- We will use all available tools to safeguard consumers from public health risks

FDA U.S. FOOD & DRUG ADMINISTRATION

Questions?