U.S. FOOD & DRUG ADMINISTRATION

Recent Trends in FDA Inspections of Homeopathic Drug Manufacturers

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

Outline

- What OMQ Does
- What is CGMP
- FY 2020 Actions
- How Homeopathy Fits In
- Homeopathic Warning Letter Case Studies
- Recent Hand Sanitizer Regulatory Actions
- Update on Alcohol Testing – Including for Homeopathy
- Key Takeaways

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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.

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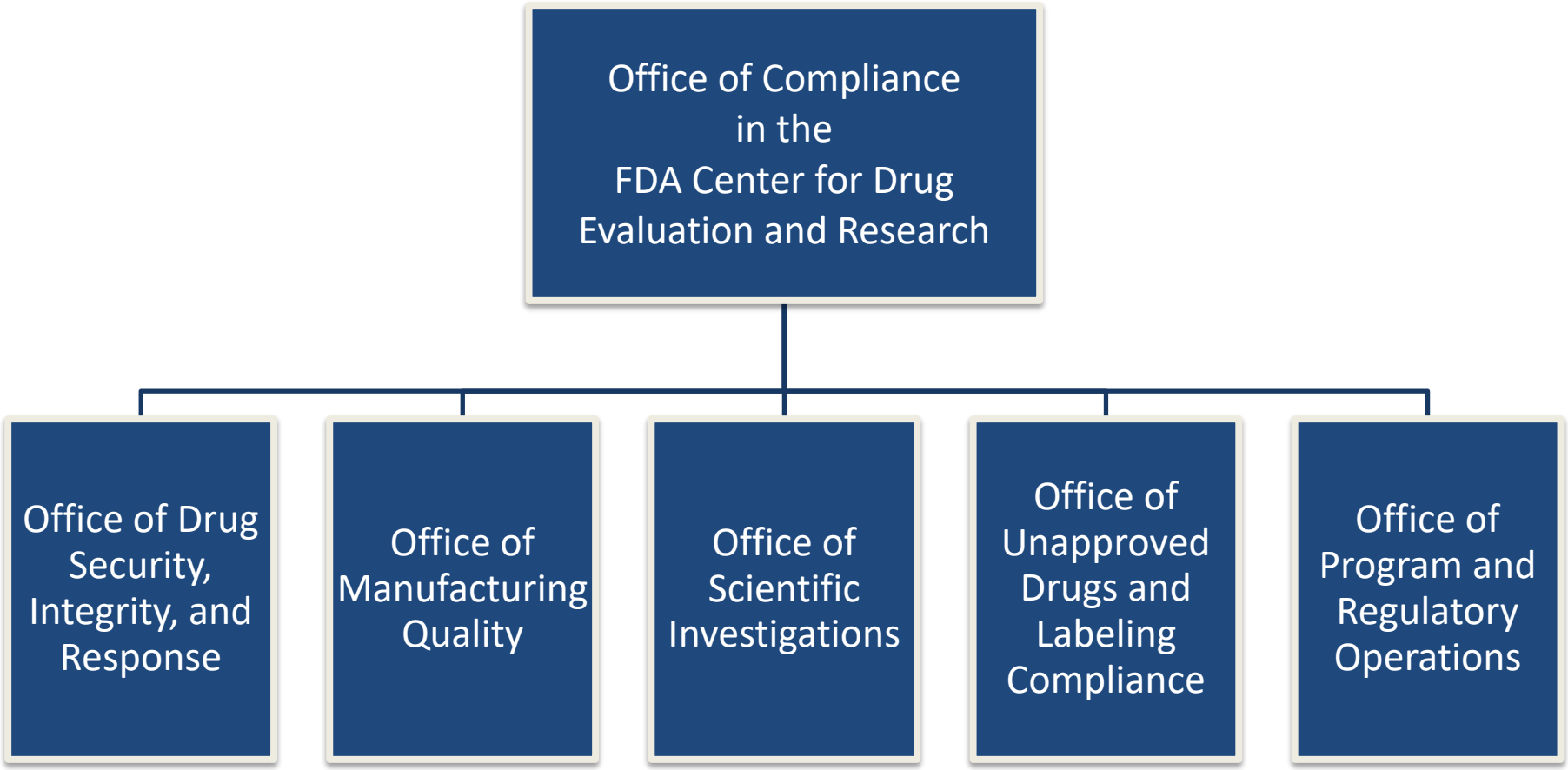

What OMQ Does

- 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

Current Good Manufacturing Practice

What is CGMP?

CGMP Legal Authority

Section 501(a)(2)(B) requires conformity with CGMP.

A drug is ***adulterated*** if the methods, facilities, or controls, used in its manufacture, processing, packing, or holding do not conform to CGMP to assure that such drug meets purported characteristics for **safety, identity, strength, quality, and purity.**

What is CGMP?

Requirements to ensure drugs:

- Meet quality specifications, including purity
- Are safe for use
- Have ingredients and strength they claim to have

Regardless of Regulatory Pathway: CGMP for All

- Prescription
- Over-the-Counter (OTC)
- Biologics (BLA)
- Biosimilars (SBLA)
- Innovators (NDA)
- Generics (ANDA)
- OTC Monograph drugs
- **Homeopathic drugs**
- 503B Pharmacy compounded drugs
- Any other article meeting the definition of “drug” under 21 USC 321(g)

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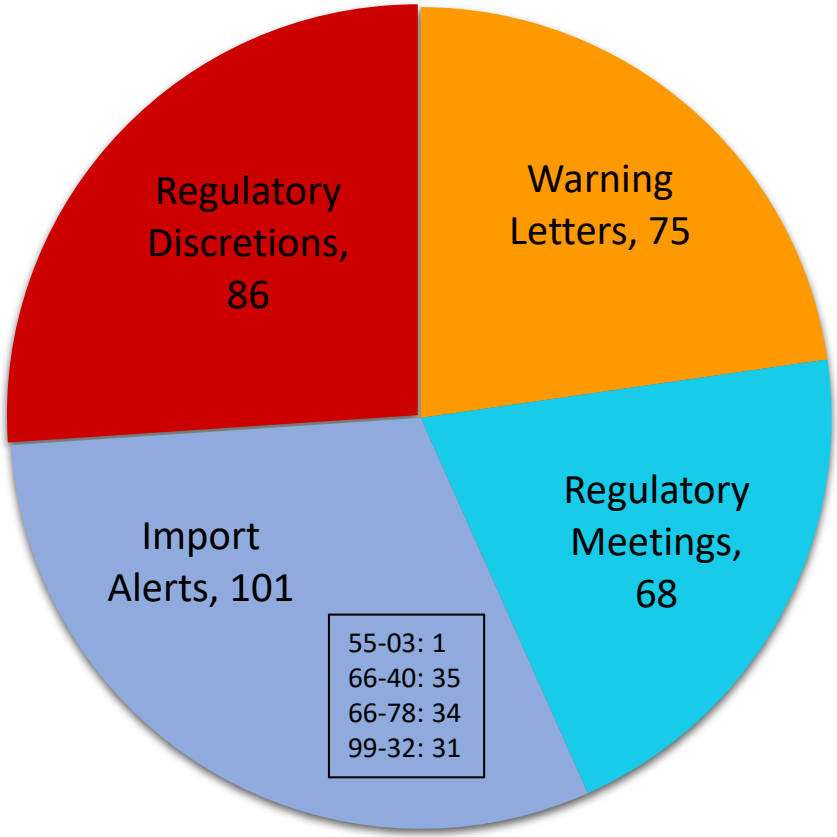
FY 2020 Actions

Enforcement and Advisory Tools

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

FY2020* Regulatory Actions

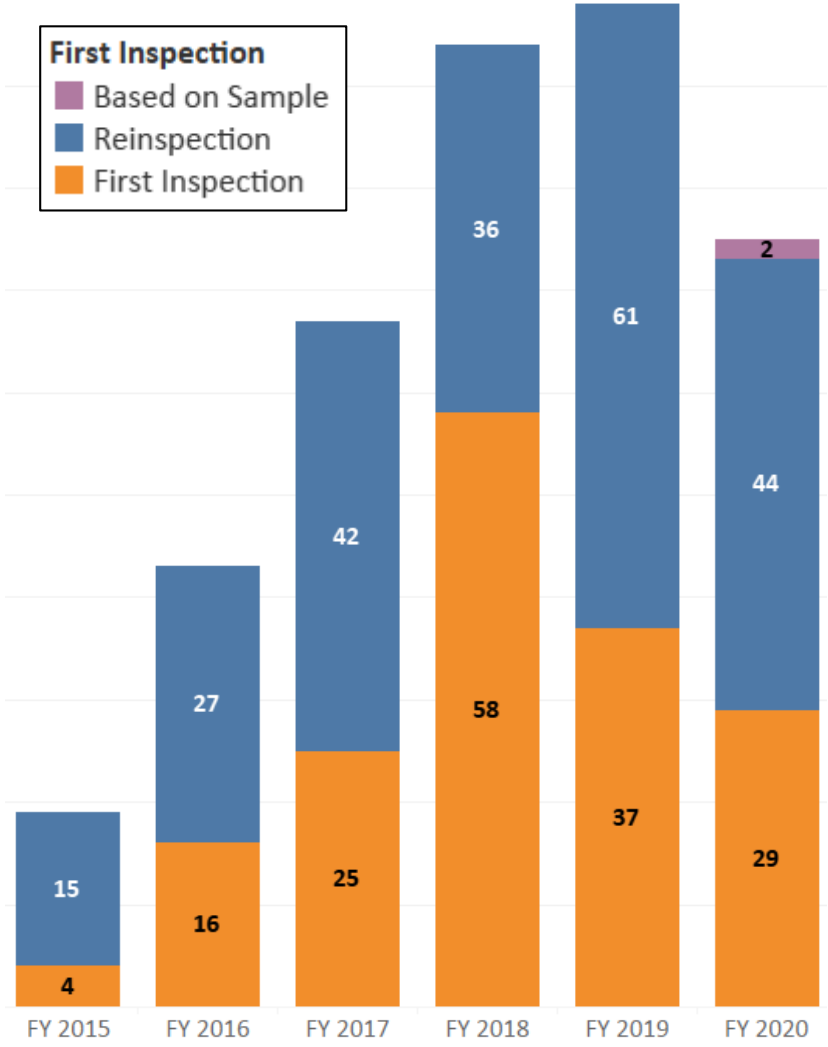


Excludes compounding-related actions

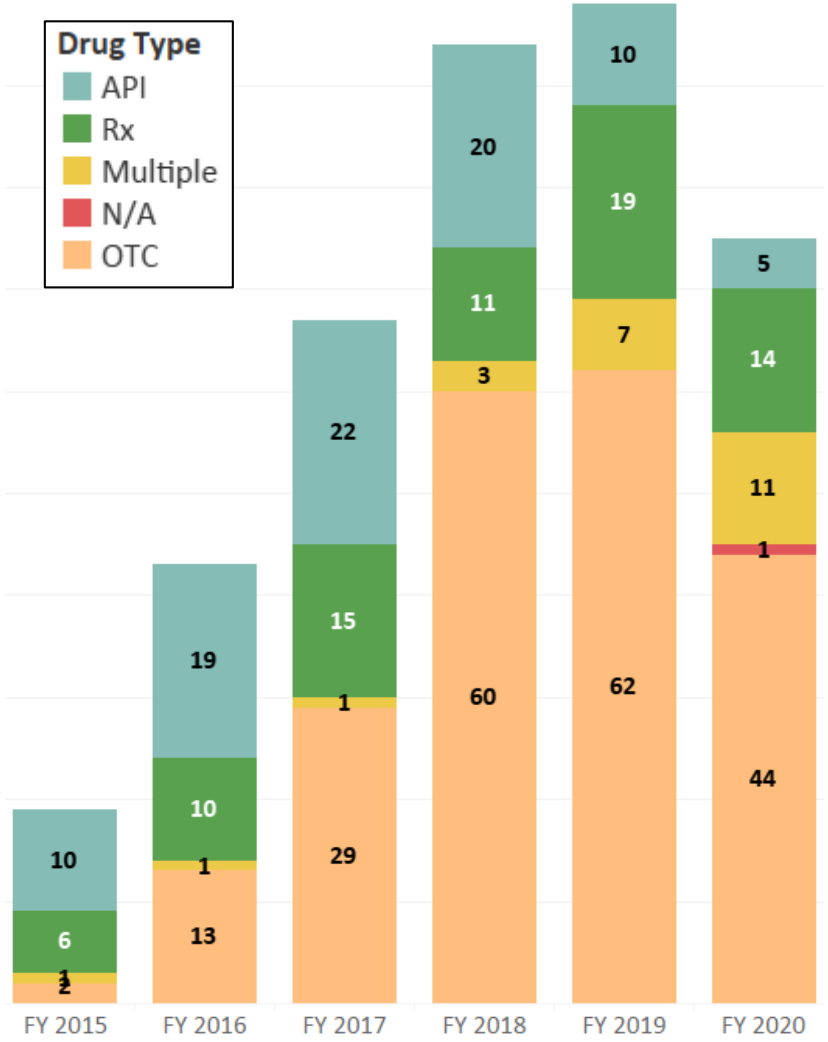
*Actions issued October 1, 2019 to August 31, 2020

Trends in CGMP Warning Letters

Warning Letters Issued after Initial Inspection vs. Reinspection by FY*

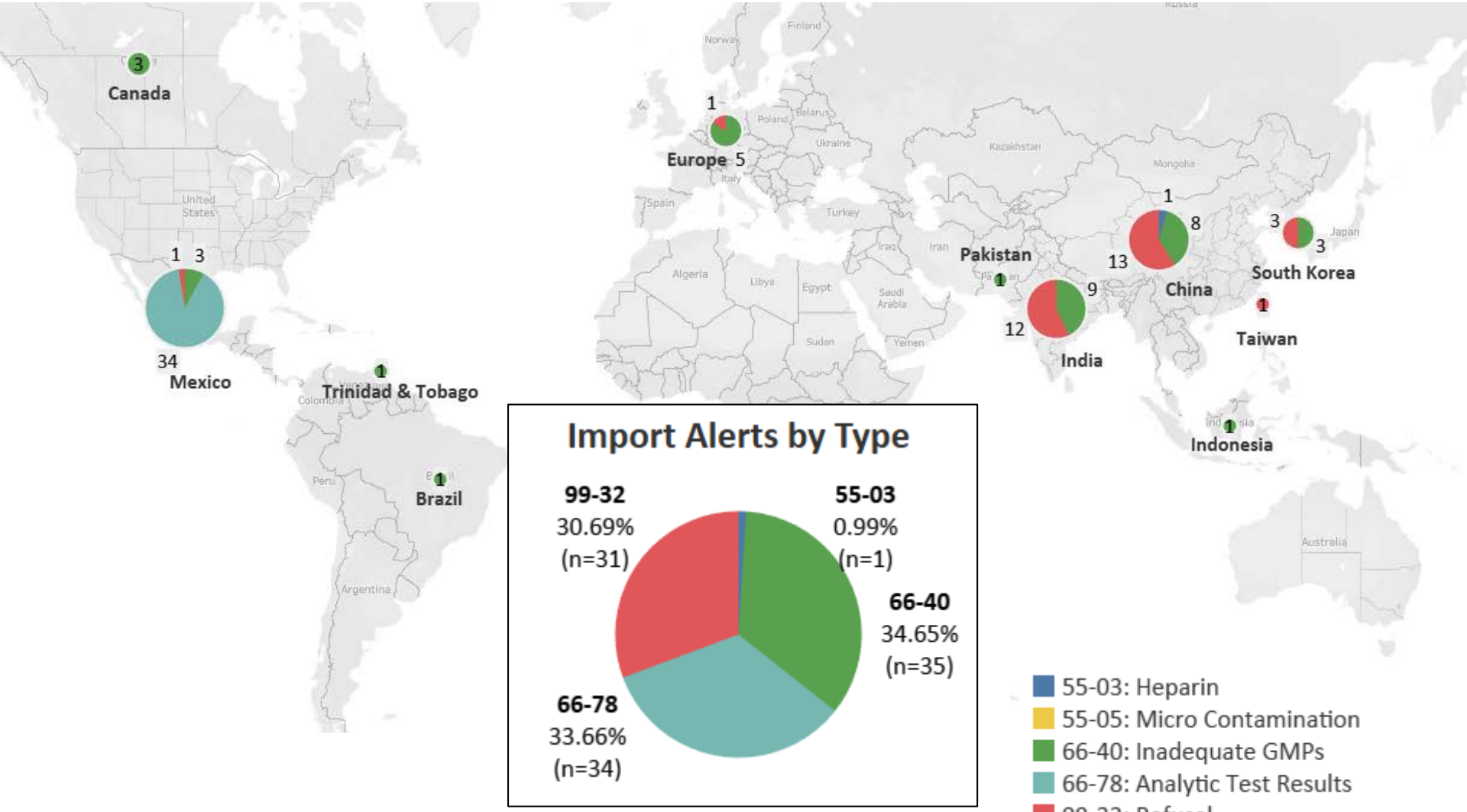


Warning Letters Issued by Drug Type Manufactured by FY*



*as of 8/31/2020

Import Alerts Issued FY20*



*as of 8/31/2020

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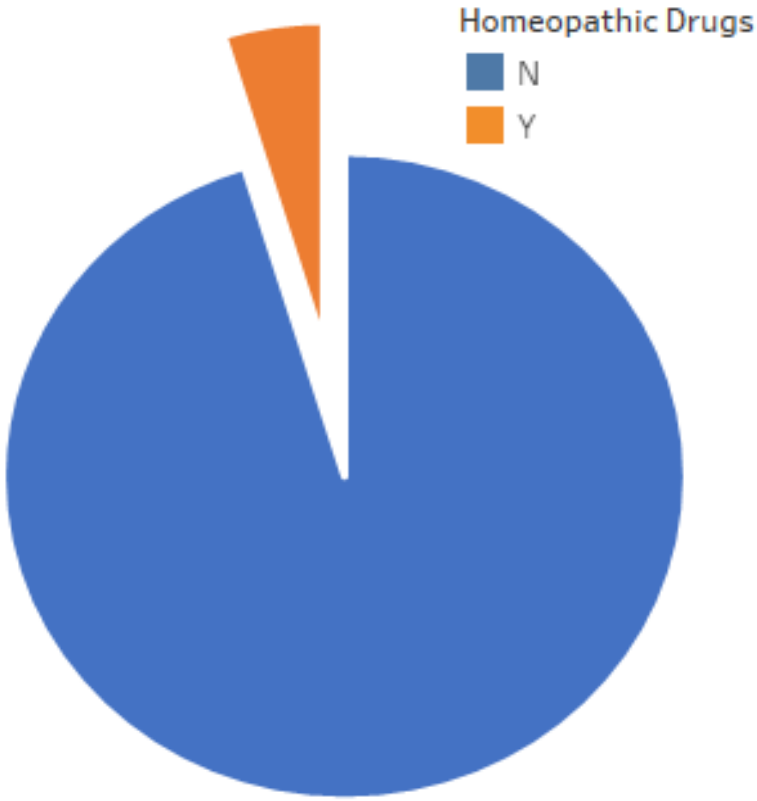
How Homeopathy Fits In

Homeopathic Manufacturing Inventory

- In the FDA inventory there are currently 186 finished dosage form manufacturers associated with Homeopathy
  - Finished Dosage Form Manufacturers (168)
  - Repackagers (18)
- Some facilities make both homeopathic drugs and others
  - Usually OTC monograph

Homeopathy represents about 2% of the inventory

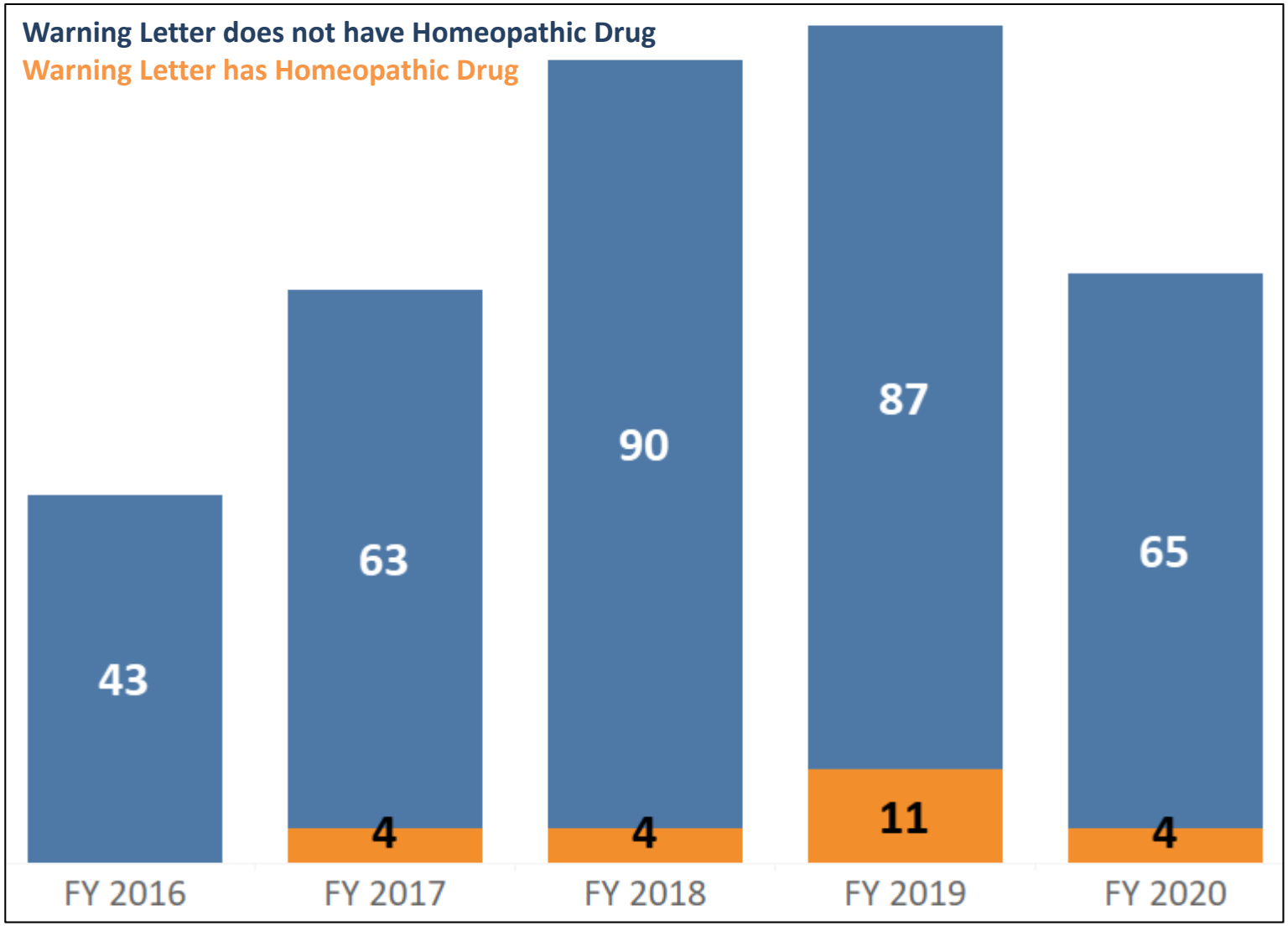


Inspectional Data of Homeopathic Drug Manufacturers

Majority of homeopathic manufacturing sites were found to be compliant with CGMP.

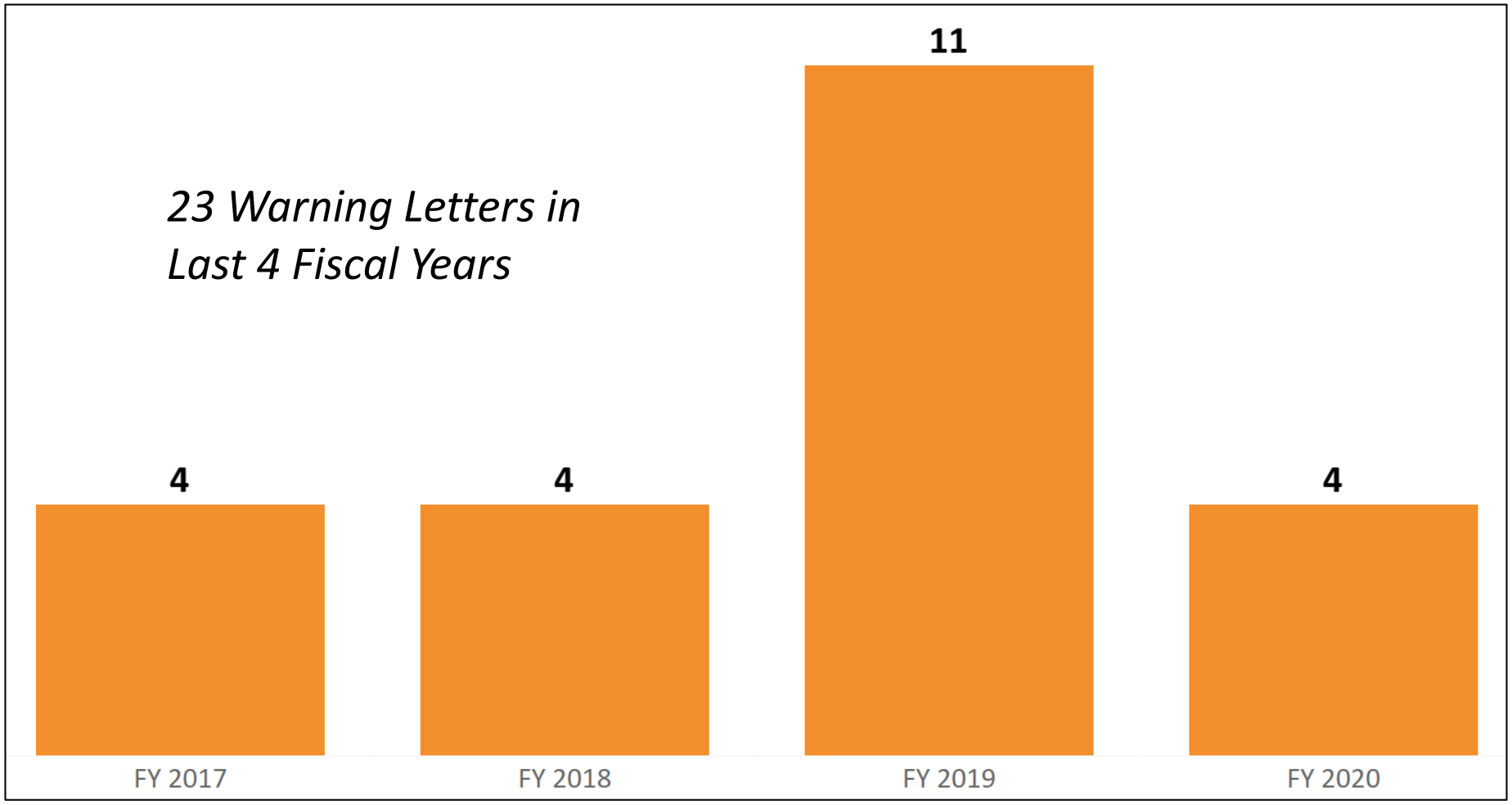
Some facilities have poor CGMP.

Warning Letters by Fiscal Year*



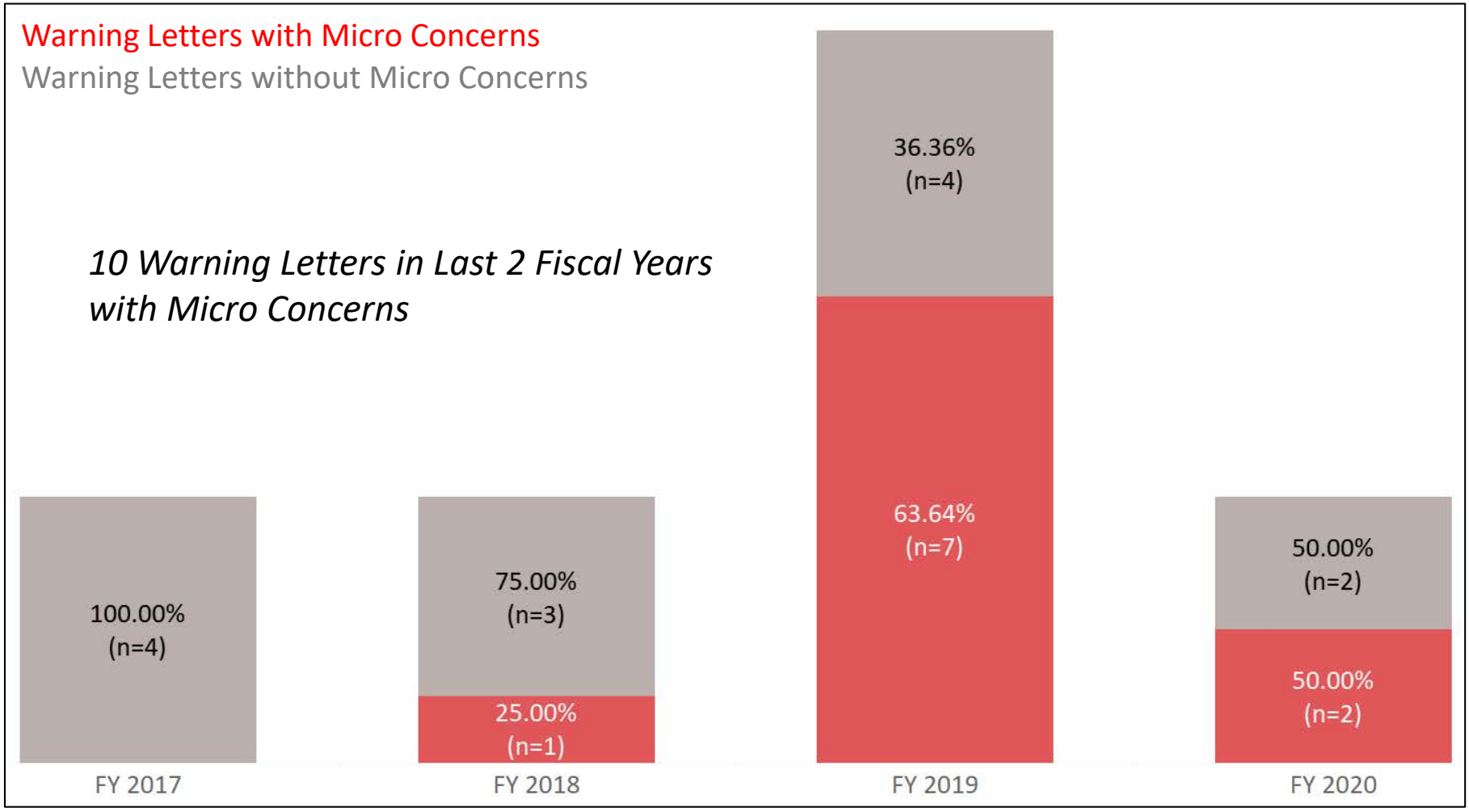
*as of 7/31/2020

Warning Letters with Homeopathic Drugs by Fiscal Year*



*as of 7/31/2020

Warning Letters with Homeopathic Drugs by FY*



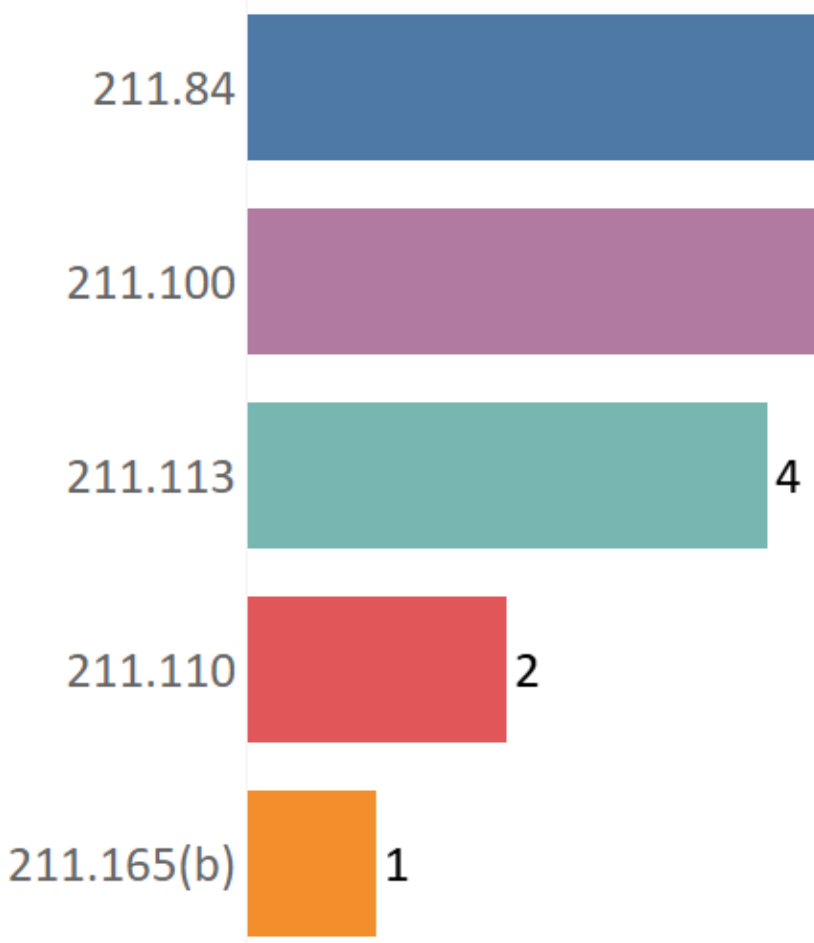
*as of 7/31/2020

List of Citations within Warning Letters with Homeopathic Drugs by FY*

Charge	2017	2018	2019	2020	Grand..
211.84(d)(1) and (2) - Components tested for identity and conformity with specifications.	3	4		2	9
211.100(a) - Validated production and process controls.	3	1	2	2	8
211.22(a) - Responsibilities of quality unit.	1		5		6
211.22(a) and (d) - Responsibilities of quality unit; written procedures.		3	1	2	6
211.192 - Investigations of discrepancies and OOS results.	1		4		5
211.113(b) - Control of microbiological contamination (sterile).		1	2	1	4
211.180(e) - No annual review of records.	1		2		3
211.67(a) - Equipment cleaning and maintenance.			2	1	3
211.165(a) - Failure to test finished products.		1		1	2
211.42(c)(10) - Separate areas to prevent contamination during aseptic processes.			2		2
211.188 - Incomplete batch production and control records.			2		2
211.165(e) - Validation of test methods.			1	1	2
211.110(a) - Adequate and validated procedures for batch uniformity.	2				2
211.84(d)(2) - Components tested for conformity with specifications.	1				1
211.22(a) and (c) - Responsibilities of quality unit.		1			1
211.67(b) - Written procedures for equipment cleaning and maintenance.		1			1
211.82(a) - Examination of untested component labelling.		1			1
211.165(a) and (b) - Failure to test finished products, including for microorganisms.		1			1
211.166(a) - Inadequate stability testing.		1			1
211.100(a) and (b) - Establish and follow procedures for production process control.			1		1
211.165(b) - Failure to test finished products for microorganisms.			1		1
211.22 - Responsibilities of quality unit.			1		1
211.22(c) - Responsibilities of quality unit.			1		1
211.56(a) - Sanitary conditions of building with no vermin.			1		1
211.63 - Equipment design, location, and maintenance.			1		1
211.84(d)(1), (2), and (3) - Components, containers, closures tested for identity and confo..			1		1
211.160(b) - Lack of established lab controls.				1	1
211.28(a) - Lack of appropriate clothing.				1	1
211.42(c)(10)(iv) and (v) - Environmental monitoring for aseptic processes and cleaning/di..				1	1
211.84(d)(1) - Components tested for identity.				1	1
Grand Total	12	15	30	14	71

*as of 7/31/2020

Specific Citations in Warning Letters with Homeopathic Drugs FY17-20*



- 12 (52%) with 211.84 citation
- 9 (39%) with 211.100 citation
- 4 (17%) with 211.113 citation
- 2 (9%) with 211.110 citation
- 1 (4%) with 211.165(b) citation

*as of 7/31/2020

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Homeopathic Warning Letter Case Studies

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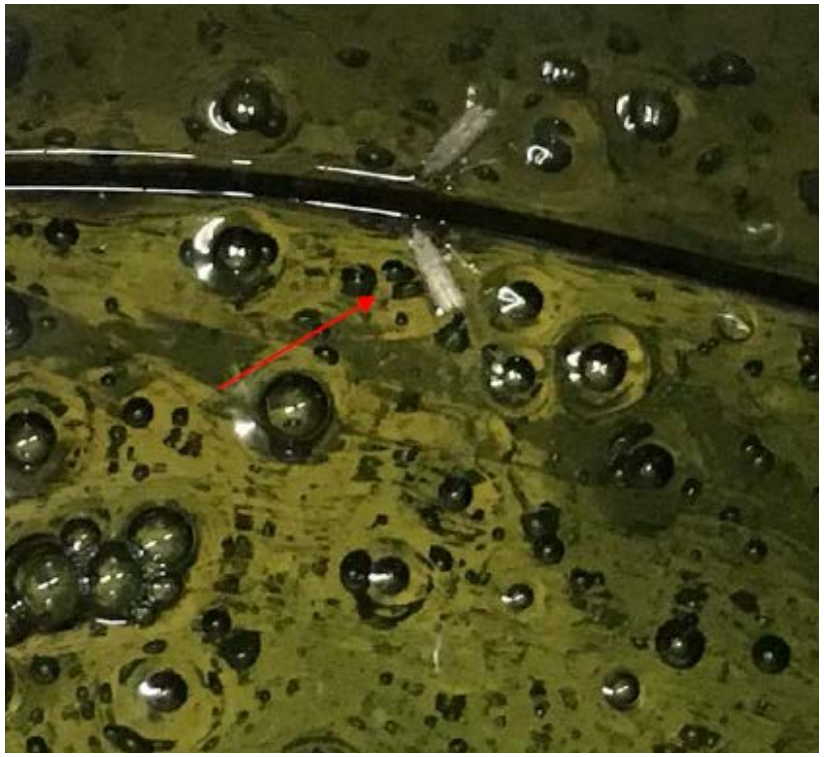
Case 1: Filth

Case 1: Filth

- Case Primer
  - Foreign Homeopathic Drug Manufacturer
  - Imported both finished drugs and tinctures/in-process materials to the United States
  - FDA conducted an on-site inspection
  - Numerous violations observed, from poor water to poor hygiene
- But, there was a showstopper…

From the Resulting Warning Letter

*"In the raw material storage room our investigator observed numerous flying insects. FDA observed your staff dispensing **[REDACTED]** raw material for use in production, batch #**[REDACTED]**, in this room and a live moth was observed floating in this raw material. You use **[REDACTED]** to manufacture your homeopathic drug products."*



But Wait, There's More…

"When the investigator pointed out the presence of this moth in your ***[Redacted]*** *raw material, you continued to manufacture homeopathic drug products using the raw material contaminated with the insect."*

Import Alert

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Case 2: Using a Bad Supplier

Case 2: Using a Bad Supplier

- Case Primer
  - Firm manufactured homeopathic drugs.
  - Firm received raw materials from various suppliers.
  - FDA conducted an inspection, and found a known violative supplier.

From The Resulting Warning Letter

"Your firm's quality unit (QU) failed to have adequate oversight for homeopathic drug products and components you receive, manufacture, or distribute. Furthermore, you lacked adequate written procedures describing the responsibilities for the QU. During the inspection, you acknowledged the failure to define the manufacturing roles and responsibilities between you and your suppliers.

*For example, **[REDACTED]** supplies you with homeopathic **[REDACTED]** and other components. On **[REDACTED]** you became aware that **[Your Supplier]** had been placed on import alert … by FDA for egregious violations of CGMP."*

Corrective Actions Driven by Inspection, vs Knowledge of Supplier…

*"Despite you becoming aware of the violative conditions described at your supplier's facility, your firm continued to distribute adulterated homeopathic drug products and components you received from **[REDACTED].** Only after the FDA inspection at your firm did you propose a potential corrective and preventive action (CAPA) plan to address the poor quality of drugs you received from **[REDACTED]**."*

*"We acknowledge you recalled homeopathic drug products manufactured and labeled for you by **[REDACTED]**"*

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Case 3: Poor CMO oversight

Case 3: Poor CMO Oversight

- Case Primer
  - Firm manufactured homeopathic drugs derived from a toxic material, in this case, *Cobra Venom.*
  - Firm outsourced manufacturing.
  - Firm provided manufacturing instructions to their contractor.
  - FDA conducted an on-site inspection of the product owner.

From the Resulting Warning Letter

"Your management confirmed the lack of a Quality Unit and acknowledged that you lack written procedures, including, but not limited to, those procedures governing the responsibilities and functions of the QU. Without an adequate QU, you lack the ability to ensure the safety, identity, strength, quality, and purity of your drug product…

In addition, when requested on inspection, you were unable to provide supportive documentation that you have qualified your CMO. Your quality agreement explicitly requires that **[Your Contractor]** maintain sufficient facilities, resources, and a qualified work force. However, there is a lack of assurance that you hired a CMO capable of manufacturing homeopathic drug products which comply with CGMP."

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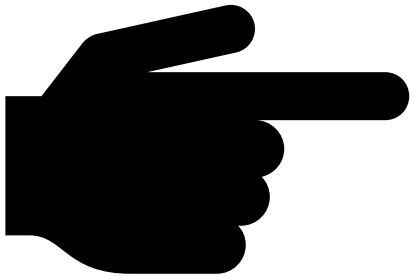
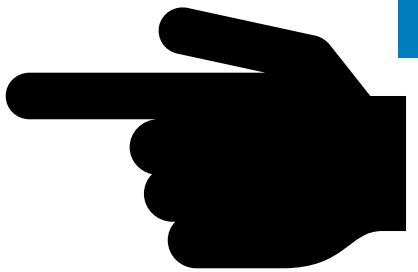
Case 4: Bad Math

Case 4: Bad Math

- Case Primer
  - FDA inspected the Contract Manufacturing Organization (CMO) that made the drug product from the previous case (Case Study 3).
  - Firm imported drugs into the United States.
- What did we find?

Finger Pointing





- CMO did not really understand dilutions, and were just following instructions their customer gave them, including formulation/dilutions instructions.
- When asked about the dilutions and the resulting drug concentration, they could not say the drugs were the same as purported on the label.
- Referred FDA to their customer for more information.

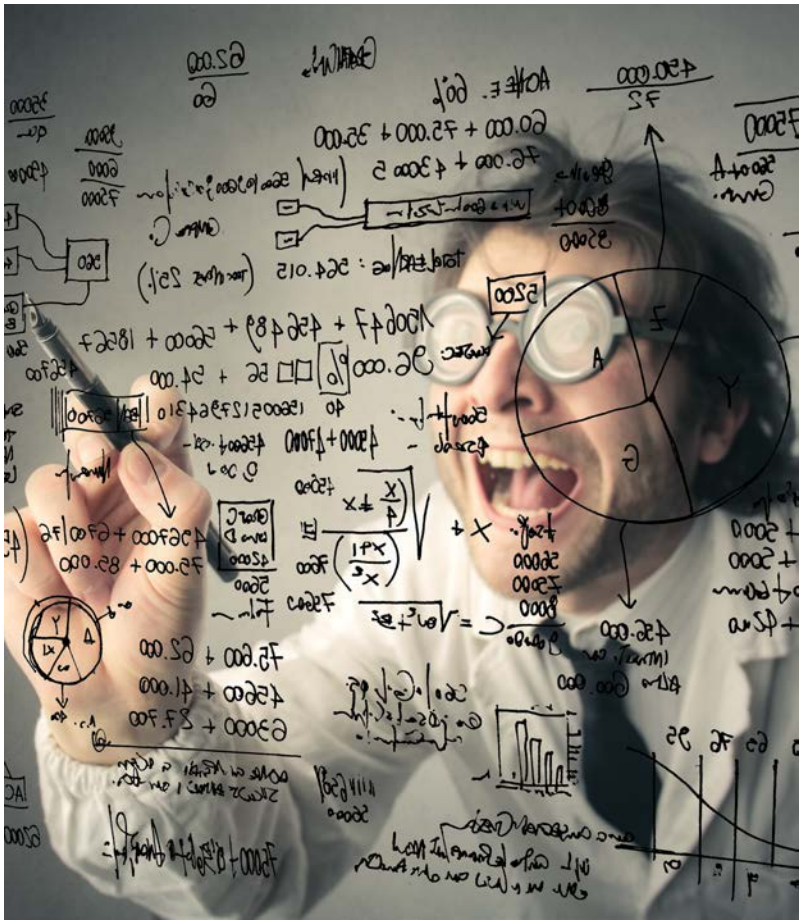
FDA collected the manufacturing records on site, and because the CMO did not do the dilution math, FDA did.

When FDA Did the Math….

Dilution Math

- Conversion Formula for Serial Dilutions vs Concentration
- g/ml = 1 x 10^-(dilutions in X)

Dilutions in X	Fraction	Concentration g/ml
1X	1/10	0.1
2X	1/100	0.01
3X	1/1,000	0.001
4X	1/10,000	0.0001
5X	1/100000	0.00001
6X	1/1,000,000	0.000001
7X	1/10,000,000	0.0000001
8X	1/100,000,000	0.00000001
9X	1/1,000,000,000	0.000000001
10X	1/10,000,000,000	0.0000000001



Manufacturing Vs Label

- Very different concentrations when compared…

Dilutions in X	Fraction	Concentration g/ml
1X	1/10	0.1
2X	1/100	0.01
3X	1/1,000	0.001
4X	1/10,000	0.0001
5X	1/100000	0.00001
6X	1/1,000,000	0.000001
7X	1/10,000,000	0.0000001
8X	1/100,000,000	0.00000001
9X	1/1,000,000,000	0.000000001
10X	1/10,000,000,000	0.0000000001

Formulation

Label Claim

End Result

- What Happened Next:
  - CMO placed on Import Alert
  - Warning Letter issued to CMO
  - Customer was also copied on the Warning Letter

- Customer lost a supply line for their drug product
  - Further Engagement with FDA after their Warning Letter

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Recent Hand Sanitizer Regulatory Actions

Hand Sanitizers

"If soap and water are not readily available, use an alcohol-based hand sanitizer that contains **at least 60% alcohol**, and wash with soap and water as soon as you can."

CDC website: https://www.cdc.gov/handwashing/hand-sanitizer-use.html

Alcohol is either ethanol or isopropyl alcohol (IPA)

Substitution Legal Authority

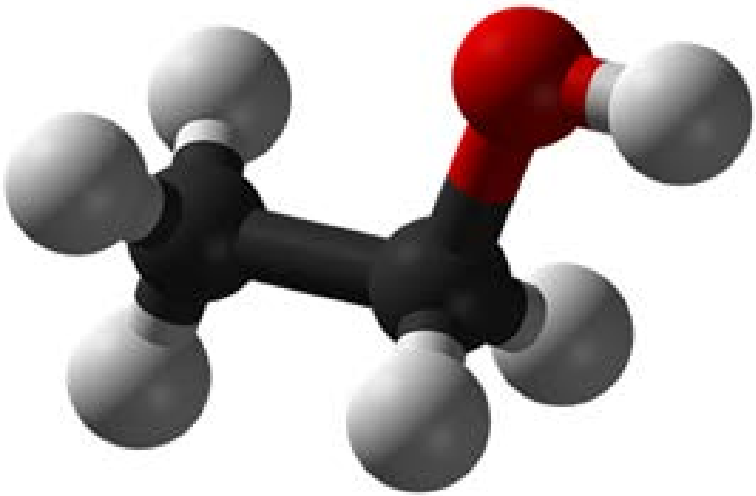
Section 501(d) requires drugs not be mixed or substituted with another substance

A drug is ***adulterated*** if it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part therefor.

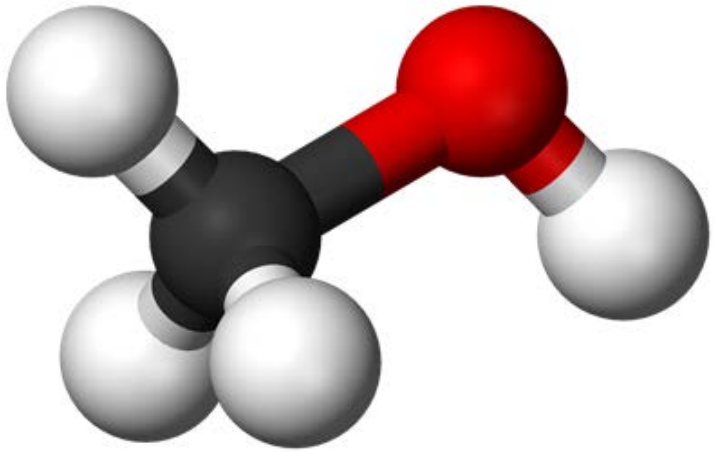
And yes, “therefor” is spelled correctly, this version means, “for that”

Substitution Legal Authority

Ethanol: valid active ingredient



Methanol: poison



Methanol vs Ethanol

- Methanol toxicity concerns exist for both ingestion and dermal exposure
- From a recent Warning Letter:
  - *"Methanol is not an acceptable ingredient for hand sanitizers and should not be used due to its toxic effects. Skin exposure to methanol can cause dermatitis, as well as transdermal absorption with systemic toxicity. Substantial methanol exposure can result in nausea, vomiting, headache, blurred vision, permanent blindness, seizures, coma, permanent damage to the nervous system, or death. Although all persons using these products on their hands are at risk, young children who accidently ingest these products, and adolescents and adults who drink these products as an alcohol (ethanol) substitute, are most at risk for methanol poisoning."*

Methanol vs Ethanol

- FDA test results showed various levels of methanol substitution
- From recent WL
  - *"FDA laboratory testing of batches of this product detained at the border found that the product contained an average of 39% ethanol and 28% methanol v/v. Additionally, the drug product [redacted], also labeled as manufactured at your facility, is labeled to contain 70% v/v of the active ingredient ethyl alcohol (ethanol). However, FDA laboratory testing of batches of this product detained at the border found that the product contained 0% ethanol and 83% methanol v/v. Therefore, these hand sanitizer drug products are adulterated under section 501(d)(2) of the FD&C Act in that the active ingredient of ethanol was substituted wholly or in part with methanol, a dangerous chemical when in contact with human skin or ingested."*

Substitution and CGMP

- Substitution, particularly with a poison, calls into question the entire quality unit's ability to oversee drug manufacturing and release

- From a Recent Warning Letter
  - *"The substitution and methanol contamination in hand sanitizer drug products manufactured in your facility is evidence that the quality assurance within your facility is not functioning in accordance with CGMP requirements under section 501(a)(2)(B) of the FD&C Act, 21 U.S.C. 351(a)(2)(B)."*

Actions Taken

- FDA has taken multiple actions when encountering substitution
  - Contacted firms about taking market action to limit patient exposure
  - Added firms to import alert 66-78 to prevent future shipments
  - Issued Warning Letters
- Drugs linked to deficient manufacturers were added to a Do Not Use List for consumers
  - https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use

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Update on Alcohol Testing, Including for Homeopathy

Recent Updates to Guidances

- Guidances including Hand Sanitizer manufacturing were updated on August 7, 2020
  - https://www.fda.gov/media/136289/download
- To fall under the enforcement discretion described in the guidance:
  - Hand sanitizer API (ethanol or isopropanol) procured from an outside source is tested for methanol content
  - Testing is done before manufacturing **regardless of what is on the COA**

Update to the Ethanol Monograph

- On July 30th, FDA sent a letter to the USP requesting an update to the identity section of the Alcohol monographs due to patient risk:
  - https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/fda-letter-alcohols-nitr-att.pdf
- The monograph was revised, and on 9/1/2020, came into affect:
  - https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/revisions/alcohol-rb-notice-20200817.pdf
- The compendial identity test for ethanol now includes a specific test for methanol content

Identity Testing and CGMP

- § 211.84 Testing and approval or rejection of components, drug product containers, and closures.

- § 211.84 (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.

- § 211.84 (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.**

Ethanol in Homeopathic Drugs

- Alcohol (Ethanol) is widely used as a component of homeopathic drugs.
- With the compendial revision, under CGMP, identity testing of incoming lots of ethanol must now include a test for methanol.
- Test method should be equivalent or better than the method detailed in the USP monograph.
- This is commensurate with the patient risk for methanol toxicity.

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Key Takeaways

Takeaways for Homeopathic Manufacturers

- Homeopathy is a small part of the FDA manufacturing inventory, hence a small portion of CGMP compliance actions

- Same CGMP requirements apply to all drugs, including homeopathics

Takeaways for Homeopathic Manufacturers

As with all CGMP case evaluations, product and patient risk are considered, with several recent key takeaways:

- Contractor and Supplier oversight
- Ensuring proper dilutions is paramount
  - Particularly for toxic ingredients
- Oversight of raw material is critical
  - Especially important with emerging concerns regarding ethanol

In Summary

- OMQ works to minimize consumer exposure to unsafe, ineffective, and poor-quality drugs.

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

Questions?