U.S. FOOD & DRUG ADMINISTRATION

Testing of High-Risk Drug Components for Diethylene Glycol and Ethylene Glycol

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Office of Compliance

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Pharmaceutical Quality Symposium: Quality, Supply Chain & Advanced Manufacturing 2023

CDER Office of Manufacturing Quality

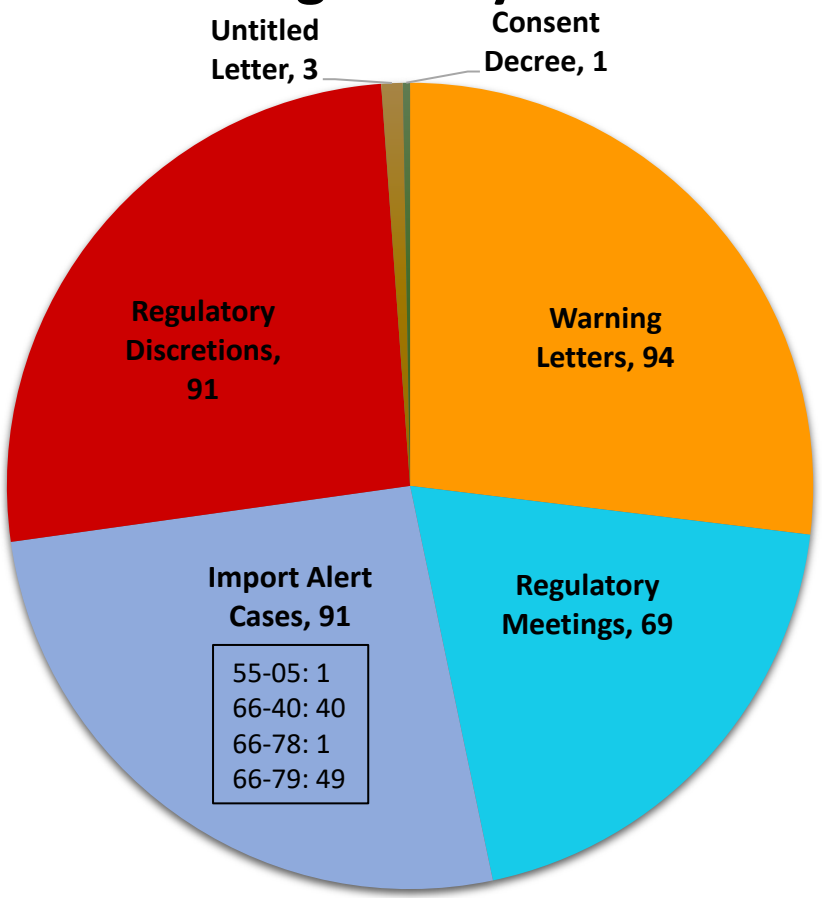
- We evaluate compliance with **C**urrent **G**ood **M**anufacturing **P**ractice (**CGMP**) for drugs based on inspection reports and evidence gathered by FDA investigators.
- We develop and implement compliance policy and take regulatory actions to protect the public from ***adulterated*** drugs in the U.S. market.

Source: FDA

Enforcement and Advisory Tools

- Regulatory Meetings
- Injunctions
- Consent Decrees
- Import Alerts
- Seizures
- Warning Letters
- Untitled Letters
- Administrative Detention

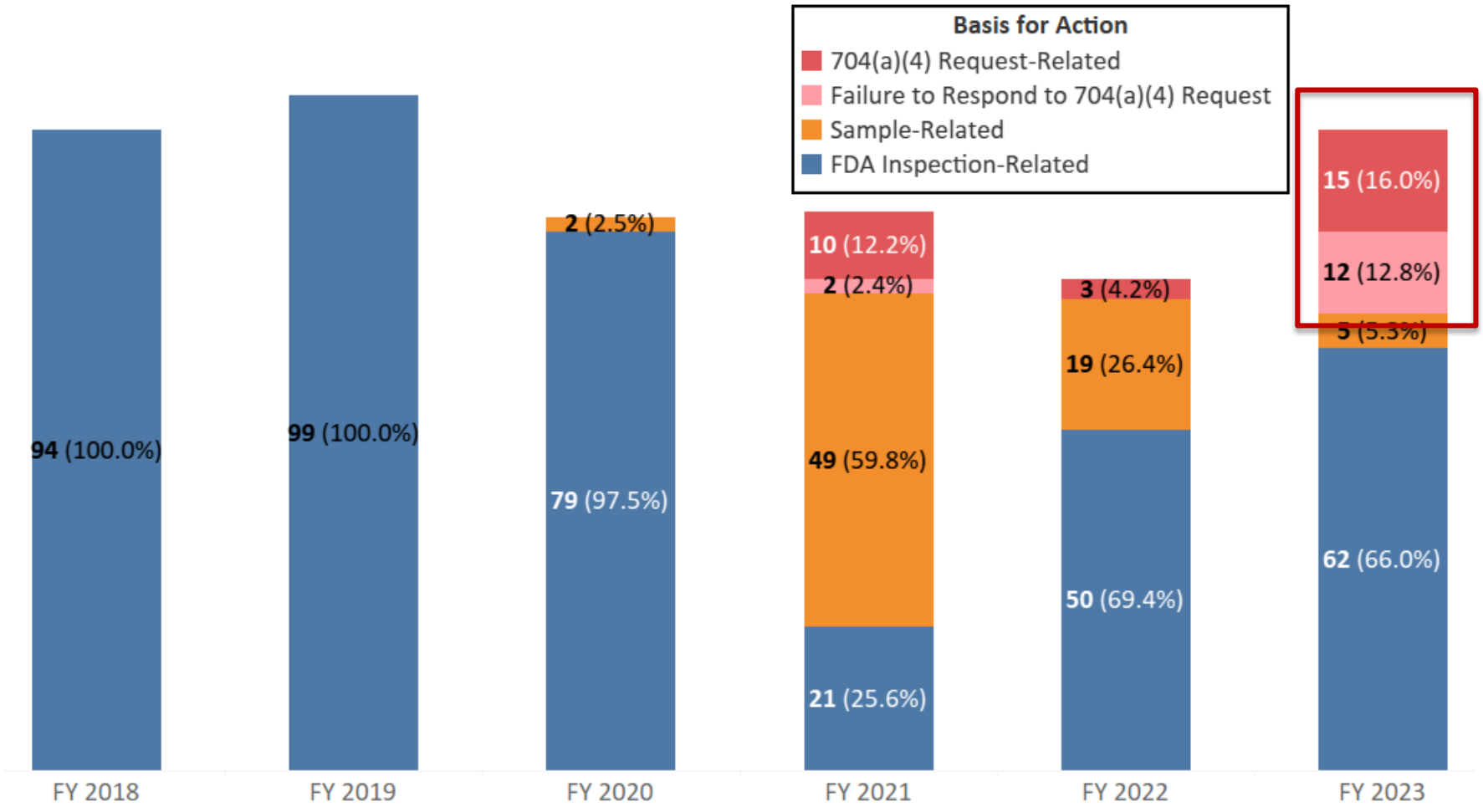
FY2023 Regulatory Actions



Excludes compounding-related actions

*Actions Taken October 1, 2022 to September 30, 2023

Shift in Basis of Action for non-compounding CGMP Warning Letters FY18-23



Data as of 9/30/2023

How FDA Looks at Excipients

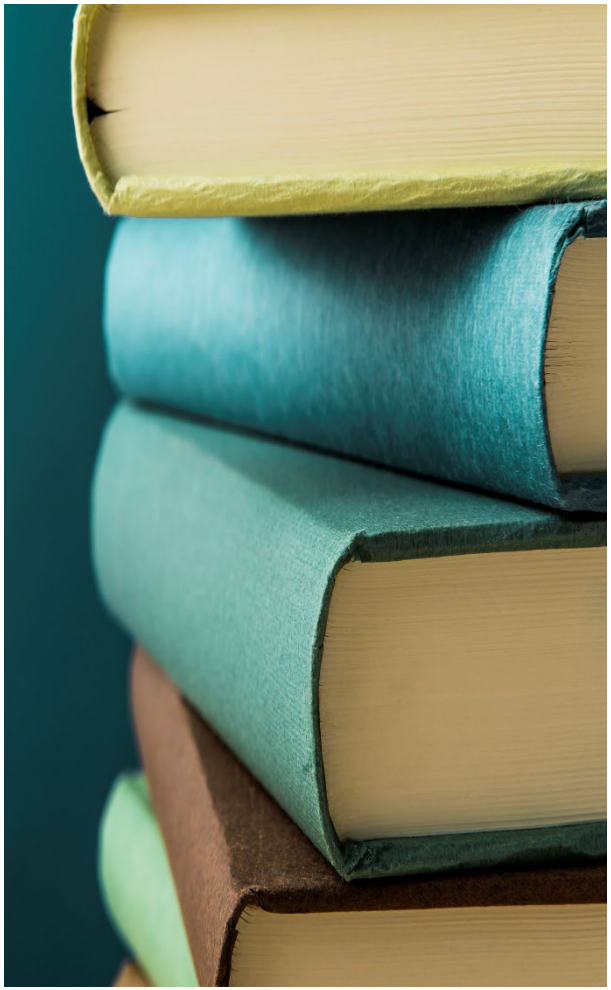
What is an Excipient?

- In FDA nomenclature, an excipient is also known as an “inactive ingredient”
  - 21 CFR 210.3(a)(8):

    “Inactive ingredient means any component other than an active ingredient.”

- But more importantly, FDA considers both active ingredients and excipients/inactive ingredients to be drug “components”:
  - 21 CFR 210.3 (a)(3):

    “Component means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product.”



Drug Components are Also Drugs

- Under the FD&C Act, a drug is defined per Sec 201 (USC 321)
  - "(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia,….; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; **and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."**
- Long story short: excipients (or inactive ingredients) are themselves considered drugs when they are intended for use, or used as, a component of a drug product.
- And all the drug adulteration provisions of the Act apply to them as well.

Who in the Supply Chain Does FDA Inspect?

- Drug manufacturers are subject to inspection (section 704 of the FD&C Act)
- FDA conducts several types of inspections to help provide access to needed medical products and to protect consumers and patients from unsafe products, such as routine CGMP surveillance inspections and for-cause inspections
- FDA implemented a risk-based approach to prioritizing human drug manufacturing facilities for routine CGMP surveillance inspections
  - FDA's site selection model prioritizes certain types of manufacturers, such as finished dosage form (FDF) manufacturers and active pharmaceutical ingredient (API) manufacturers
- Some types of manufacturers are not prioritized for routine CGMP surveillance inspections such as excipient manufacturers
  - These drug manufacturers may be inspected for-cause

Diethylene Glycol/Ethylene Glycol (DEG/EG)

Background on DEG/EG

- Diethylene glycol (DEG) is an industrial chemical, used as an antifreeze, and is poisonous.
- In 1937 a DEG poisoning outbreak occurred when DEG was used as a solvent in Sulfanilamide:
  - Led to 107 deaths, many of them children
  - This led to the enactment of the FD&C Act in 1938

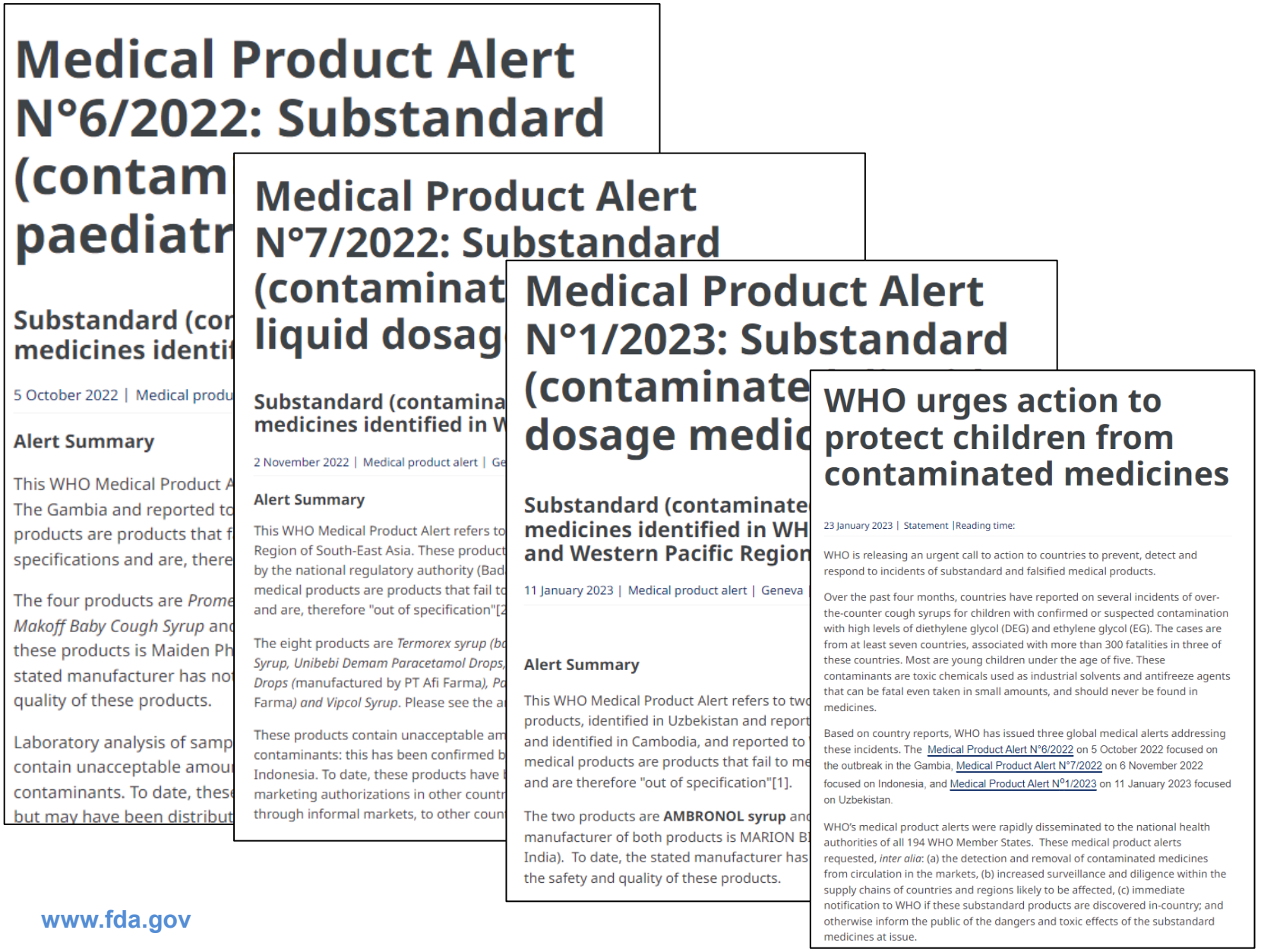
Background on DEG/EG

- Unscrupulous manufacturers/suppliers have used DEG/EG in excipients, or as an excipient, in lieu of costlier ingredients (for economic gain).
- Typically in the excipient distribution/repacking supply chain
- Lack of CGMP controls at finished dosage form sites allowed for the contamination to enter drug products.

Background on DEG/EG

- Periodic DEG/EG events have occurred:
  - DEG substitution for glycerin in Central America in the late 2000s,
  - FDA took actions against Chinese toothpastes containing DEG in 2007
- History repeats itself:
  - 2022/2023 outbreaks in children's drug products overseas

Recent DEG/EG Outbreaks Overseas



Medical Product Alert N°6/2022: Substandard (contam paediatr

Substandard (cor medicines identif

5 October 2022 | Medical produ

Alert Summary

This WHO Medical Product A
The Gambia and reported to
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The four products are *Prome*
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Medical Product Alert N°7/2022: Substandard (contaminat liquid dosag

Substandard (contamina medicines identified in W

2 November 2022 | Medical product alert | Ge

Alert Summary

This WHO Medical Product Alert refers to
Region of South-East Asia. These product
by the national regulatory authority (Bad
medical products are products that fail to
and are, therefore "out of specification"[2

The eight products are *Termorex syrup (ba*
Syrup, Unibebi Demam Paracetamol Drops,
Drops (manufactured by PT Afi Farma), *Pa*
Farma) *and Vipcol Syrup*. Please see the a

These products contain unacceptable am
contaminants: this has been confirmed b
Indonesia. To date, these products have
marketing authorizations in other countr
through informal markets, to other coun

Medical Product Alert N°1/2023: Substandard (contaminate dosage medic

Substandard (contaminate medicines identified in WH and Western Pacific Region

11 January 2023 | Medical product alert | Geneva

Alert Summary

This WHO Medical Product Alert refers to two
products, identified in Uzbekistan and report
and identified in Cambodia, and reported to
medical products are products that fail to me
and are therefore "out of specification"[1].

The two products are **AMBRONOL syrup** and
manufacturer of both products is MARION B
India). To date, the stated manufacturer has
the safety and quality of these products.

WHO urges action to protect children from contaminated medicines

23 January 2023 | Statement |Reading time:

WHO is releasing an urgent call to action to countries to prevent, detect and respond to incidents of substandard and falsified medical products.

Over the past four months, countries have reported on several incidents of over-the-counter cough syrups for children with confirmed or suspected contamination with high levels of diethylene glycol (DEG) and ethylene glycol (EG). The cases are from at least seven countries, associated with more than 300 fatalities in three of these countries. Most are young children under the age of five. These contaminants are toxic chemicals used as industrial solvents and antifreeze agents that can be fatal even taken in small amounts, and should never be found in medicines.

Based on country reports, WHO has issued three global medical alerts addressing these incidents. The Medical Product Alert N°6/2022 on 5 October 2022 focused on the outbreak in the Gambia, Medical Product Alert N°7/2022 on 6 November 2022 focused on Indonesia, and Medical Product Alert N°1/2023 on 11 January 2023 focused on Uzbekistan.

WHO's medical product alerts were rapidly disseminated to the national health authorities of all 194 WHO Member States. These medical product alerts requested, *inter alia*: (a) the detection and removal of contaminated medicines from circulation in the markets, (b) increased surveillance and diligence within the supply chains of countries and regions likely to be affected, (c) immediate notification to WHO if these substandard products are discovered in-country; and otherwise inform the public of the dangers and toxic effects of the substandard medicines at issue.

FDA's Role

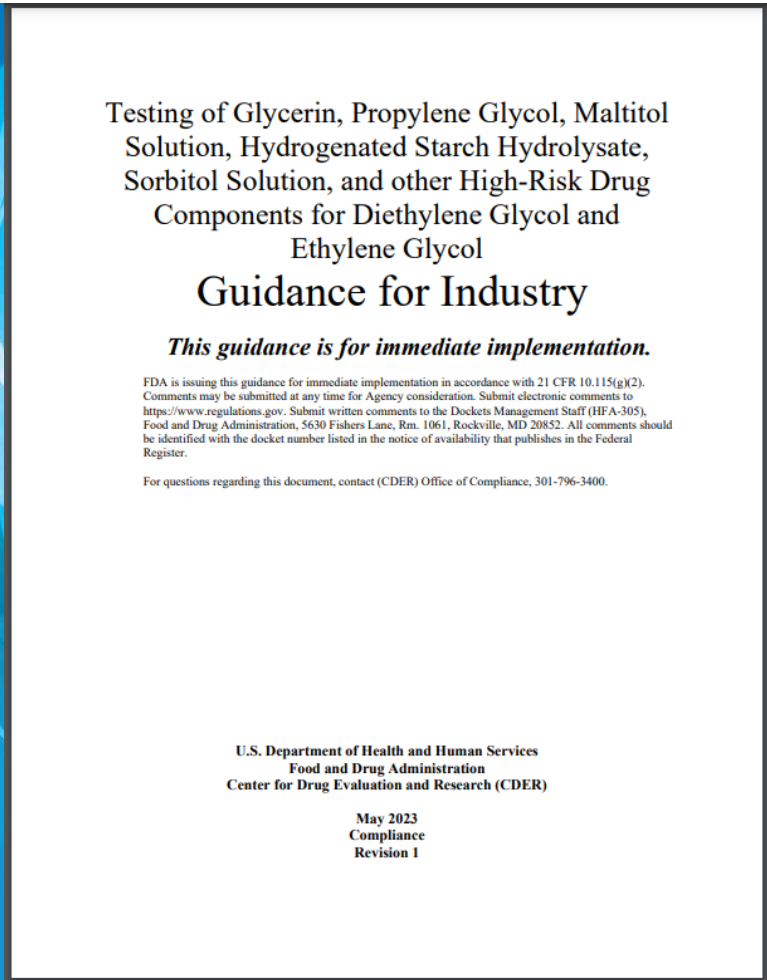
- Following the 2022/2023 reports of overseas deaths, FDA extensively interacted with WHO, other regulators, and industry.

- Unlike the 2006 incidents resulting from DEG/EG substitution in glycerin, the 2022/23 incidents appear related to substitution of DEG/EG in propylene glycol.

- While FDA has ramped up monitoring, FDA has not seen data indicating the contamination has affected the US drug supply.

DEG/EG Guidance Published

In 2023, FDA published a final guidance (replacing a 2007 guidance) that provides updated recommendations on testing and other activities that will help pharmaceutical manufacturers, repackers, other suppliers, and compounders prevent the use of high-risk components that are contaminated with DEG and EG.



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

CGMP Identity Requirements

- 211.84 Testing and approval or rejection of components, drug product containers, and closures.
  - "(a) **Each lot of components**, drug product containers, and closures **shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate**, and released for use by the quality control unit.
  - (b) **Representative samples of each shipment of each lot shall be collected for testing or examination**….
  - (d) Samples shall be examined and tested as follows:
    - (1) At least one test shall be conducted to **verify the identity of each component** of a drug product. Specific identity tests, if they exist, shall be used."

CGMP Identity Requirements

- **Question**: Can a drug product manufacturer rely on a supplier Certificate of Analysis (COA) and not conduct raw material testing?

- **Answer**: Potentially for some attributes, **but never for identity.**

- 211.84 Testing and approval or rejection of components, drug product containers, and closures.
  - "(d) Samples **shall be** examined and tested as follows:
  - (1) At least one test **shall be** conducted to verify the identity of each component of a drug product. **Specific identity tests, if they exist, shall be used.**
  - (2) Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, **provided that at least one specific identity test is conducted on such component by the manufacturer,** and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals."

CGMP Identity Requirements

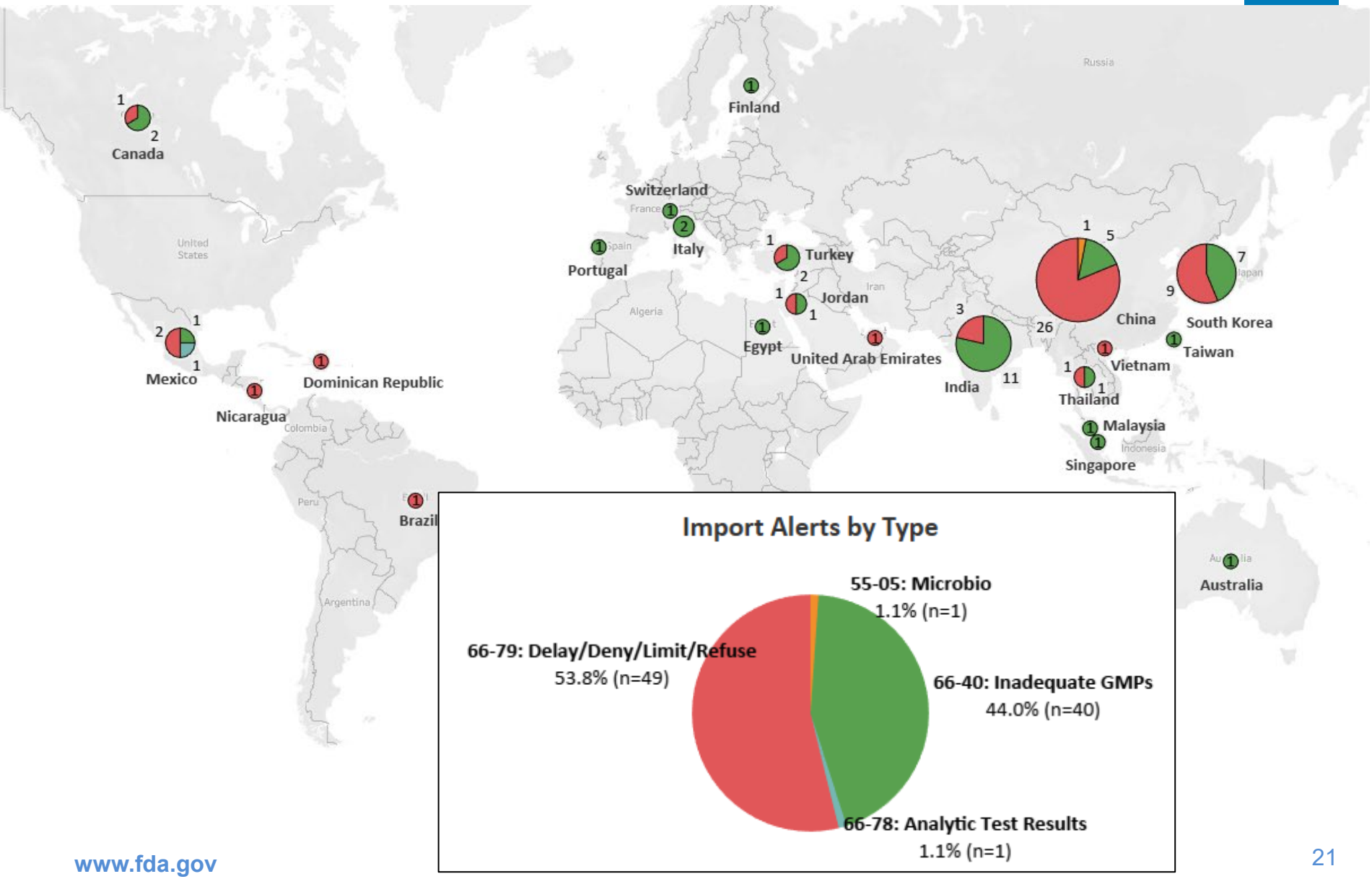
- 211.84 states "**Specific identity tests, if they exist, shall be used"**
- If a USP monograph includes testing for DEG/EG in the identity section, it is required of the drug product manufacturer under CGMP.
- This includes DEG/EG identity testing in the following excipients:
  - Glycerin,
  - Propylene Glycol,
  - Maltitol Solution,
  - Hydrogenated Starch Hydrolysate,
  - Sorbitol Solution,
  - and other High-Risk Drug Components
- Also, other drugs with history of similar contaminant specific identity testing requirements:
  - Over-sulfated Chondroitin Sulfate (OSCS) in Heparin:
    - https://www.fda.gov/media/82924/download
  - Methanol in Alcohol:
    - https://www.fda.gov/media/145262/download

Recent DEG/EG Compliance Actions

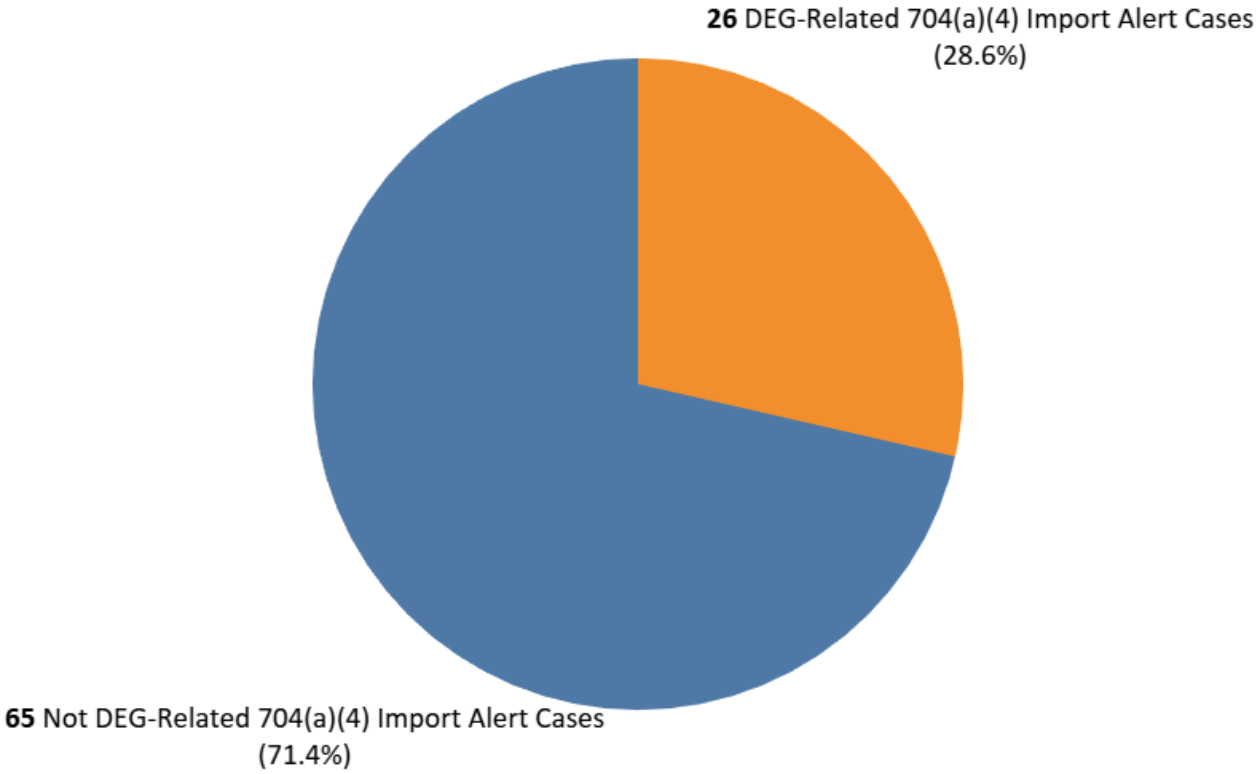
Heightened Supply Chain Monitoring

- As FDA evaluated the recent outbreaks, we are closely scrutinizing multiple liquid formulations of FDA-regulated drug products
- FDA sent a reminder of CGMP requirements to registered manufacturers using high risk components.
- FDA reviewed the drug manufacturing inventory, and sent 704(a)(4) Records Requests to:
  - Drug product manufacturers in geographies of concern,
  - Who use excipients of concern,
  - Asking for information on their CGMP controls for DEG/EG
- FDA has also sent records requests and been in contact with **excipient manufacturers and distributors** of note.
- And FDA has increased sampling, inspections, and other activities in this space.

Resulting Compliance Actions

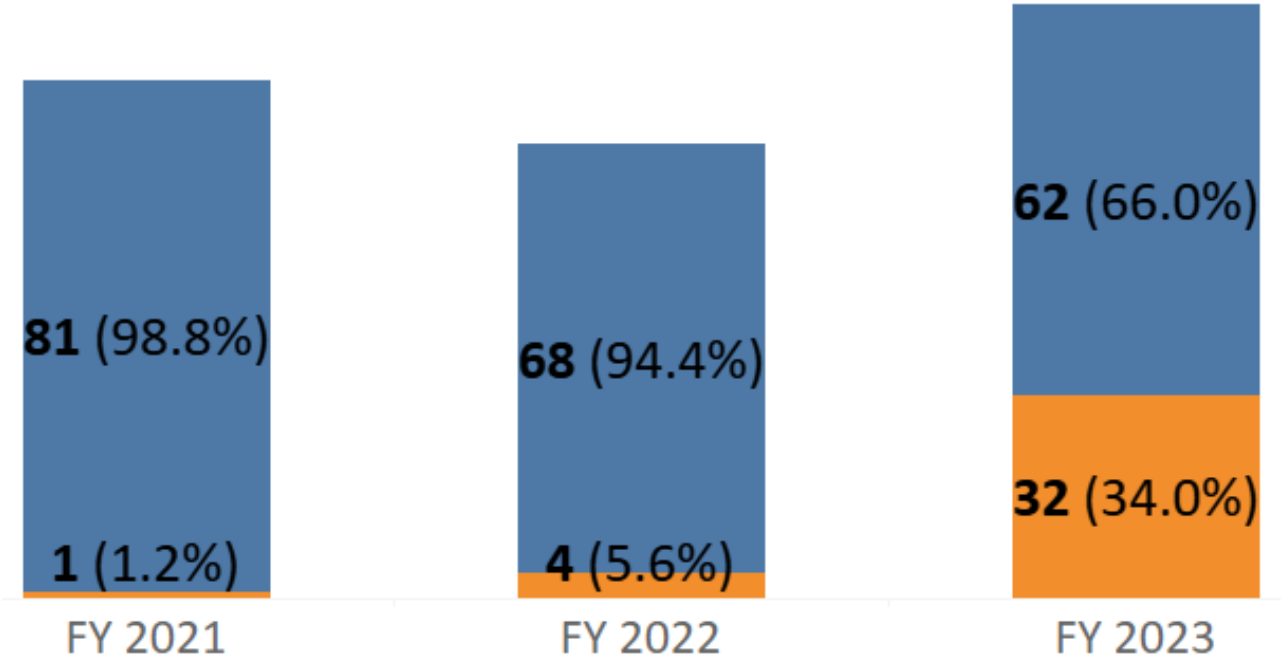


Increased Number of DEG/EG-Related Import Alerts Issued



FY23 Data: 10/1/22-9/30/23

Increasing Reference to DEG/EG Testing in CGMP Warning Letters FY21-23



Non-Compounding CGMP Warning Letters

Does Not Reference DEG/EG testing
References DEG/EG Testing

Warning Letters Issued 10/1/2020 to 9/30/2023

Case Examples: Lack of Controls for Components at Risk of DEG/EG Contamination

Excerpts from Warning Letters:

"you did not demonstrate that you adequately tested each shipment of each lot of incoming components at high-risk of diethylene glycol (DEG) or ethylene glycol (EG) contamination. These include, but are not limited to, **testing of glycerin, propylene glycol, and sorbitol solution** you used in manufacturing drug products to determine their appropriate identity…"

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/lcc-ltd-657336-08032023

"in response to our record request, you tested retain samples of some finished product batches that had been shipped to or distributed in the United States for the presence of DEG and EG impurities using the **2018 Indian Pharmacopeia (IP) monograph for glycerin**. However, you did not demonstrate that the 2018 IP method used for glycerin testing is suitable to identify the levels of DEG or EG in the finished drug product. Furthermore, you did not test every lot of drug product shipped to or distributed nor provide any evidence that would substantiate the results of the analytical testing (e.g., quantitative worksheets and chromatograms for impurities for each batch that was tested)…."

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/champaklal-maganlal-homeo-pharmacy-private-limited-652319-04102023

In each case FDA placed all drugs and drug products manufactured by the firms on Import Alert 66-40.

In Summary

- OMQ works to minimize consumer exposure to unsafe, ineffective, and poor-quality drugs.
- Excipients are drugs, and we have seen recent quality issues with certain excipients.
- We take actions to protect the public from adulterated drugs in the US market.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