U.S. FOOD & DRUG ADMINISTRATION

CDER CGMP Update

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GMP by the Sea

- DISCLAIMER: The views and opinions expressed in this presentation are those of the authors and do not necessarily represent official policy or position of the Food and Drug Administration

Outline

- What OMQ Does
- FY 2023 Updates and Warning Letter Data
- Parametric Release Q&A
- Multidose Opthalmics
- Benzene
- Diethylene Glycol/Ethylene Glycol

Office of Manufacturing Quality

What We Do

CDER/OC Mission

To shield patients from poor quality, unsafe and ineffective drugs through proactive compliance strategies and ***risk-based*** enforcement action.

What OMQ Does

- 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

Drug Adulteration Provisions

U.S. Federal Food, Drug, & Cosmetic Act

- 501(a)(2)(A): Insanitary conditions
- 501(a)(2)(B): Failure to conform with CGMP
- 501(b): Strength, quality, or purity differing from official compendium
- 501(c): Misrepresentation of strength, etc., where drug is unrecognized in compendium
- 501(d): Mixture with or substitution of another substance
- 501(j): Deemed adulterated if owner/operator delays, denies, refuses, or limits inspection

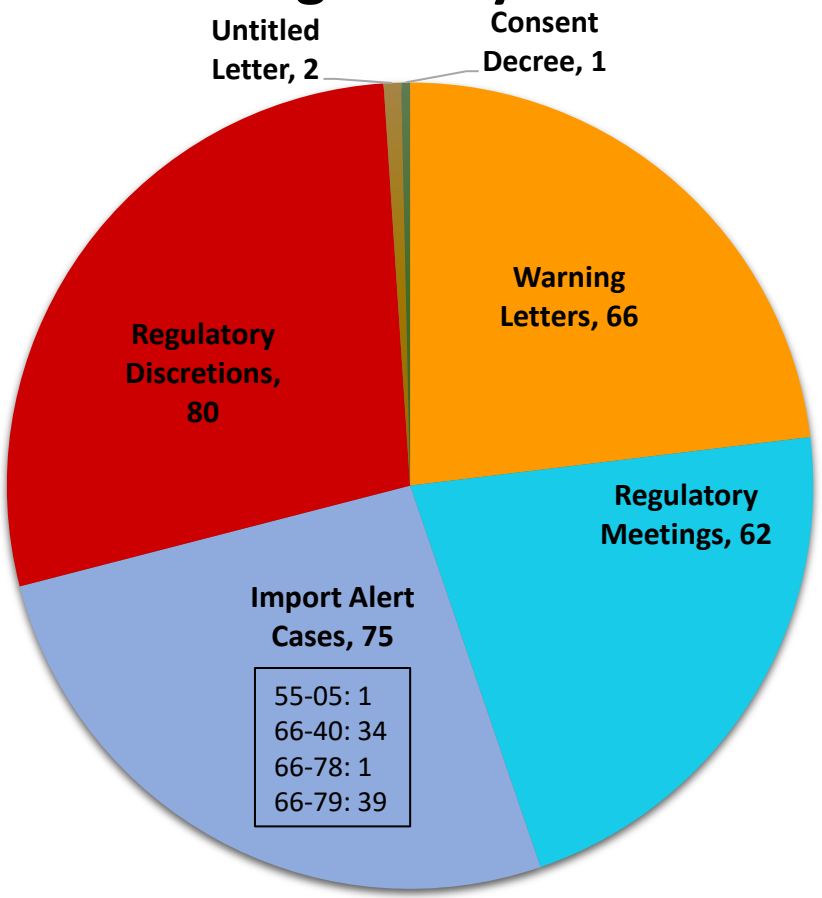
Office of Manufacturing Quality

FY 2023 Updates

Enforcement and Advisory Tools

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

FY2023 Regulatory Actions

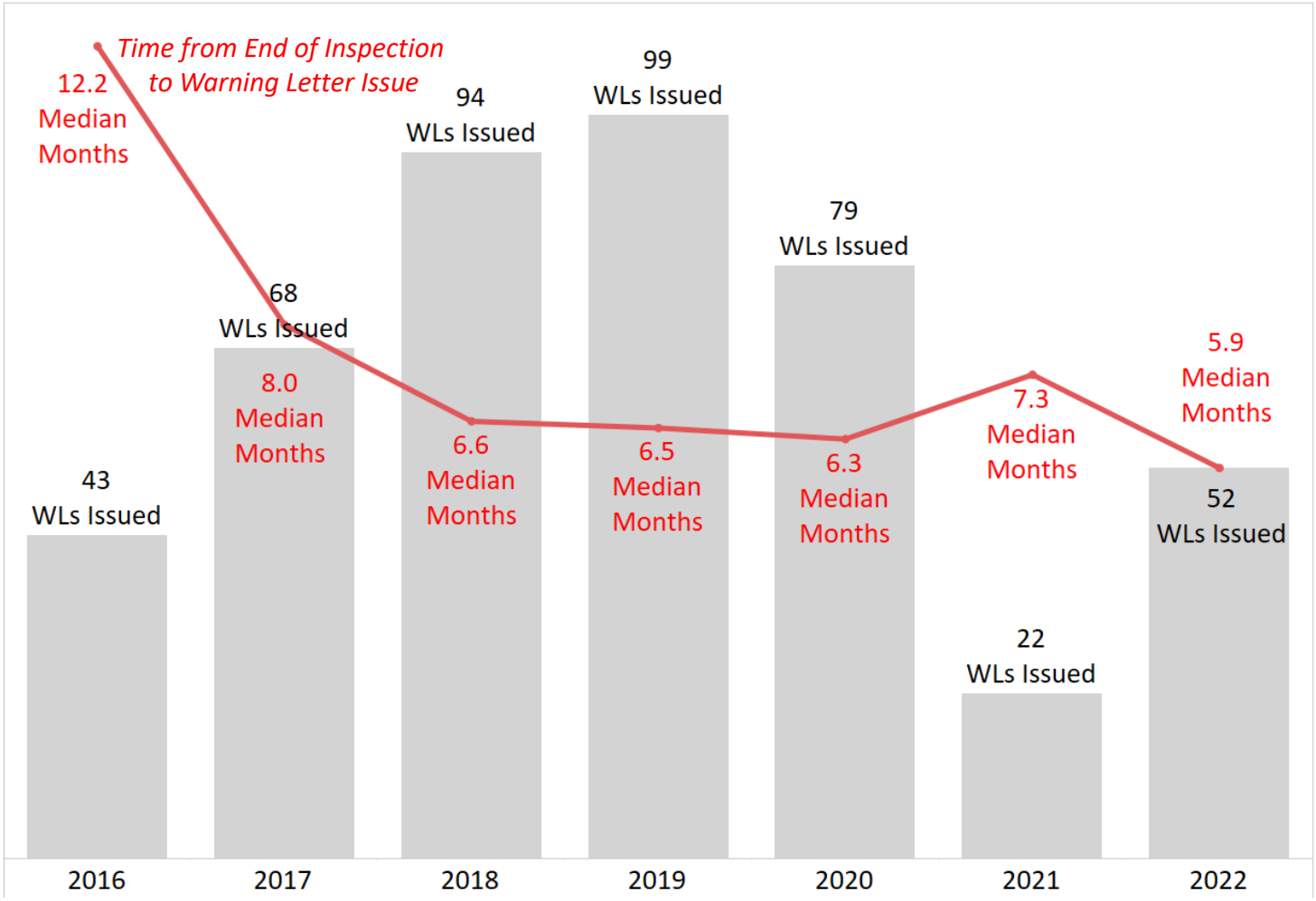


Excludes compounding-related actions

*Actions Taken October 1, 2022 to July 31, 2023

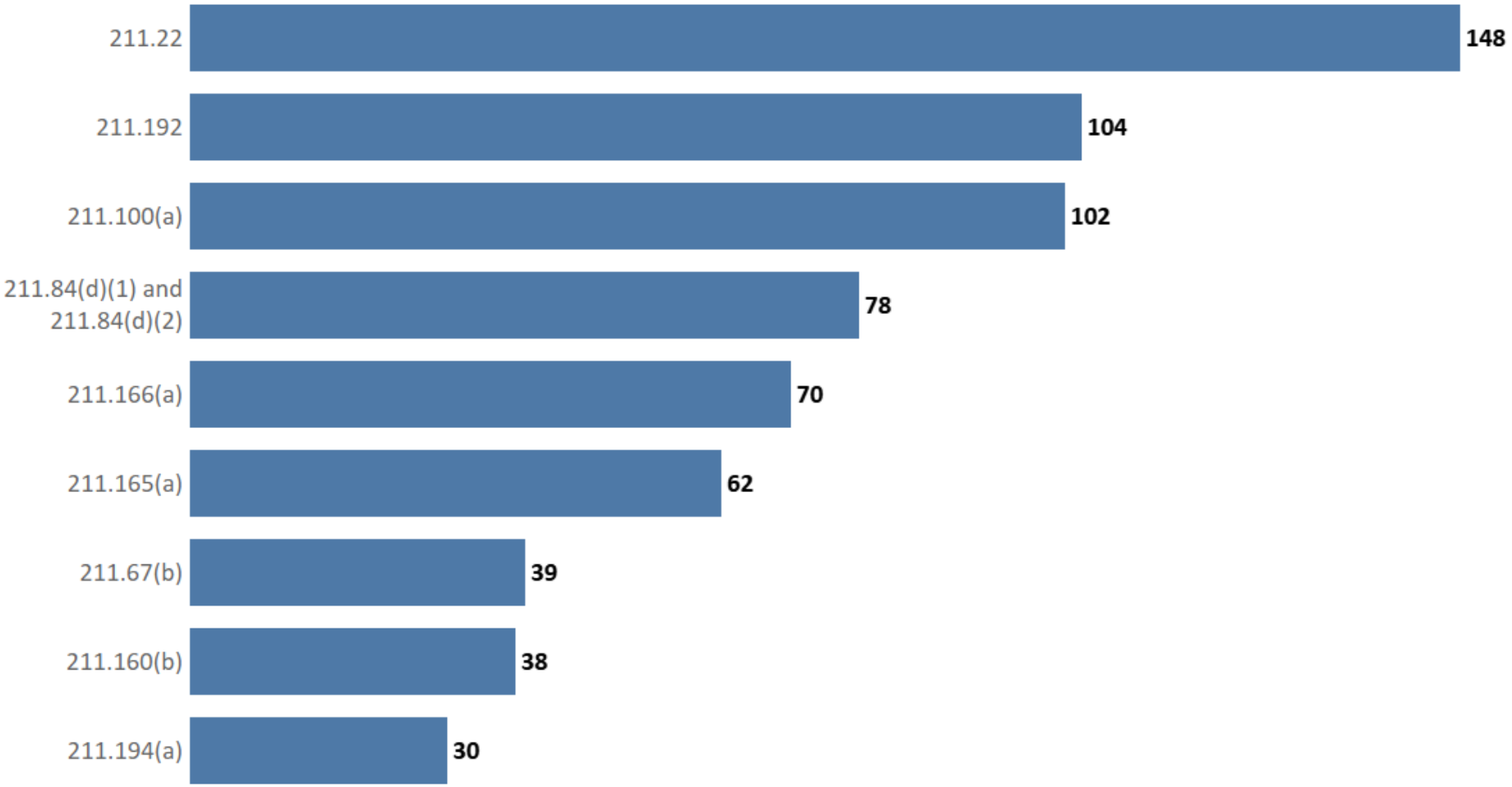
Agency Progress Towards 6-Month Compliance Actions

From FY2016 to FY2022, there has been an overall median
52% improvement while increasing inspection-based Warning Letter issuance



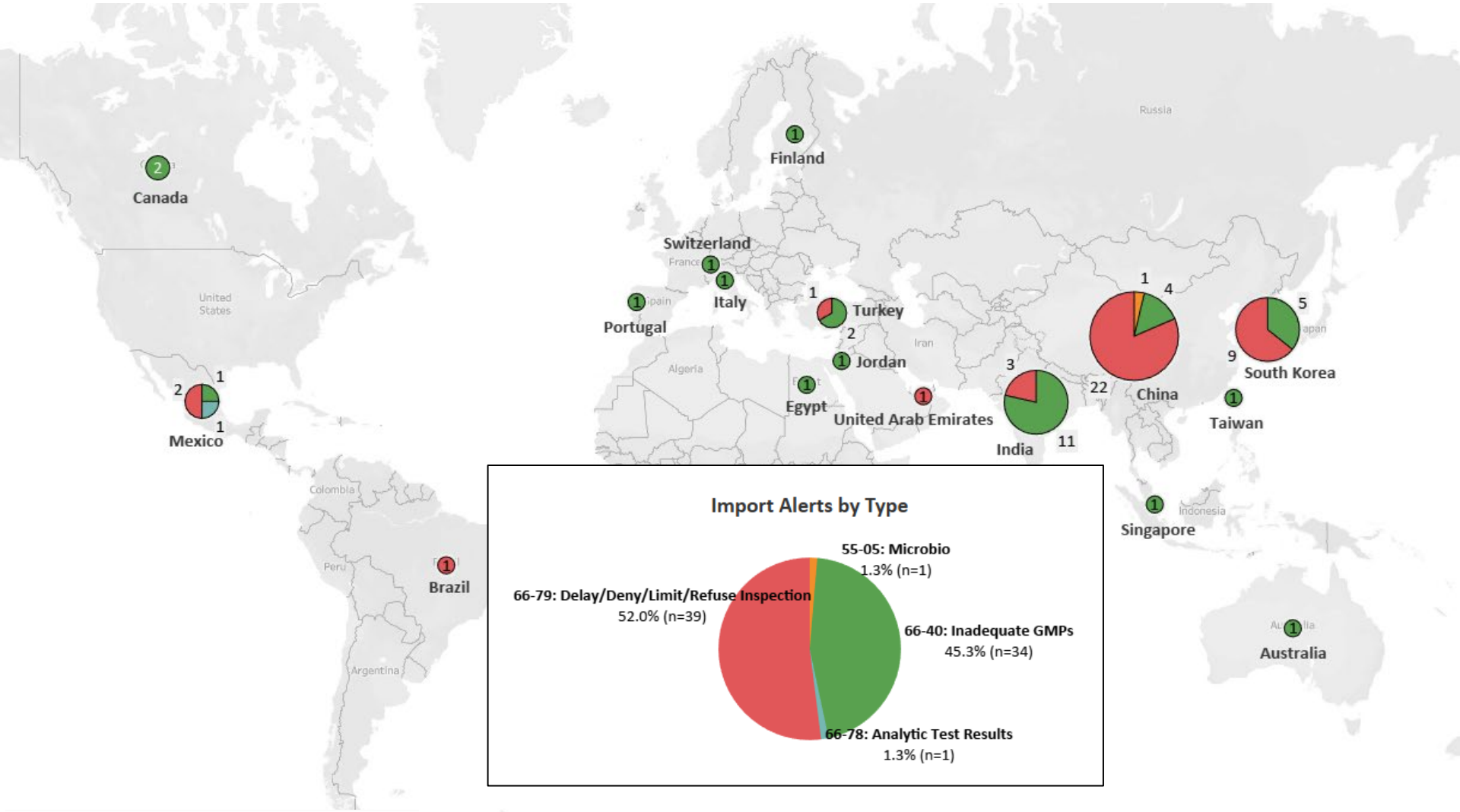
Does not include compounding Warning Letters.

Top 211 Citations in Warning Letters to Finished Dosage Manufacturers FY2018 to FY2022



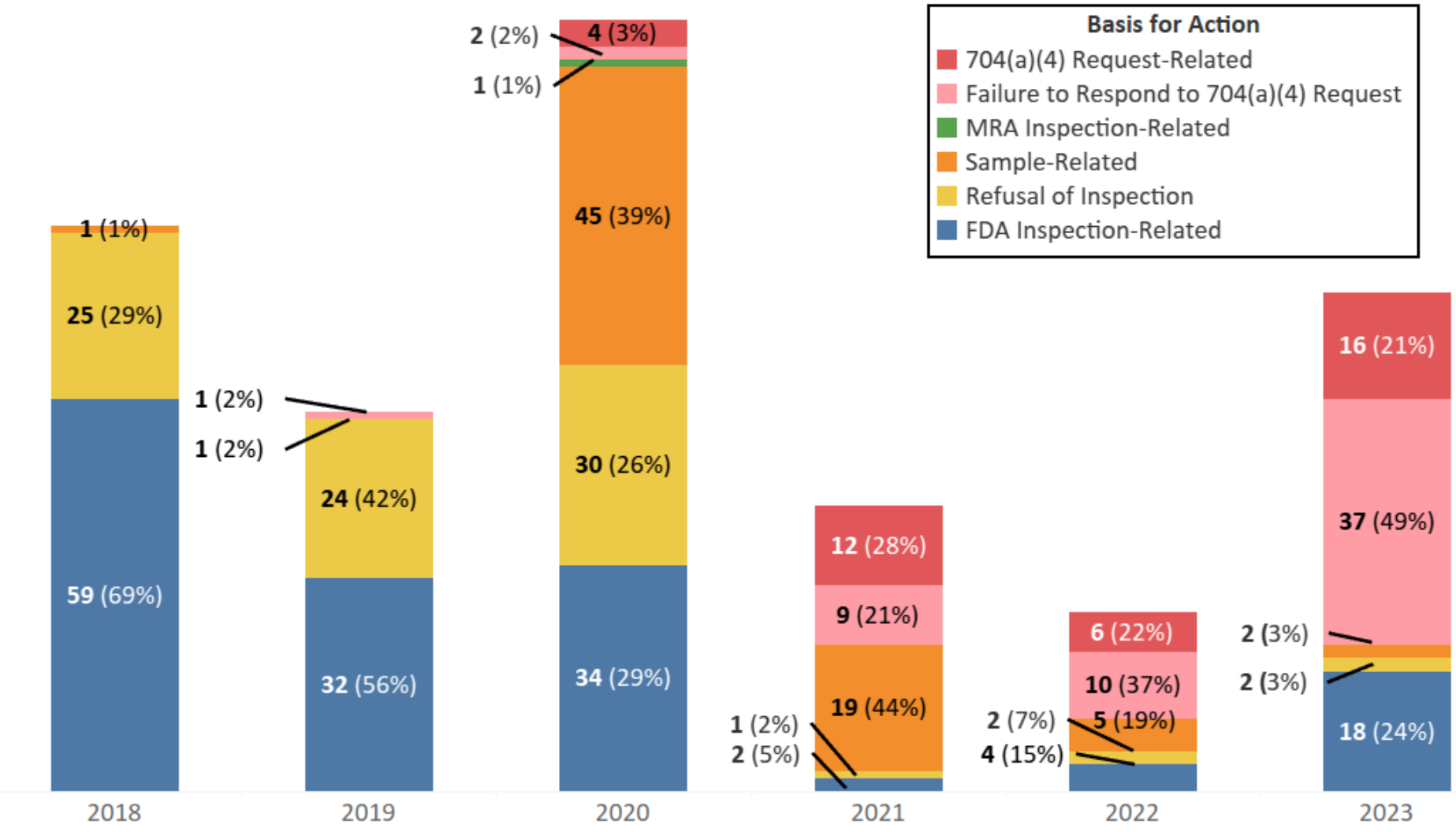
Warning Letters Issued 10/1/2017 to 9/30/2022

Import Alert Cases FY2023*



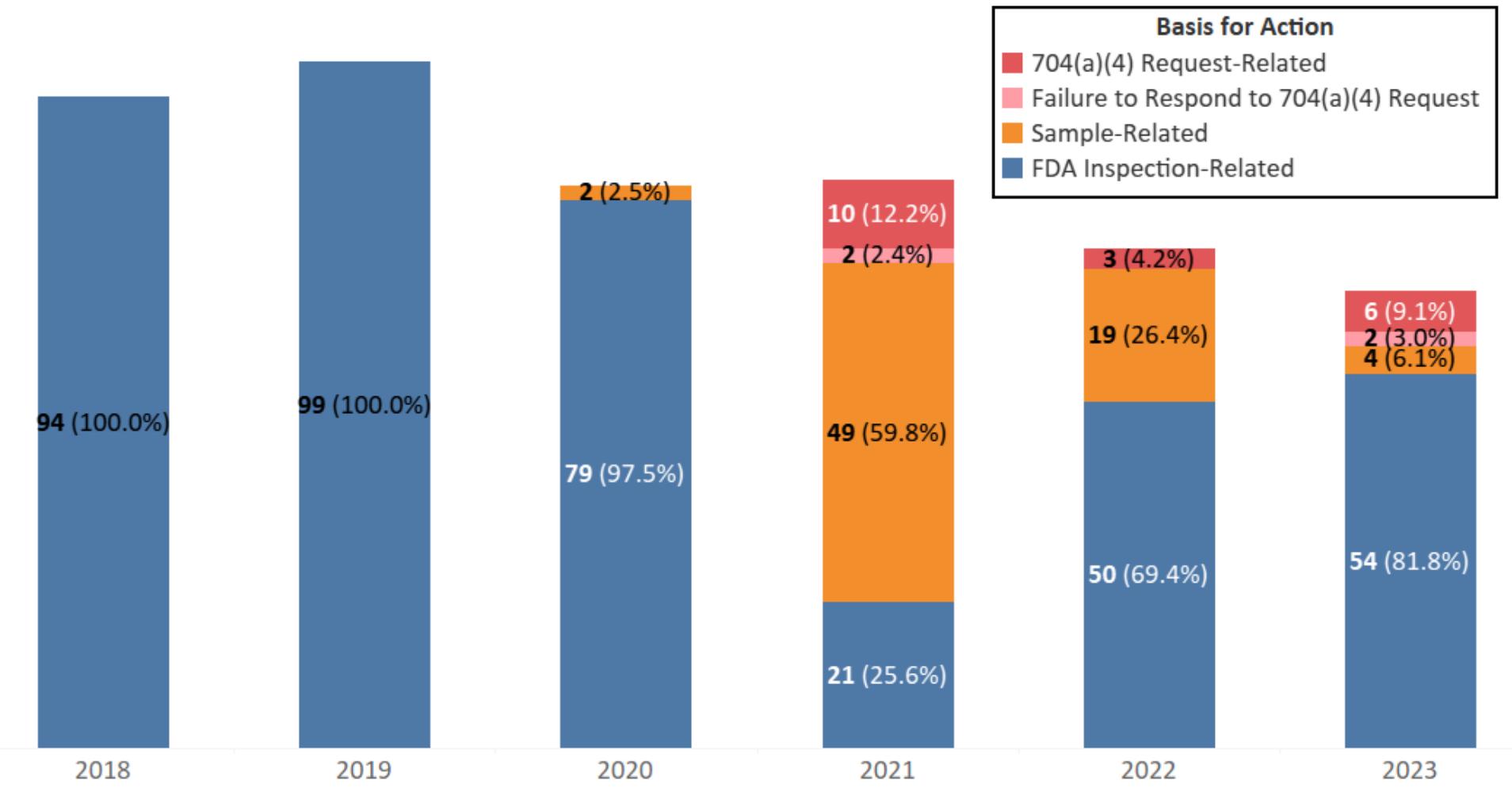
*as of 7/31/2023

Shift in Source of Drug Adulteration
Import Alert Cases FY18-23*



*as of 7/31/2023

Shift in Source of Drug Adulteration Advisory Actions –Warning Letters FY18-23*



*as of 7/31/2023

Key Takeaway

- During the Pandemic, as travel restrictions reduced inspections, FDA used alternate evidence sources.

- As FDA ramps inspections back up, inspection-based actions are increasing in parallel.
  - Especially as FDA prioritizes inspections based on risk

- However, actions from alternates to inspections remain, particularly from:
  - Sampling
  - 704(a)(4) Record Requests

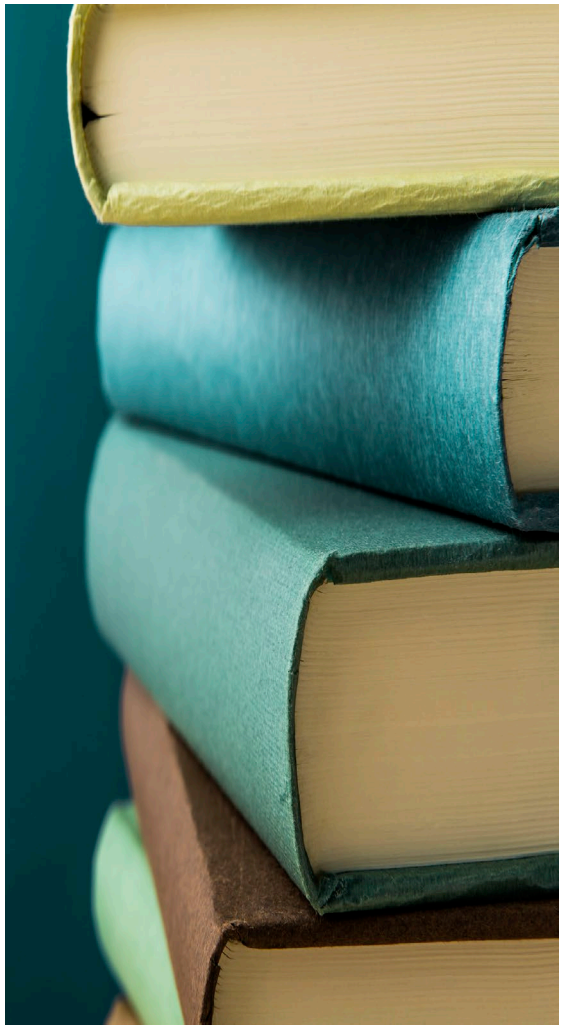
Parametric Release Q&A

What is Parametric Release

- Definition
- "Parametric release is defined as a sterility assurance release program where demonstrated control of the sterilization process enables a firm to use defined critical process controls, in lieu of the sterility test, to fulfill the intent of 21 CFR 211.165(a), and 211.167(a).5 Under this strategy, market release of terminally sterilized products can be based upon meeting the defined sterilization parameters and not on performing an approved sterility test. Meeting the requirements of the parametric release process can provide greater assurance that a batch meets the sterility requirement than can be achieved with a sterility test of finished units drawn from the batch."

- From FDA's *Guidance for Industry Submission of Documentation in Applications for Parametric Release of Human and Veterinary Drug Products Terminally Sterilized by Moist Heat Processes*

- https://www.fda.gov/media/71461/download



Sterilization

- Note that the definition talks about the "sterilization process"
  - This means a terminal sterilization process, with an active mode of lethality, typically heat.
  - And under CGMP, these process must be validated with data to ensure sterilization of all units.
- Recently FDA has encountered misinterpretation of the applicability of parametric release as suitable for aseptic processing.

Terminal vs Aseptic Operations

Factor	Terminal Sterilization	Aseptic Processing
Products are rendered sterile in their final, sealed units	Yes	No
Discrete physical parameters (e.g., temperature, pressure, and time) are continuously measured and controlled with robust precision and accuracy	Yes	No, only indirect measurements of sterility hazards.
Thermal lethality can be determined (i.e., sterility can be confirmed) through adherence to sterilization cycle parameters coupled with a sterilization load monitor that satisfies the requirement for a sterility test (see § 211.167(a))	Yes	No

Updated CGMP Q&A

- **Question**: Is parametric release an appropriate control strategy for sterile drug products that are not terminally sterilized?

- **Short Answer**: **NO**. Although parametric release may be appropriate for terminally sterilized products, there are inherent differences between the production of sterile drug products using terminal sterilization and aseptic processing.

- Even contemporary aseptic operations conducted in closed RABS and isolators can experience sterility and media fill failures.

- For aseptic processing operations, the sterility test is an essential element to monitor the state of control of an aseptic operation, and it is the last step in a series of fundamental, required controls that collectively contribute to the minimum assurance that a given manufacturing operation produced a drug that meets its sterility claim.

- More can be found on FDA's CGMP Q&A website, which FDA updated on 8/11/2023:

  https://www.fda.gov/drugs/guidances-drugs/questions-and-answers-current-good-manufacturing-practice-regulations-production-and-process#22

FDA Review of Parametric Release

- For application holders, to obtain approval to conduct parametric release of a terminally sterilized product, submit data via the application for FDA review.
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-documentation-applications-parametric-release-human-and-veterinary-drug-products

- However, after approval, firms should periodically monitor, review, and understand the production facility's microbiological flora and fauna for changes.
  - If new potentially highly resistant organisms or abnormally high bioburden counts are detected prior to the terminal sterilization process, the firm may need to update and validate their processes accordingly.

- And, while FDA's approves parametric release for certain processes, FDA can, and has, revoked/suspended parametric release based upon further information found via inspection or otherwise.

Multidose Opthalmics

Opthalmic Requirements

- 21 CFR 200.50 Ophthalmic preparations and dispensers:

- "(a)(2) The Food and Drug Administration concludes that all such preparations, if they are not sterile, fall below their professed standard of purity or quality and may be unsafe." In a statement of policy issued on September 1, 1964, the Food and Drug Administration ruled that liquid preparations offered or intended for ophthalmic use that are not sterile may be regarded as adulterated within the meaning of section 501(c) of the Federal Food, Drug, and Cosmetic Act (the act)…"

Multidose Opthalmics Requirements

- And for multidose ophthalmic products:
- 200.50 (b)(1) “Contain one or more suitable and harmless substances that will inhibit the growth of microorganisms; or
- (2) Be so packaged as to volume and type of container and so labeled as to duration of use and with such necessary warnings as to afford adequate protection and minimize the hazard of injury resulting from contamination during use.”

Preservatives

- Multidose opthalmics typically use preservatives or come in packages comprised of multiple single use blow fill sealed units.

- But what can happen if a multidose ophthalmic doesn’t contain a preservative?

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

FDA is warning consumers and health care practitioners not to purchase and to immediately stop using EzriCare Artificial Tears or Delsam Pharma's Artificial Tears due to potential bacterial contamination. Using contaminated artificial tears increases risk of eye infections that could result in blindness or death. Patients who have signs or symptoms of an eye infection should talk to their health care provider or seek medical care immediately.

These are over-the-counter products, manufactured by Global Pharma Healthcare Private Limited, intended to be sterile.

Global Pharma initiated a voluntary recall at the consumer level of all unexpired lots of EzriCare Artificial Tears and Delsam Pharma's Artificial Tears. FDA recommended this recall due to the company's current good manufacturing practice (CGMP) violations, including lack of appropriate microbial testing, formulation issues (**the company manufactures and distributes ophthalmic drugs in multi-use bottles, without an adequate preservative**), and lack of proper controls concerning tamper-evident packaging.

https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-consumers-not-purchase-or-use-ezricare-artificial-tears-due-potential-contamination

COMPANY ANNOUNCEMENT

Global Pharma Healthcare Issues Voluntary Nationwide Recall of Artificial Tears Lubricant Eye Drops Due to Possible Contamination

When a company announces a recall, market withdrawal, or safety alert, the FDA posts the company's announcement as a public service. FDA does not endorse either the product or the company.

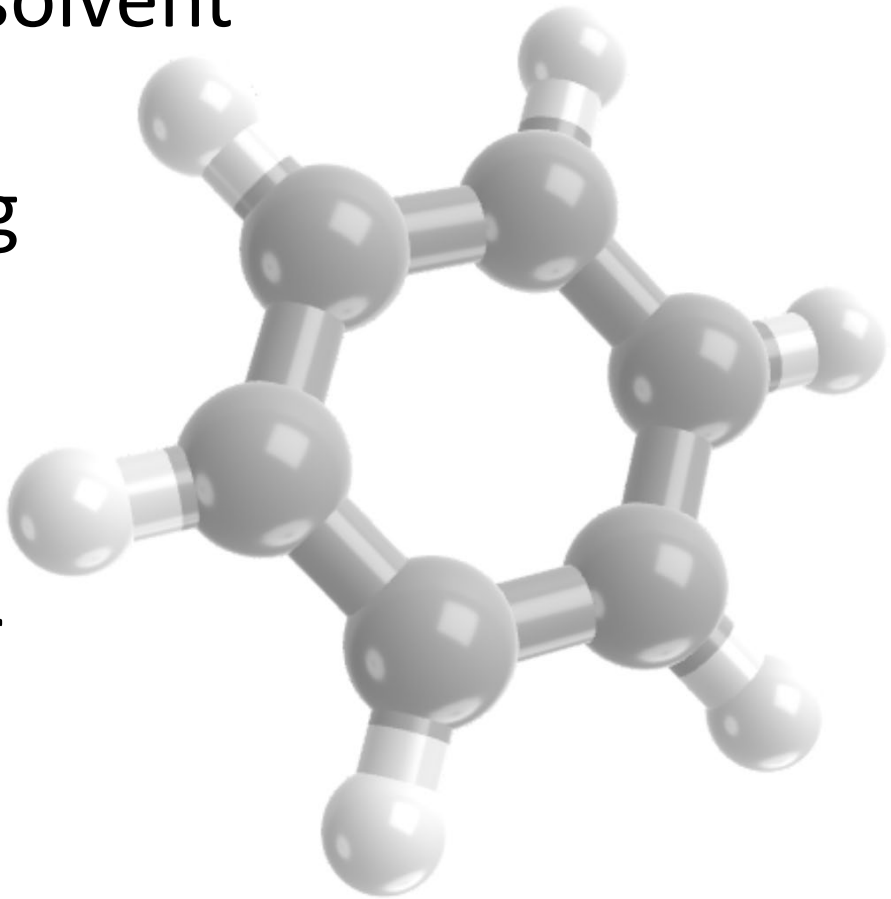
Read Announcement | View Product Photos

https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/global-pharma-healthcare-issues-voluntary-nationwide-recall-artificial-tears-lubricant-eye-drops-due

Benzene in Excipients

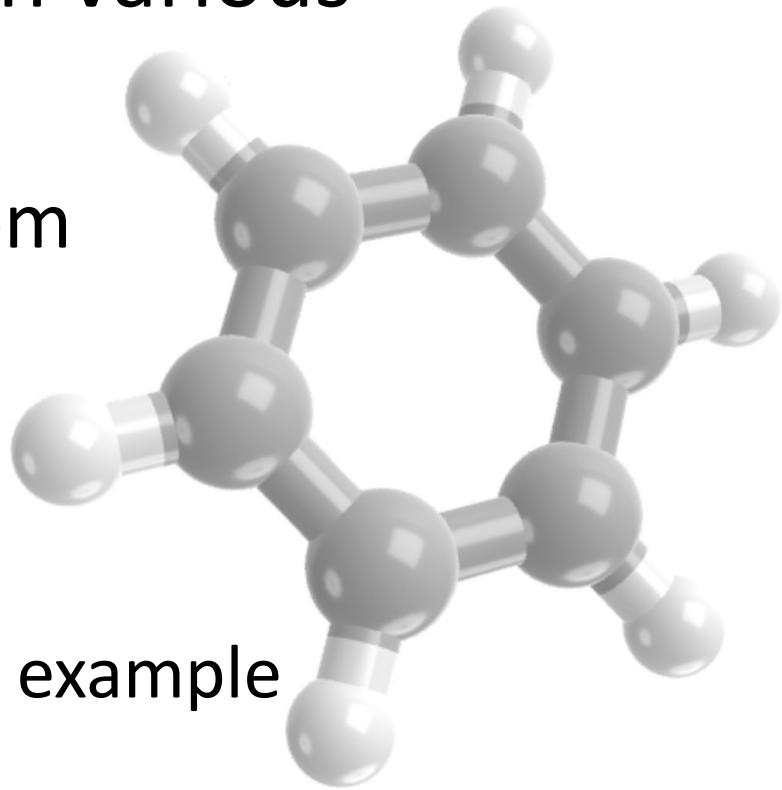
Benzene Background

- Benzene is a hydrocarbon
- Used as an industrial solvent
- Can be sourced from petrochemical refining operations
- Is a known human Carcinogen
- Its use as a solvent for pharmaceutical use is restricted



Benzene Presence in Excipients

- Benzene can be found in various excipients:
  - As a residual solvent from production
    - In certain carbomers
  - As a degradant
    - Of sodium benzoate for example
  - Or as an impurity
    - Particularly in other hydrocarbons



Benzene Prescence in Excipients

- FDA has been active in the benzene space for several years:
  - In early 2020, FDA met with USP regarding omitting monographs for carbomers made with benzene as a solvent:
    - https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/carbomer_monographs_letter_REF11-22-001-PN.pdf
  - Multiple recalls related to FDA testing finding unacceptable levels of benzene in drug products.
  - In late 2021, FDA put out a statement on Benzene for industry:
    - https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs

FDA Statement on Benzene

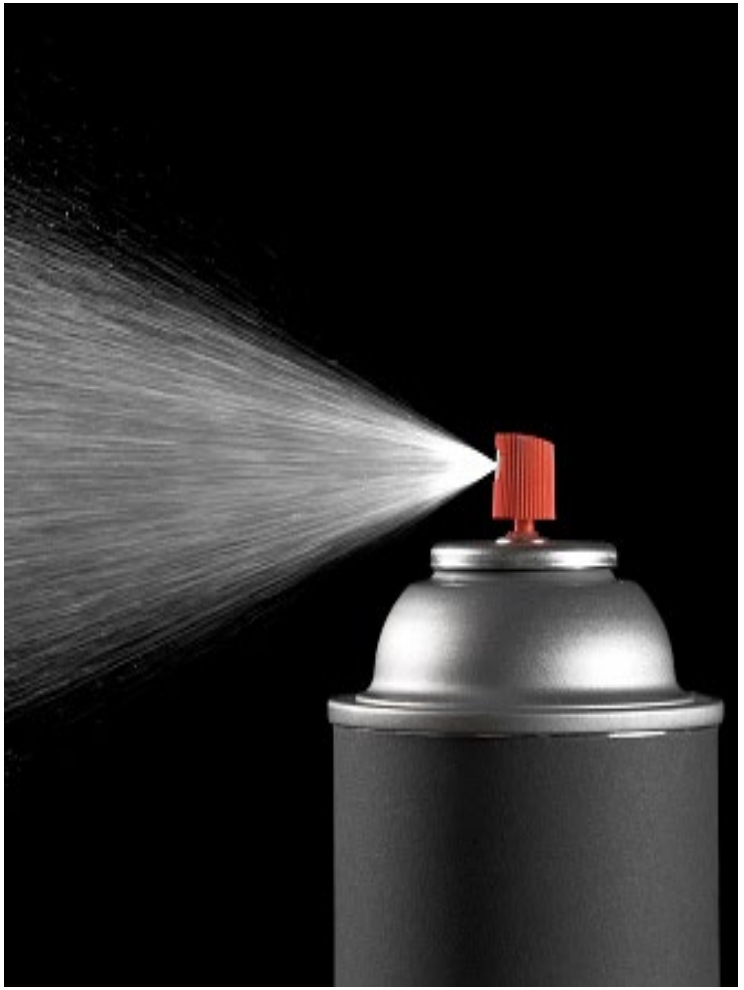
- "FDA reminds drug manufacturers they are required to establish scientifically sound and appropriate specifications and test procedures to assure drug components (active and inactive ingredients) and finished drug products conform to appropriate quality specifications (21 CFR 211.84, 21 CFR 211.160). This includes testing of raw materials and finished product batches (21 CFR 211.165) prior to release to ensure they meet appropriate specifications for identity, strength, quality, and purity.

- One way manufacturers can meet the requirements of 211.84, 211.160 and 211.165 is by using tools such as risk assessments to determine they have the appropriate specifications, test methods, and controls to ensure drugs are free from contamination. FDA has discussed with manufacturers conducting risk assessments to evaluate the possible presence of benzene in their drug products and components, including active ingredients and inactive ingredients. **In particular, FDA has also discussed with manufacturers the need for a special focus on ingredients that are hydrocarbons or are manufactured with benzene or other hydrocarbons."**

Case Example: Are You Sure You Know Where It Came From?

- Background
  - Drug product contract manufacturer specializes in aerosol products
  - Recalls occur due to elevated levels of benzene
  - Suspected root cause is related to benzene impurity in isobutane (hydrocarbon propellent)

- As part of FDA's investigation, FDA conducts a for cause inspection to, in part:
  - Evaluate the firm's investigation
  - Determine if the recall scope was adequate



Case Example: Are You Sure You Know Where It Came From?

- From the resulting Warning Letter:
  - "Your firm failed to perform adequate investigations into benzene contamination in your drug products as high as 13.3 parts per million (ppm). After obtaining information, including data from your customers, indicating that your finished drug products manufactured with isobutane propellants were contaminated with benzene, **your propellant investigation was limited to isobutane propellants. However, you failed to expand your investigation to other propellants, such as dimethyl ether, when you received information from a customer that your cosmetic products using dimethyl ether as the propellant also contained unacceptable levels of benzene.** We note that you also use dimethyl ether as a propellant in drug products. Your investigation, focused on isobutane's role in the benzene contamination, was therefore flawed…"

- FDA's Takeaway:
  - The contamination could be from one or multiple raw materials, but there also could be cross contamination at work…

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/accra-pac-inc-dba-voyant-beauty-643600-04202023

Case Example Part 2: And Did You Remove All of It?

- From the same Warning Letter:

"During the inspection, FDA investigators collected samples of three drug products. FDA laboratory testing of these samples found the following:

Product Name	Customer Lot Number	Expiration Date	Benzene Test Results (ppm)
Redacted	**Redacted**	**Redacted**	6
Redacted	**Redacted**	**Redacted**	3
Redacted	**Redacted**	**Redacted**	1

"FDA recommended your customer, **Redacted**, consider removing the adulterated batch of **Redacted** drug product from the U.S. market.

…**Redacted** expanded an ongoing voluntary nationwide recall to include the contaminated batch of **Redacted** due to the presence of benzene above 2 ppm."

- Key Takeaway:
  - Don't jump to conclusions when investigating contamination, and cast a wide net when trying to determine its scope

Diethylene Glycol/Ethylene Glycol (DEG/EG)

Background on DEG/EG

- Diethylene glycol (DEG) is an industrial chemical, used as an antifreeze, and is poisonous.
- Sadly, FDA has a long history with DEG/EG poisonings.
- 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

- FDA has a specific guidance related to CGMP controls for DEG/EG:
  - *Guidance for Industry Testing of Glycerin for Diethylene Glycol*
    - https://www.fda.gov/media/167974/download

Background on DEG/EG

- Historically, DEG/EG has been substituted, in part or in whole, in various excipients, and for economic gain.
- Typically in the distribution/repacking supply chain
- And lacking CGMP controls at finished dosage form sites allowed for the contamination to enter drug products.
- Periodic DEG/EG events have occurred:
  - DEG substitution for glycerin in Central America in the late 2000s,
  - And FDA took actions against Chinese toothpastes containing DEG in 2007
- Sadly, history is again repeating:
  - 2022/2023 outbreaks in children's drug products overseas

Recent DEG/EG Outbreaks Overseas

In late 2022/2023, multiple outbreaks of DEG/EG contamination occurred in:

- **Gambia**

https://www.who.int/news/item/05-10-2022-medical-product-alert-n-6-2022-substandard-(contaminated)-paediatric-medicines

- **Indonesia**

https://www.who.int/news/item/02-11-2022-medical-product-alert-n-7-2022-substandard-(contaminated)-paediatric-liquid-dosage-medicines

- **Uzbekistan**

https://www.who.int/news/item/11-01-2023-medical-product-alert-n-1-2023-substandard-(contaminated)-liquid-dosage-medicines

- **Marshall Islands**

https://www.who.int/news/item/25-04-2023-medical-product-alert-n-4-2023--substandard-(contaminated)-syrup-medicines

- **Iraq**

https://www.who.int/news/item/07-08-2023-medical-product-alert-n-6-2023--substandard-(contaminated)-syrup-medicines

- Information thus far indicates the contaminated finished drug products were manufactured in India and Indonesia.

FDA's Role

- As the outbreaks were tackled, FDA extensively interacted with WHO, other regulators, and industry.

- Unlike the 2006 outbreak of DEG/EG substitution in glycerin, these appear to be related to substitution of DEG/EG in propylene glycol.

- Economic data indicates that ethylene glycol costs half as much as propylene glycol, which may be a financial motive behind the substitution.

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

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?

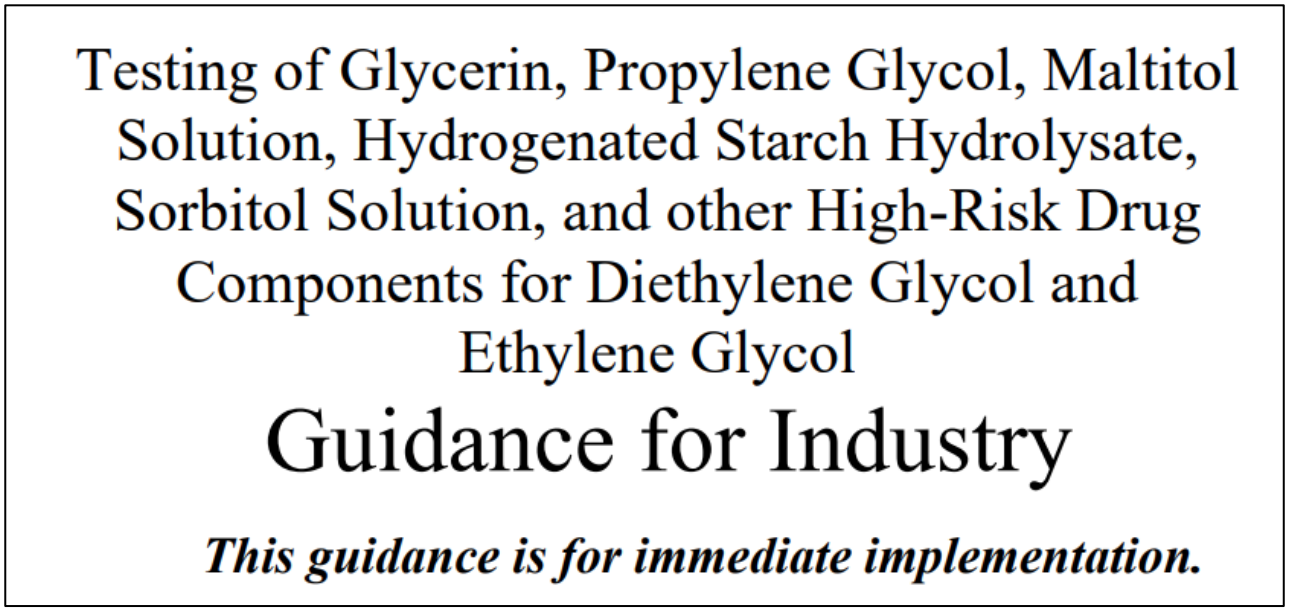
- **Answer**: Potentially for some attributes, **but never for identity**:

- 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 substitution have 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

Updated Guidance



https://www.fda.gov/media/167974/download

- In May, FDA updated the guidance on testing requirements for DEG/EG in High Risk Drug Components
- Elucidates what was discussed on the previous slide
- Previous version focused on Glycerin, now expanded to cover additional excipients

Why is FDA so Strict?

Can You Spot What's Wrong?

- https://nasional.kompas.com/read/2022/11/09/14492351/bpom-temukan-cemaran-etilen-glikol-sampai-99-persen-seharusnya-01-persen

A Wolf in Sheep's Clothing – Pure EG

- https://nasional.kompas.com/read/2022/11/09/14492351/bpom-temukan-cemaran-etilen-glikol-sampai-99-persen-seharusnya-01-persen

Recent DEG/EG Compliance Actions

Heightened Supply Chain Monitoring

- As FDA evaluated the recent outbreaks, FDA set up screening criteria for drugs at risk.
- 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

- FDA has been evaluating manufacturers, focusing on firms using at risk excipients and located in high-risk geographies, including (but not limited to):
  - India,
  - Indonesia,
  - Gambia,
  - Uzbekistan,
  - Korea,
  - The Philippines,
  - And the Marshall Islands

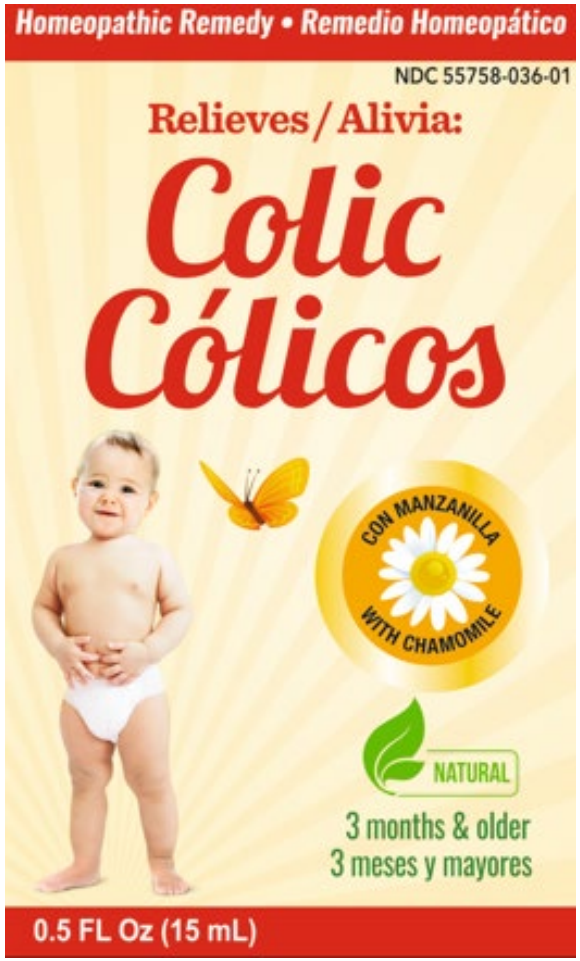
- As of today we have sent over 150 704(a)(4) records requests related to required CGMP controls for DEG/EG.

- Thus far, over 20 firms have been placed on import alert, and multiple Warning Letters were recently issued.

https://www.fda.gov/drugs/news-events-human-drugs/our-perspective-fda-actions-continue-ensure-safety-nations-drug-supply

Case Example: Lack of Controls with a Very High Risk Drug

- Background
  - Firm manufacturers drug products, including for infants.
  - Dosage form predominantly contains an excipient at risk for DEG/EG substitution.
  - Manufacturer located in a country linked to current DEG/EG outbreaks.
  - FDA asked firm if they tested for DEG/EG in the excipient.



Case Example: Lack of Controls with a Very High Risk Drug

- From the Resulting Warning Letter:

"Based on the records and information you provided, **you did not demonstrate that you adequately tested each shipment of each lot of the incoming high-risk component, glycerin, you use in manufacturing drug products to determine their appropriate identity**....

Additionally, 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)....

Note that FDA placed all drugs and drug products manufactured by your firm on Import Alert 66-40 on March 3, 2023"

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

In Summary

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 against firms with poor CGMP or when other information calls into question the quality of drugs for U.S. patients.


FDA
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ADMINISTRATION