Public Health Significance of High-quality Registration and Listing Data

Mission

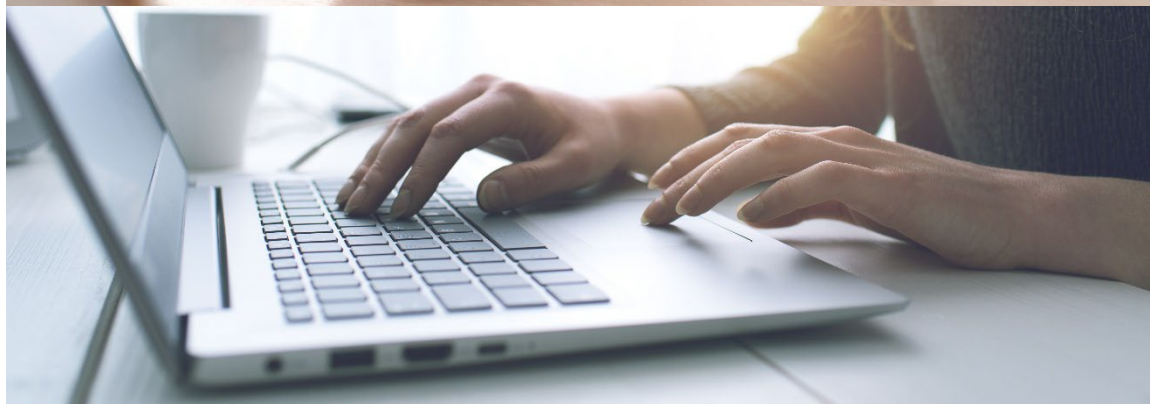
To shield the public from poor-quality, unsafe, and ineffective drugs through proactive compliance strategies and risk-based enforcement actions

Accurate Data is **Essential** to Patient Safety

FDA relies on DRLS data to protect public health to help:

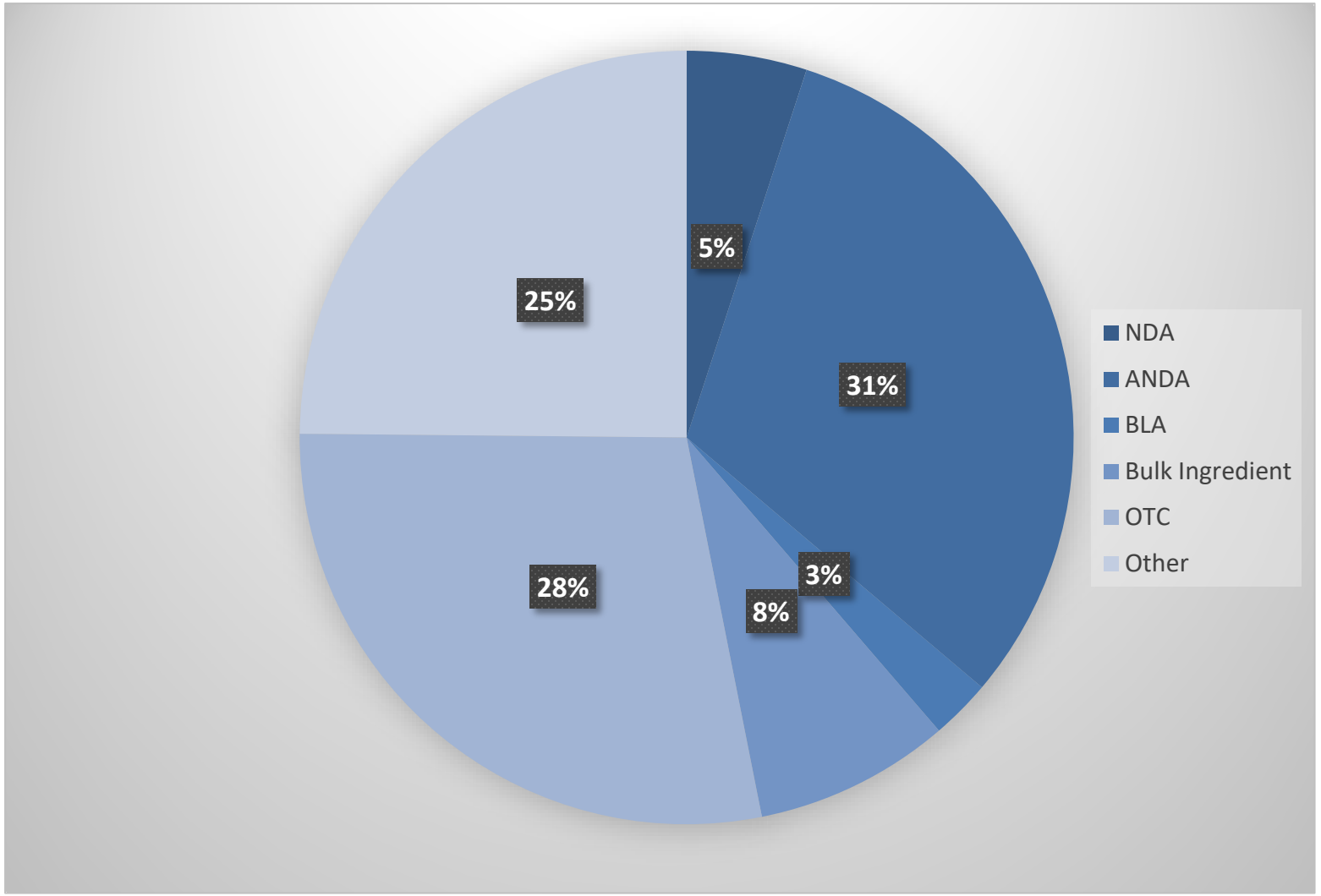
- Drug establishment inspection planning
- Drug import and export review
- Recall oversight
- Tracking reports of injury
- Monitoring of drug shortages

DRLS data is **also widely used outside FDA** for electronic prescribing and electronic health records, reimbursement and patient education.



By the Numbers

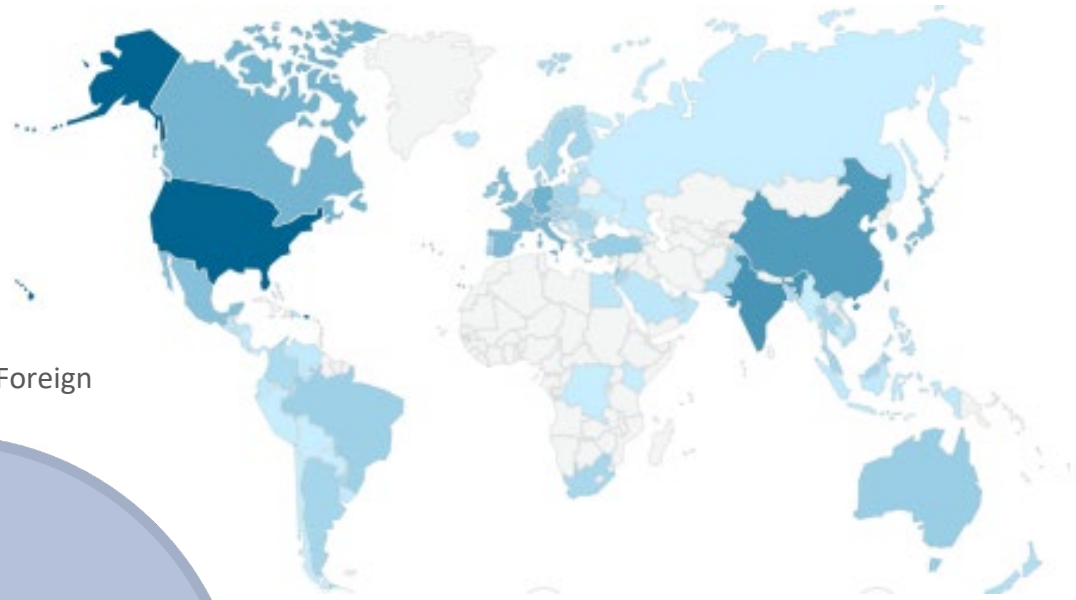
There are over 144,000 drugs currently listed with FDA.



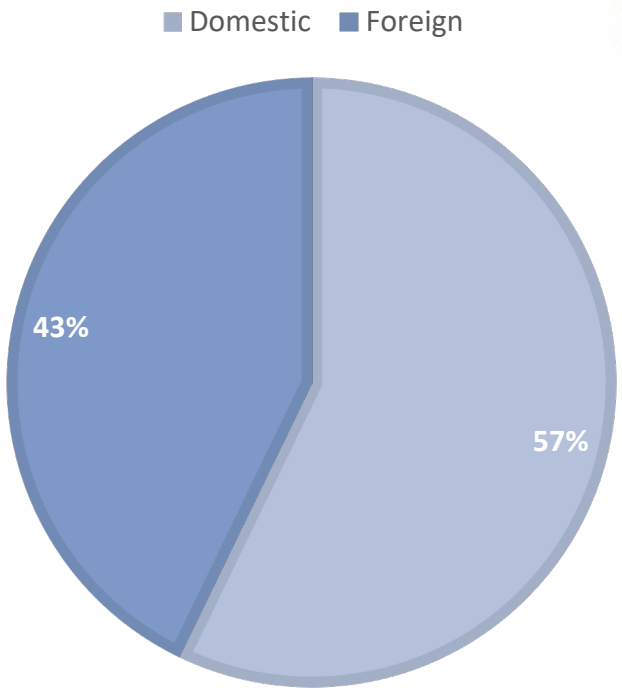
Source: FDA. Other includes animal drugs, drugs for further processing, medical gas, homeopathic drugs, etc.

By the Numbers

There are over 10,600 manufacturing establishments currently registered with FDA.



Registration Heat Map



Source: FDA

Registration and Listing **Compliance Activities**

In Fiscal Year 2022

21,440 drug listings were inactivated due to either not being certified as active or associated with an unregistered manufacturing establishment

1,119 unused labeler codes and issued

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

DRLS Warning Letters

"Our review determined that your firm has submitted contradictory information between the labeling and the electronic listing files. As such, your firm is in violation of the Federal Food, Drug, and in Cosmetic Act (FD&C Act) as explained below.

Please notify FDA in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to address any violations."

Warning Letter/Company	Issue Date	Closeout Date
Lydia Co.	6/26/2023	
Procter & Gamble Manufactura S. de R.L. de C.V.	3/14/2023	Close Out Letter (03/27/2023)
The Body Bean, LLC	02/06/2023	
Unit Dose Services, LLC	10/19/2022	Close Out Letter (12/21/2022)
RiteAid Corporation	10/17/2022	Close Out Letter (12/20/2022)
Grimann S.A. de C.V.	5/23/2022	Close Out Letter 06/03/2022
ECI Pharmaceuticals,LLC	2/3/2022	Close Out Letter 03/16/2022

Why does FDA take the data seriously?

How has drug registration and listing data impacted public health in 2023?

Ophthalmic Product Activities

- In general, certain routes of administration, such as ophthalmic products, can pose a greater risk of harm because they bypass the body's natural defenses
- In 2023, FDA and CDC collaborated to address an outbreak of extensively drug-resistant pseudomonas aeruginosa
- **In general, accurate DRLS data is:**
  - Helping stop importation of potentially harmful products
  - Aiding inspection planning
  - Assisting identification of products for FDA testing

Ophthalmic Compliance Activities

- Testing
- Labeling Review
- Consumer Advisories
- Recall Oversight
- Inspections
- Warning Letters

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857 ORAPHARMInternational483responses@fda.hhs.gov	02/20/2023-03/02/2023 FEI NUMBER 3012323885
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Dr. Venkatesh, A.R. CEO	
FIRM NAME	STREET ADDRESS
Global Pharma Healthcare Pvt. Ltd.	A-9, SIDCO Pharmaceutical Complex
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Thiruporur – 603110, Tamilnadu, India	Drug Product Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include validation of the sterilization process.

Specifically,

A. You aseptically fill the (b) (4) mg/mL to manufacture (b) (4) for the US market. You intend to achieve the sterilization of the drug product through (b) (4) filtration on a (b) (4) (b) (4) filter for sterilization. There is not adequate validation data to demonstrate that the (b) (4) and the accompanying filter housing and equipment can reliably sterilize the (b) (4) solution. In addition, you have not established that the sterilization process is effective across different manufacturing conditions such as the pH and temperature of the solution, filtration pressure, flow rate, maximum filtration time, batch size (volume) and effect of (b) (4) sterilization on the filter's retention capability. You have also not established the worst-case scenario for the bioburden.

Your General Manager of the Quality Assurance stated that a controlled filling room temperature (b) (4) °C) established the filtration temperature, and the passing assay of the drug product confirms the filter compatibility.

FDA NEWS RELEASE

FDA Issues Warning Letters to Firms Marketing Unapproved Eye Products

Agency Warns Eight Companies Regarding Their Unapproved Ophthalmic Drugs

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For Immediate Release: September 12, 2023

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 warning letters also cite the companies involved for quality issues related to product sterility.

The FDA is particularly concerned that these illegally marketed, unapproved ophthalmic drug products pose a heightened risk of harm to users because drugs applied to the eyes bypass some of the body's natural defenses. Some of these eye products are labeled to contain silver, which may be characterized as silver sulfate, silver sulphate or argentum. Long-term use of drugs containing silver can cause some areas of the skin and other body tissues, including in the eye, to permanently turn gray or blue-gray, which is called "argyria." Additionally, unapproved drugs that claim to cure, treat or prevent serious conditions may cause consumers to delay or stop medical treatments that have been found safe and effective through the FDA review process.

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

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Update **[8/30/2023]** Dr. Berne's Whole Health Products voluntarily recalled Dr. Berne's MSM Drops 5% and 15% 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 LightEyez 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; LightEyez' products are distributed by LightEyez Limited.

FDA recommends consumers properly discard these products as 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 this time. Patients who have signs or symptoms of an eye infection should talk to their health care professional or otherwise seek medical care immediately.

The Dr. Berne's and LightEyez eye drop products also contain methylsulfonylmethane (MSM) as an active ingredient. These products are unapproved drugs and illegally

FDA warns consumers not to purchase or use EzriCare Artificial Tears due to potential contamination

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Update [8/25/2023] FDA is reminding the public that these recalled products should not be used, including off-label use in animals. FDA does not have direct knowledge of veterinary use of these products or of animal adverse events that are linked to the products; however, on August 14, 2023, the New Jersey Department of Health issued a Health Alert Network message calling for animal caretakers to immediately discontinue using EzriCare Artificial Tears, Delsam Pharma Artificial Tears, and Delsam Pharma Artificial Ointment on animal patients.

If you suspect that an animal under your care contracted an infection or serious side effects from these products, please report it to FDA: How to Report Animal Drug and Device Side Effects and Product Problems.

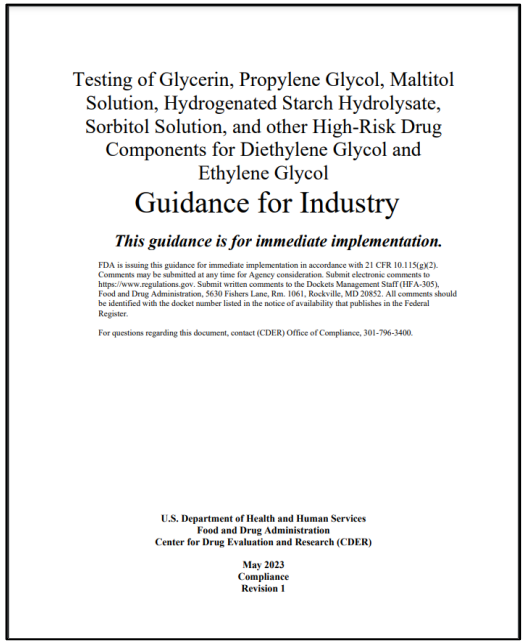
Update [2/22/2023] FDA recommended that Global Pharma recall Delsam Pharma's Artificial Eye Ointment, and the firm agreed to initiate a recall.

Update [2/21/2023] In addition to Artificial Tears products, FDA is also now warning consumers and health care professionals not to purchase or use Delsam Pharma's Artificial Eye Ointment due to potential bacterial contamination. This is an over-the-counter product, manufactured by Global Pharma Healthcare Private Limited, intended to be sterile.

Safeguarding against Contamination

- From October 2022 to July 2023, the World Health Organization (WHO) issued medical product alerts about contaminated medications, including children's cough and cold syrup, found with unacceptable amounts of the contaminants diethylene glycol or ethylene glycol.
- Contamination was associated with more than 300 deaths abroad, many in young children under the age of five.
- This is one of the largest epidemics of DEG poisoning in history.
- Similar contamination in 1937 led to the creation of the modern Food, Drug, and Cosmetic Act.

World Health Organization



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

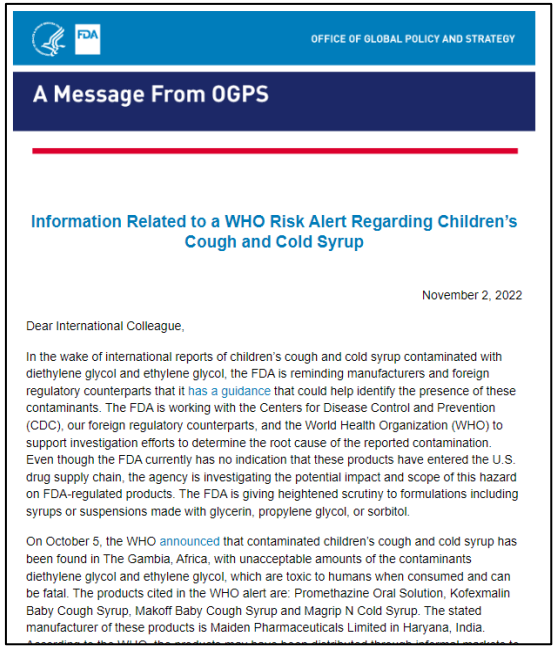
This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2). Comments may be submitted at any time for Agency consideration. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this document, contact (CDER) Office of Compliance, 301-796-3400.

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

OFFICE OF GLOBAL POLICY AND STRATEGY

A Message From OGPS

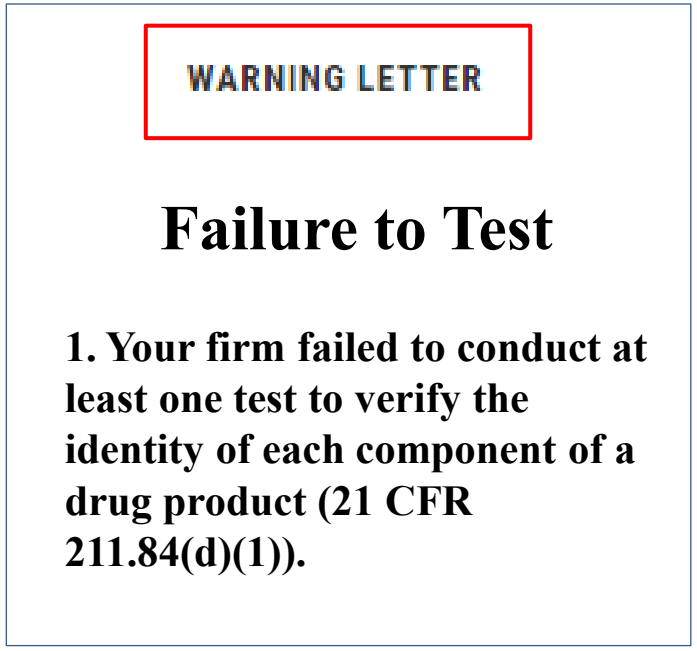
Information Related to a WHO Risk Alert Regarding Children's Cough and Cold Syrup

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.

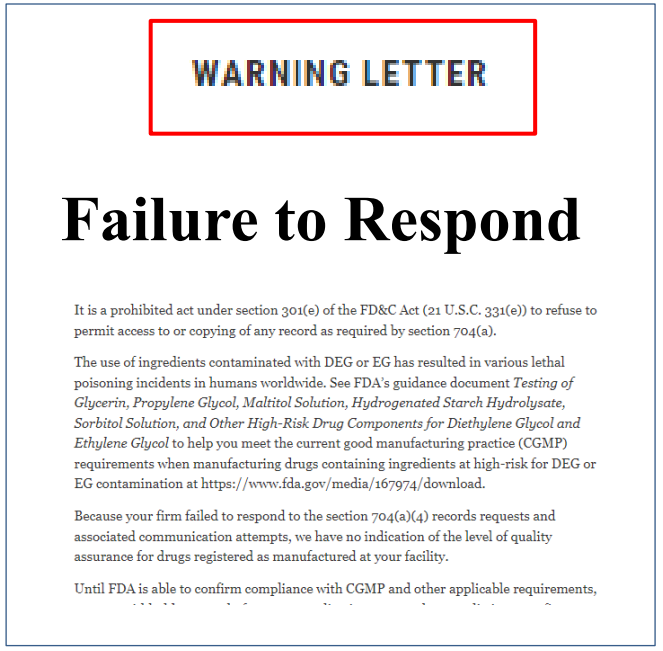
On October 5, the WHO announced that contaminated children's cough and cold syrup has been found in The Gambia, Africa, with unacceptable amounts of the contaminants diethylene glycol and ethylene glycol, which are toxic to humans when consumed and can be fatal. The products cited in the WHO alert are: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



WARNING LETTER

Failure to Test

1. Your firm failed to conduct at least one test to verify the identity of each component of a drug product (21 CFR 211.84(d)(1)).



WARNING LETTER

Failure to Respond

It is a prohibited act under section 301(e) of the FD&C Act (21 U.S.C. 331(e)) to refuse to permit access to or copying of any record as required by section 704(a).

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 Glycol* to help you meet the current good manufacturing practice (CGMP) requirements when manufacturing drugs containing ingredients at high-risk for DEG or EG contamination at https://www.fda.gov/media/167974/download.

Because your firm failed to respond to the section 704(a)(4) records requests and associated communication attempts, we have no indication of the level of quality assurance for drugs registered as manufactured at your facility.

Until FDA is able to confirm compliance with CGMP and other applicable requirements,

Import Alert 66-40

Detention Without Physical Examination of Drugs From Firms Which Have Not Met Drug GMPs

Import Alert 66-79

Detention Without Physical Examination of Drugs From Foreign Establishments Refusing FDA Inspection

DEG Compliance Activities

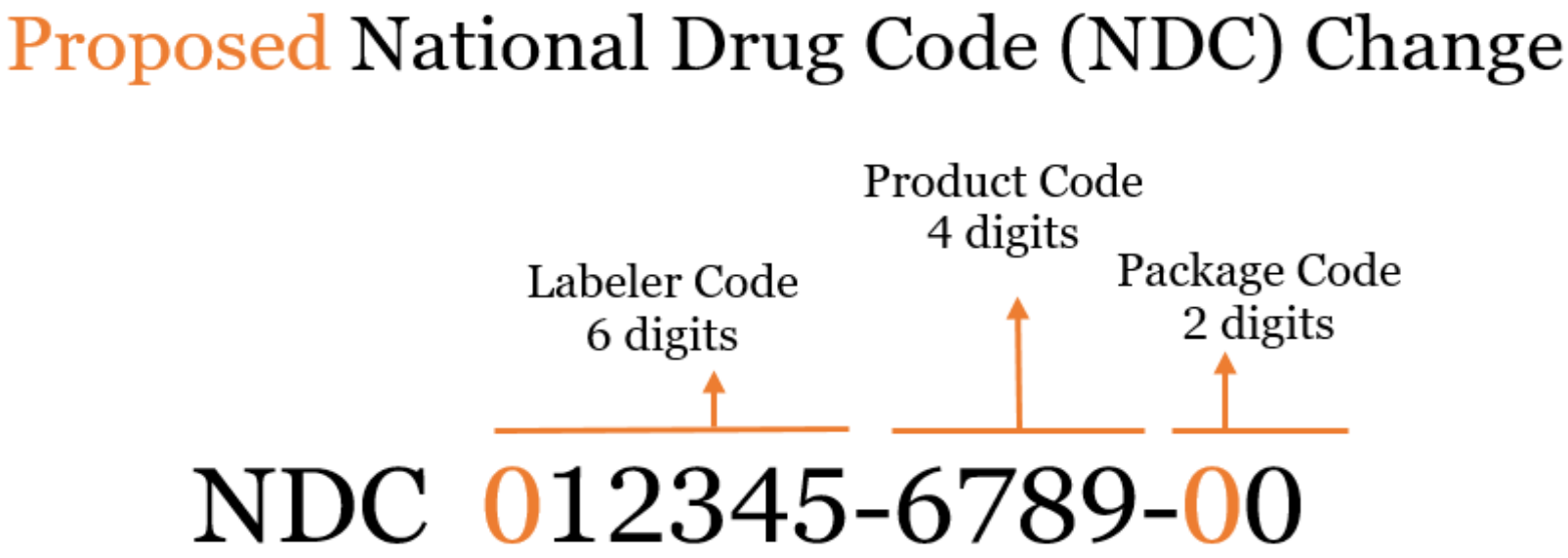
DRLS DATA PLAYED A VITAL ROLE

- Work with public health agencies and foreign authorities
- Industry outreach
- Updated DEG guidance
- Issued records requests
- Increased sampling and inspections
- Warning letters
- Screening criteria and import alerts

NDC Proposed Rule Overview

Proposed Rule Overview

- Proposed rule, if finalized, would update the length of NDCs
- Under the proposed rule, if finalized, NDCs would expand from 10 digits to 12 digits

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