API Sourcing, or Buyer Beware!!!

Francis Godwin
Director, Office of Manufacturing Quality, Office of Compliance
Center for Drug Evaluation and Research, FDA

- 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
- API Sourcing Requirements / Guidance for Compounders
- API Site Case Studies
- API Repackager/Relabeller Case Studies
- Compounding Hand Sanitizer
- API Sourcing Considerations

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

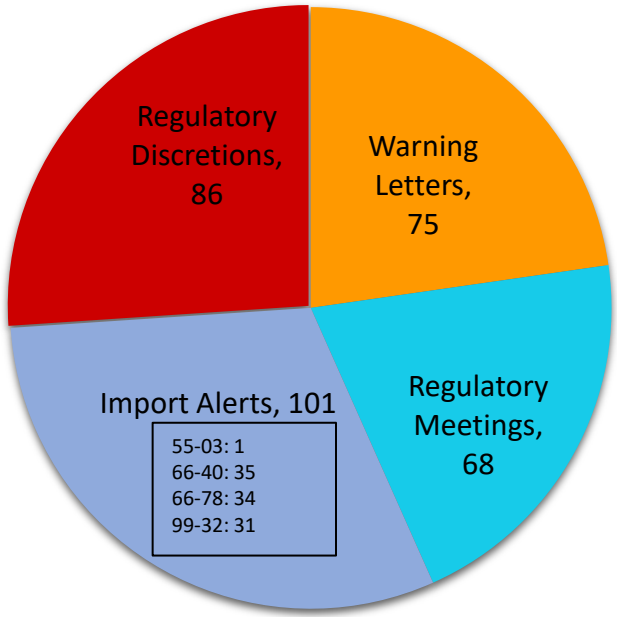
U.S. Federal Food, Drug, & Cosmetic Act

- 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

Enforcement and Advisory Tools

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

FY2020* Regulatory Actions

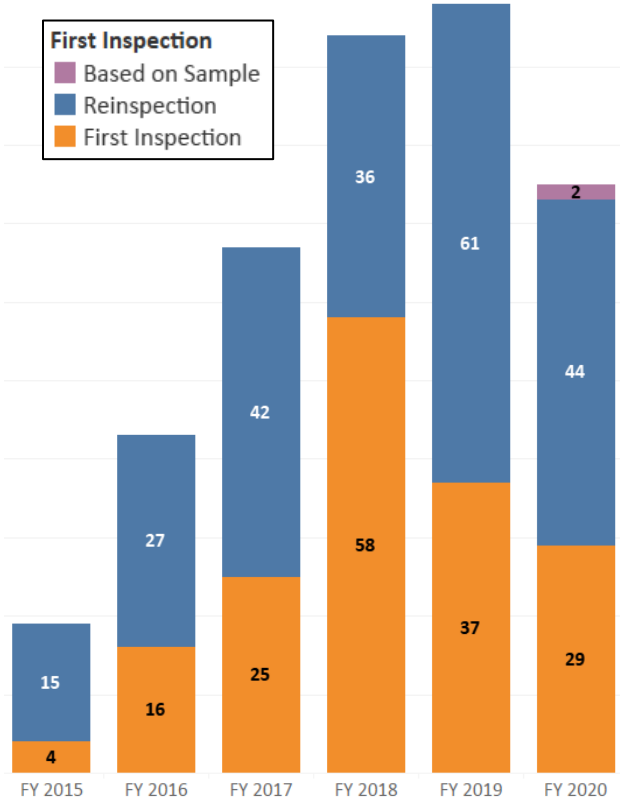


Excludes compounding-related actions

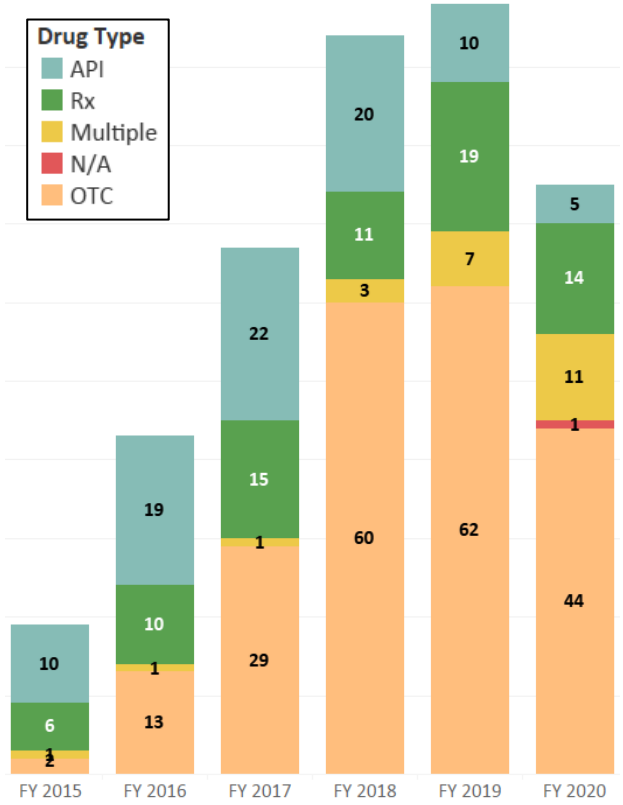
*Actions issued October 1, 2019 to August 31, 2020

Trends in CGMP Warning Letters

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

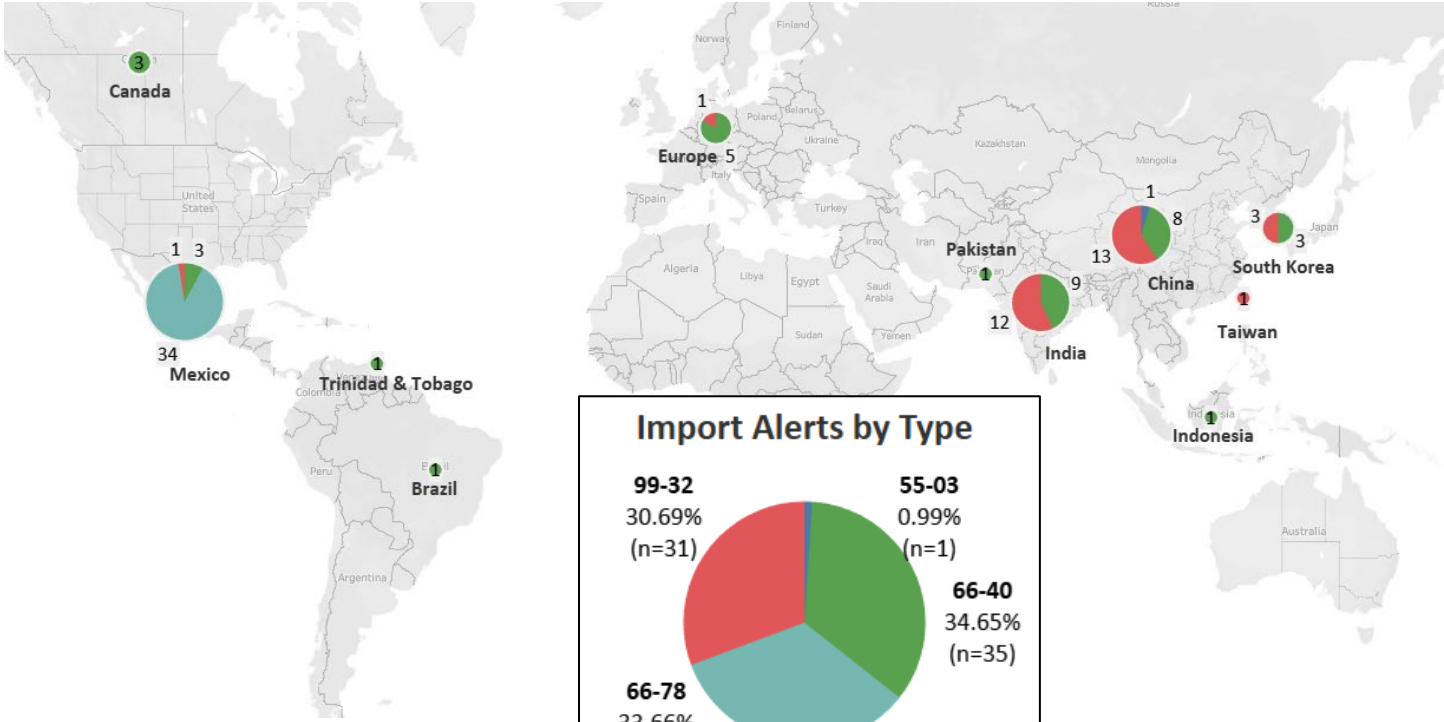


Warning Letters Issued by Drug Type Manufactured by FY*



*as of 8/31/2020

Import Alerts Issued FY20*



*as of 8/31/2020

API SOURCING REQUIREMENTS / GUIDANCE FOR COMPOUNDERS

503A Pharmacies

To be eligible for the exemptions provided by section 503A of the FD&C Act, bulks used in compounding must (among other conditions of section 503A):

- comply with the standards of an "applicable" U. S. Pharmacopeia or National Formulary monograph, if one exists;
- Be manufactured by an establishment that is registered under section 510 (including a foreign establishment that is registered under section 510(i));
- Be accompanied by valid certificates of analysis for each bulk drug substance.

"The following are examples of insanitary conditions that have been observed and are applicable to both sterile and non-sterile drug production.

Using ingredients, both active and inactive ingredients, or processing aides, that have or may have higher levels of impurities compared to compendial or pharmaceutical grade equivalents (e.g., ingredients with potentially harmful impurities, ingredients labeled with "not for pharmaceutical use" or an equivalent statement)"

FDA draft Guidance: https://www.fda.gov/media/124948/download

503B Outsourcing Facilities

"To be eligible for the exemptions provided in section 503B of the FD&C Act, each bulk drug substance used in compounding must be "accompanied by a valid certificate of analysis"(section 503B(a)(2)(D))"

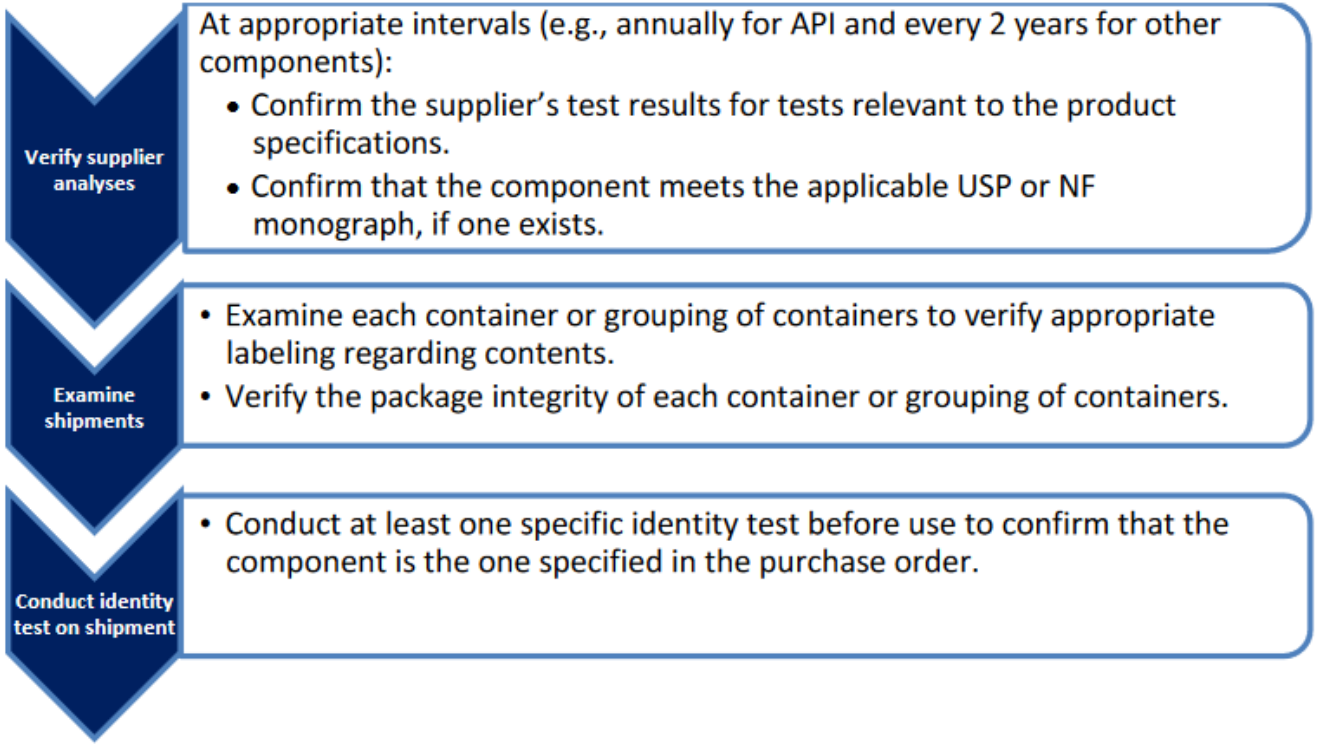
In addition, the bulk drug substance must be manufactured by an establishment that is registered under section 510 of the FD&C Act (section 503B(a)(2)(C) of the FD&C Act).

"Each shipment of each lot of components must be tested to verify identity and evaluated for conformity with appropriate specifications before use (see § 211.84)"

COAs can be used for attributes other than identity testing, but only if the reliability of the suppliers analysis has been established. (§ 211.84)

FDA draft Guidance: https://www.fda.gov/media/88905/download

Figure 1. Using a Supplier's COA in Lieu of Testing*



* See §§ 211.84(d)(2) and 211.82(a).

FDA draft Guidance: https://www.fda.gov/media/88905/download

API CASE STUDIES, OR…

BUYER BEWARE!!!

Case 1: Pharmacopeia Shell Game

Case Primer

- Foreign firm manufactures APIs for multiple markets.
- Multiple APIs imported into US, specifically for pharmacy compounding.
- APIs labelled as meeting USP compendial requirements.
- FDA inspects the manufacturer…

Case 1: Pharmacopeia Shell Game

- From the resulting Warning Letter:

"For **[redacted]** API, the laboratory stability protocols used to support expiration dating of these API are based on methods and specifications in the 2015 Chinese Pharmacopeia. You were not able to demonstrate that the tests used are equivalent to or better than the current USP 42 compendial methods. FDA compared your test methods, based on the Chinese Pharmacopeia, to the current standard in the USP. We found multiple differences in specifications and test methods. We also found that required tests for quality attributes in the USP were not part of the Chinese Pharmacopeia or your stability protocols."

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/jiangsu-nhwa-pharmaceutical-co-ltd-582511-09102019

Case 2: Variation

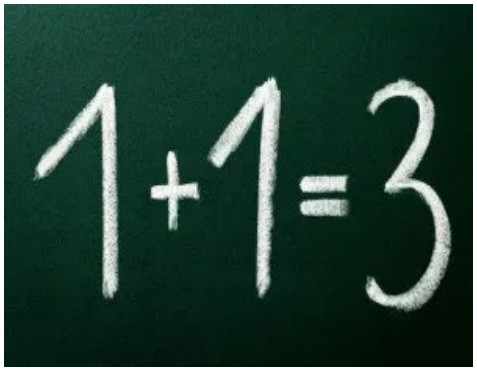
Case Primer

- API is a narrow therapeutic
  - Consistency is key for patients
- COAs include assay/potency data used by compounders to calculate formula and dosages in finished drugs.
- FDA conducts an inspection of the API manufacturer….

Case 2: Variation

- From the resulting Warning Letter:

"You used a non-validated Excel spreadsheet to calculate assay results for **[redacted]** USP for product release and stability testing. Our investigator found that this spreadsheet lacked password protection and contained unlocked calculation formulas which were incorrect.



During the inspection, your QC manager acknowledged that the formula in the spreadsheet used to calculate assay results was incorrect. Because of these incorrect formulas, multiple certificates of analysis (COA) contained inaccurate data."

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/sichuan-friendly-pharmaceutical-co-ltd-546990-06222018

Case 2: Variation

- FDA also tested the API and posted an alert

"FDA laboratory testing confirmed the Sichuan Friendly API has inconsistent levels of the active ingredients – levothyroxine and liothyronine – and should not be used to manufacture or compound drugs for patient use. Risks associated with over or under treatment of hypothyroidism could result in permanent or life-threatening adverse health consequences."

FDA placed Sichuan Friendly on import alert 66-40 on March 22, 2018, based on current good manufacturing practice (CGMP) deviations observed during an FDA inspection."

https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-drug-makers-recall-porcine-thyroid-api-sichuan-friendly-pharmaceutical-co-limited-china

Case 2: Variation

- More from the FDA Alert:

"However, FDA confirmed Sichuan Friendly's thyroid API remains in the U.S. supply chain. This API and the drug products made from it, present a safety risk to patients. Sichuan Friendly API may be repackaged and/or relabeled before it is further distributed, and not all of the repackaged/relabeled API identifies Sichuan Friendly as the original API manufacturer. Therefore, manufacturers and compounders who make levothyroxine and liothyronine drug products should contact their API supplier to verify the actual manufacturer of the thyroid API they received before using it. Sichuan Friendly's products may be labeled as "Thyroid Powder" or "Thyroid Powder USP.""

https://www.fda.gov/drugs/drug-safety-and-availability/fda-alerts-drug-makers-recall-porcine-thyroid-api-sichuan-friendly-pharmaceutical-co-limited-china

A QUICK DETOUR

A Quick Detour

1990s: DEG poisoning occurred in many countries.

The origin of the glycerin was not easily apparent from the COA. The COA obtained by the pharmaceutical manufacturers of the syrups was often a copy of a COA on the letterhead of the distributor and not the COA provided by the manufacturer of the glycerin. The chain of custody or distribution history of the glycerin was also not readily known because the glycerin may have been sold several times between its manufacture and its use in medicinal syrup or other drug product…. As a result of these practices, DEG-contaminated glycerin entered the pharmaceutical raw material supply chain.

FDA Guidance for Industry Testing of Glycerin for Diethylene Glycol
www.fda.gov/downloads/Drugs/.../Guidances/ucm070347.pdf

A Quick Detour

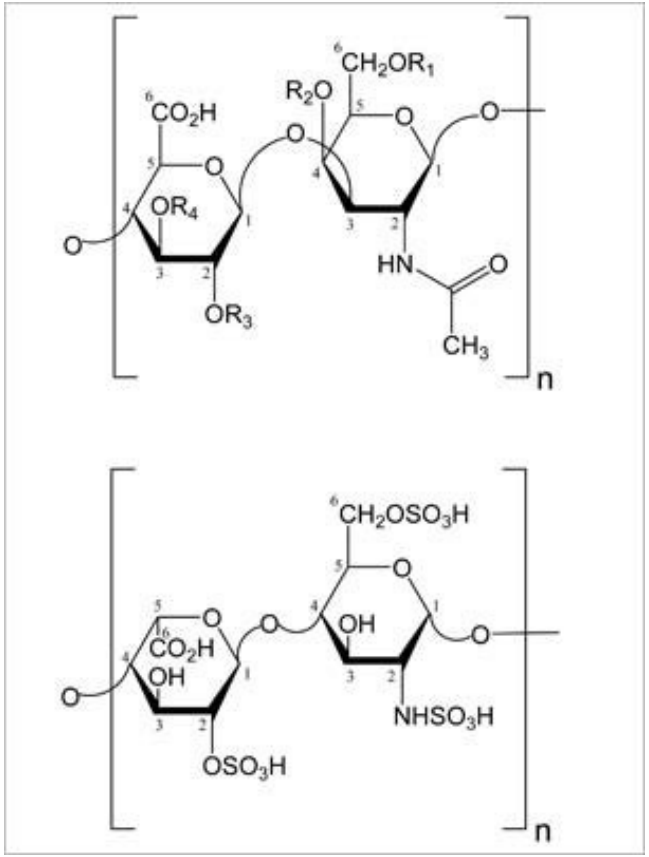
2000's: Over Sulfated Chondroitin Sulfate (OSCS) contamination in Heparin API supply lines

- Heparin is derived from pigs
- Disease in pig supply causes a price spike
  - Caused incentive for economically motivated adulteration
- Opaque supply chain
  - Many didn't know who their true suppliers were, and bought material from brokers/consolidators
- Entities in the supply chain added OSCS to increase the price of heparin
  - Results were horrifying.

Heparin vs OSCS

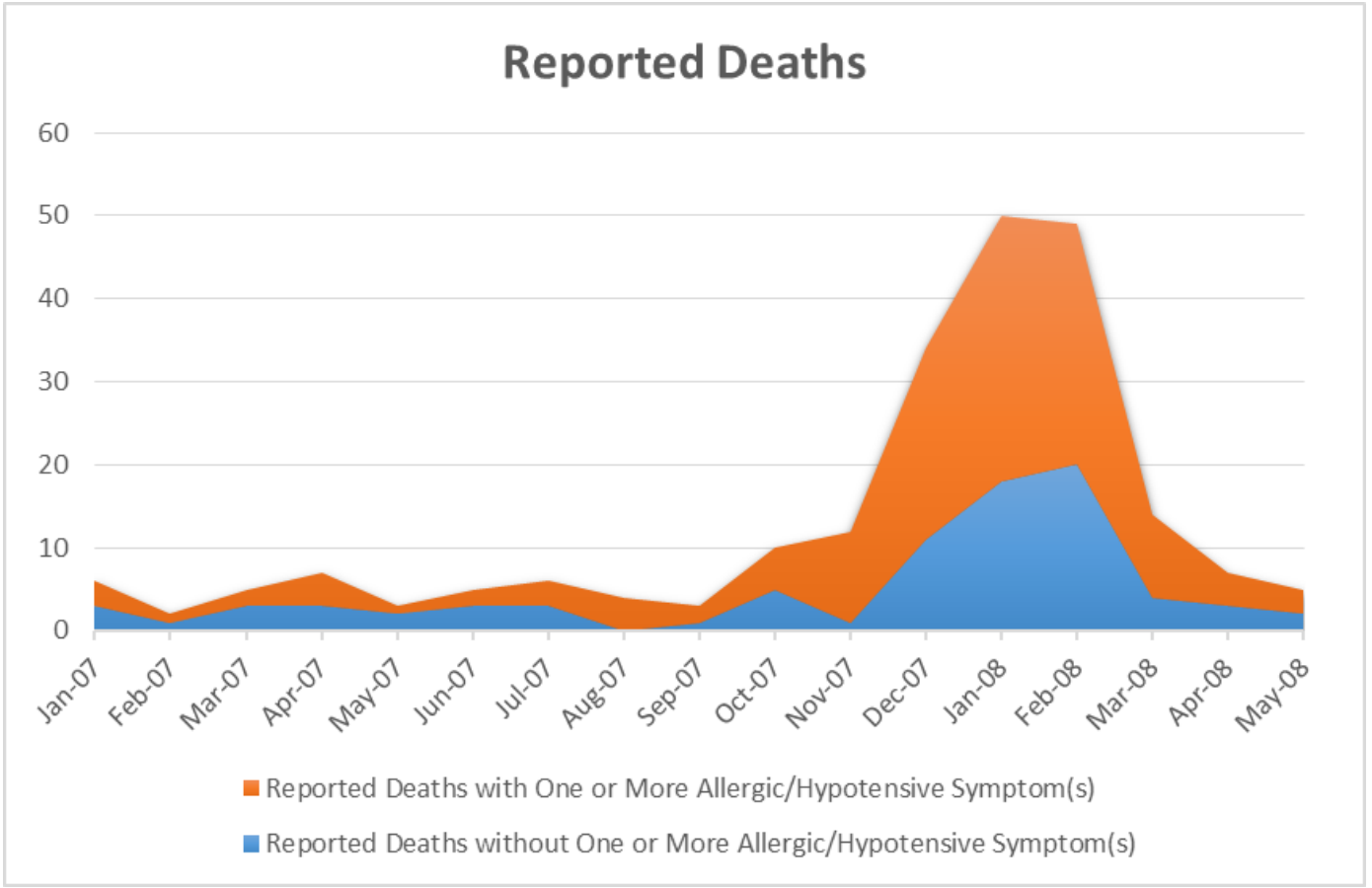
Chondroitin Sulfate

Heparin



http://web.mit.edu/newsoffice/2008/heparin-1203.html

Adverse Event Trends



https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM112669

API REPACKAGING CASE STUDIES

Case 3: Pharma, or Industrial Grade?

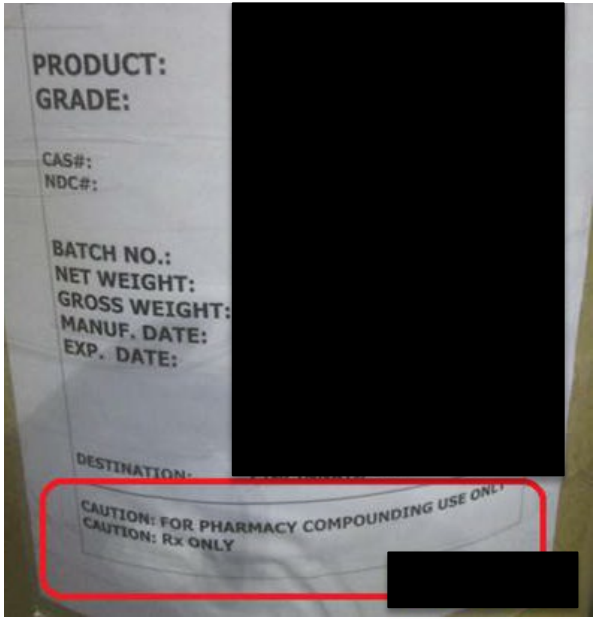
Case Primer

- API imported into the US,
  - Manufacturing site was registered/declared at border
- FDA inspected the facility accordingly
  - Became apparent site did not make drugs, and hadn't registered themselves
- Entities down the line were taking the site's industrial chemicals and relabeling it:
  - for Pharmacy Compounding
  - Broker registered the site without their knowledge to meet an importation requirement
- Firm added to Import alert to prevent adulterated drugs entering the US

What was leaving the manufacturer

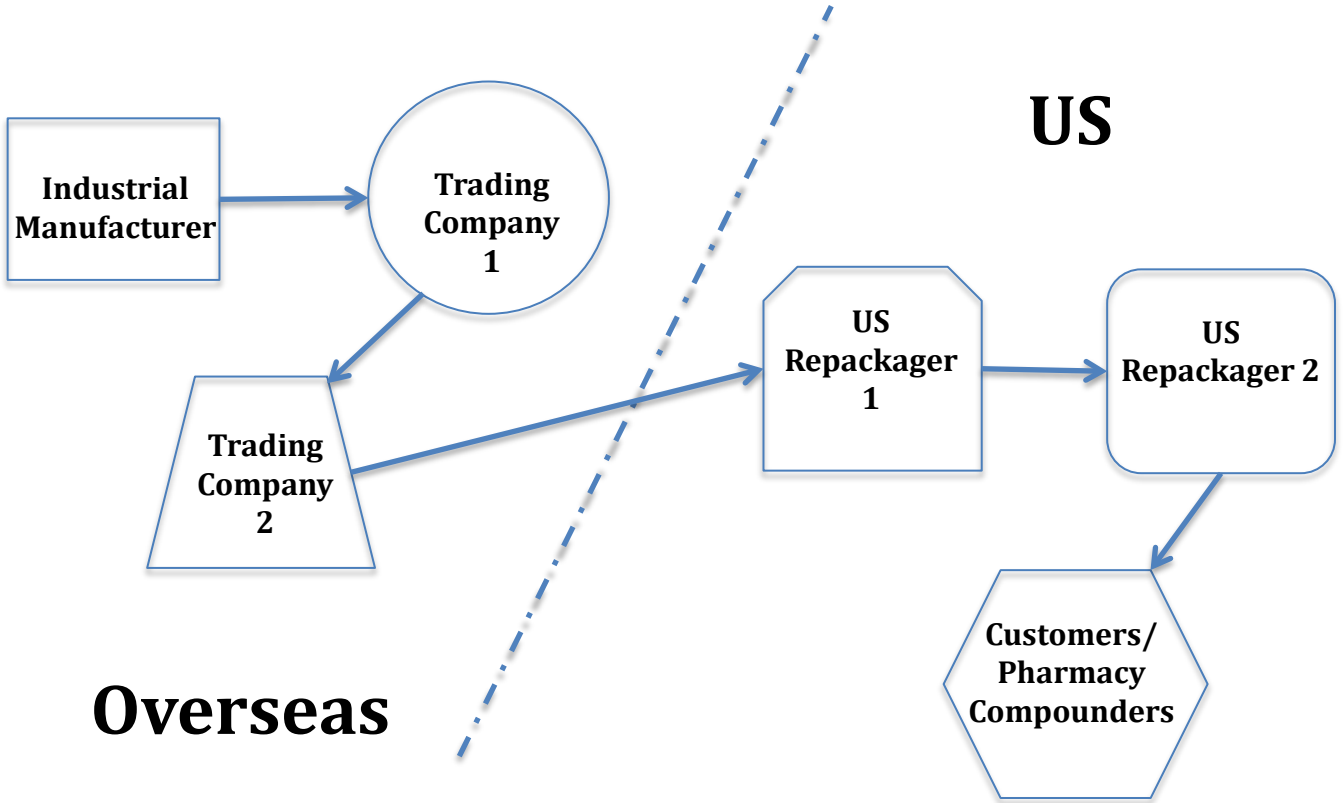
It states: "**FOR INDUSTRIAL USE ONLY! CANNOT BE USED IN HUMAN FOOD, ANIMAL FEED ADDITIVE OR ANY RELATED RAW MATERIALS!**"

What was later in the supply chain



It states:
"**CAUTION: FOR PHARMACY COMPOUNDING USE ONLY**
CAUTION: Rx ONLY"

A Convoluted Path Through Brokers, Repackers and Relabellers



Case 4: Injectable or Oral Grade?

- API being sold by repackagers to compounders
  - Marketed as suitable for injection
- FDA encounters instances of particulates in the API and finished drugs.
- FDA contacted the API manufacturer
  - Manufacturer explicitly stated their API is not injectable grade and did not label it that way.
- Entities down the line were taking the site's oral grade API and relabeling as injectable grade
- FDA published alert to notify the industry
  - https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-potential-contamination-baclofen-active-pharmaceutical-ingredient-taizhou-xinyou

Case 5: API Relabeller on Wheels

Case Primer

- APIs imported into the US, “manufacturer” declared on labels
- FDA inspected the “manufacturer” accordingly,
- From the warning letter:

  “During the inspection, you stated that you drive your car and pick up API from various suppliers, relabel API in your car with **[Your]** information, and then transport API to your clearing agent. “

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/sal-pharma-516205-04202017

Case 5: API Relabeller on Wheels

More from the Warning Letter:

- "You omitted the names and addresses of the original manufacturers of your API on certificates of analysis (COA) you issued to your customers. You generated your COA by replacing the original manufacturers' information with your letterhead.

- During our inspection, we found that two of your suppliers were not registered with the FDA as drug manufacturers at the time of inspection. However, you shipped API from these firms to the United States, and declared on importation documents and the COA that you provided to your customers that you were the manufacturer. Your failure to declare the original manufacturers on your importation documents and COA provided to your customers enabled the entry of unregistered firms' products into the United States."

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/sal-pharma-516205-04202017

COMPOUNDING HAND SANITIZER

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 being ethanol or isopropyl alcohol (IPA)

No Substitution: Legal Authority

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

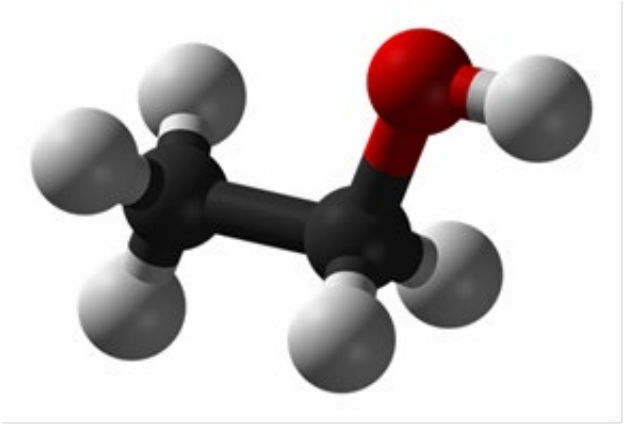
A drug is ***adulterated*** if it is a drug and any substance has been (1) mixed or packed therewith so as to reduce its quality or strength or (2) substituted wholly or in part therefor.

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

Ethanol vs Methanol

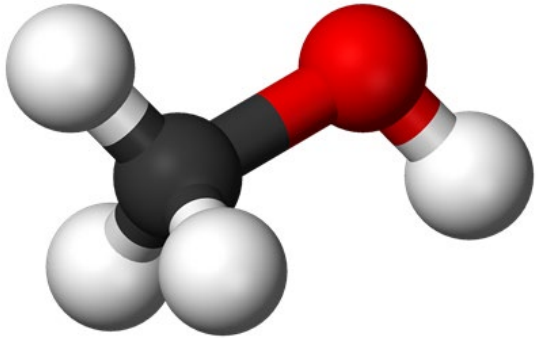
Ethanol

- 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."*

https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eskbiochem-sa-de-cv-608690-07232020

Methanol vs Ethanol

- FDA has seen test results showing various levels of methanol substitution
- From a 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."*
  - https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eskbiochem-sa-de-cv-608690-07232020

Actions Taken

- *FDA has taken multiple actions when encountering substitution*
  - *Contact with firms about taking market action to limit patient exposure*
  - *Firms added to import alert 66-78 to prevent future shipments*
  - *Warning Letters issued*
- *Drugs linked to deficient manufacturers are 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*

Recent Updates to Guidances

- Guidances, including for Compounding of Hand Sanitizers updated on August 7, 2020
  - https://www.fda.gov/media/136118/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 prior to compounding*
  - ***Both*** *for 503A pharmacies and 503B Outsourcing Facilities*
  - ***Regardless of what is on the COA***

API SOURCING CONSIDERATIONS

API Sourcing Considerations

- Take COAs with a grain of salt
  - *Over the years, multiple outbreaks, including fatalities, have been linked with false/misleading COAs.*
- Conduct identity testing on every lot of API you receive
  - *Required for 503B facilities under CGMP,*
  - *Appropriate for 503A facilities*
- If a broker/trader/repackager/relabeller won't tell you who actually made the API you're buying
  - *Try to find another source, as too often obfuscation has led to substitution and patient harm*
  - *If you do buy material from them, strongly consider full COA testing for every lot your receive, regardless of what the COA says.*

- Remember….

BUYER BEWARE!!!

IN SUMMARY

In Summary

- API supply chain is generally safe
- However API for pharmacy compounding has had problems with product quality, especially associated with poor supply chain practices
- As compounders, know your legal requirements, as well as the controls to ensure you use API with the appropriate identity, strength, quality, and purity.

In Summary

- OMQ works to minimize consumer exposure to unsafe, ineffective, and poor quality drugs
- We take actions against firms with poor CGMP or when other information calls into question the quality of drugs for U.S. patients

Questions?


FDA
U.S. FOOD & DRUG
ADMINISTRATION