



FDA 483 Observations and Warning Letter Trends

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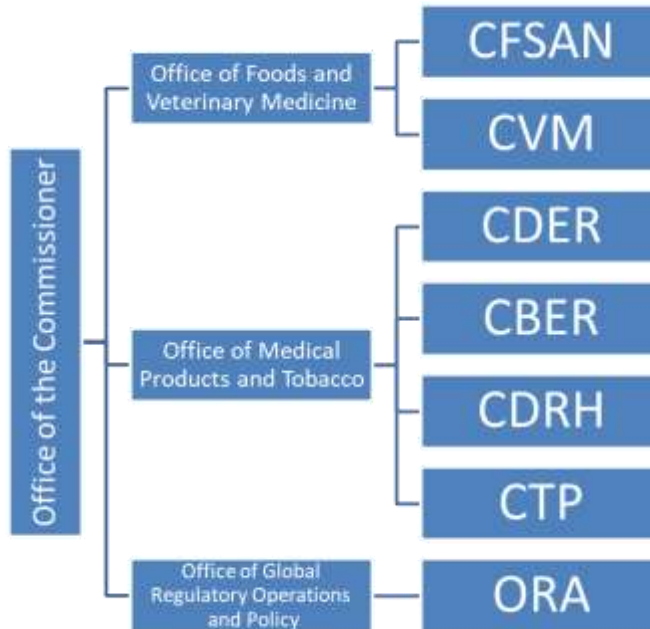


General Overview: FDA Structure and Enforcement



U.S. Food and Drug Administration

Broad Regulatory Authority



Jurisdiction defined by the Federal Food, Drug, and Cosmetic Act (FDCA) and the Public Health Service Act.

- Human food, including dietary supplements and color additives
- Rx and OTC medications, and APIs
- Vaccines, blood products, and biologics
- Medical devices
- Radiation-emitting products
- Cosmetics
- Animal food, feed, and veterinary medicines
- Tobacco products

Enforcement

Form 483s

- Notifies management at the conclusion of an inspection of objectionable conditions
- Does not constitute a final Agency determination
- Companies are encouraged to respond

Warning Letters

- Sent by FDA to advise of violations
- Request written response as to steps taken to address violation

Seizure

- Action brought against product that is adulterated and/or misbranded
- Removes violating products from commerce

Injunction

- Court-ordered
- May be sought by FDA to require an individual or corporation to do or refrain from doing a specific act

Criminal Prosecution & Fines

- May recommend prosecution for certain violations
- Fines ranging from \$100k-500k; imprisonment for up to 1 year

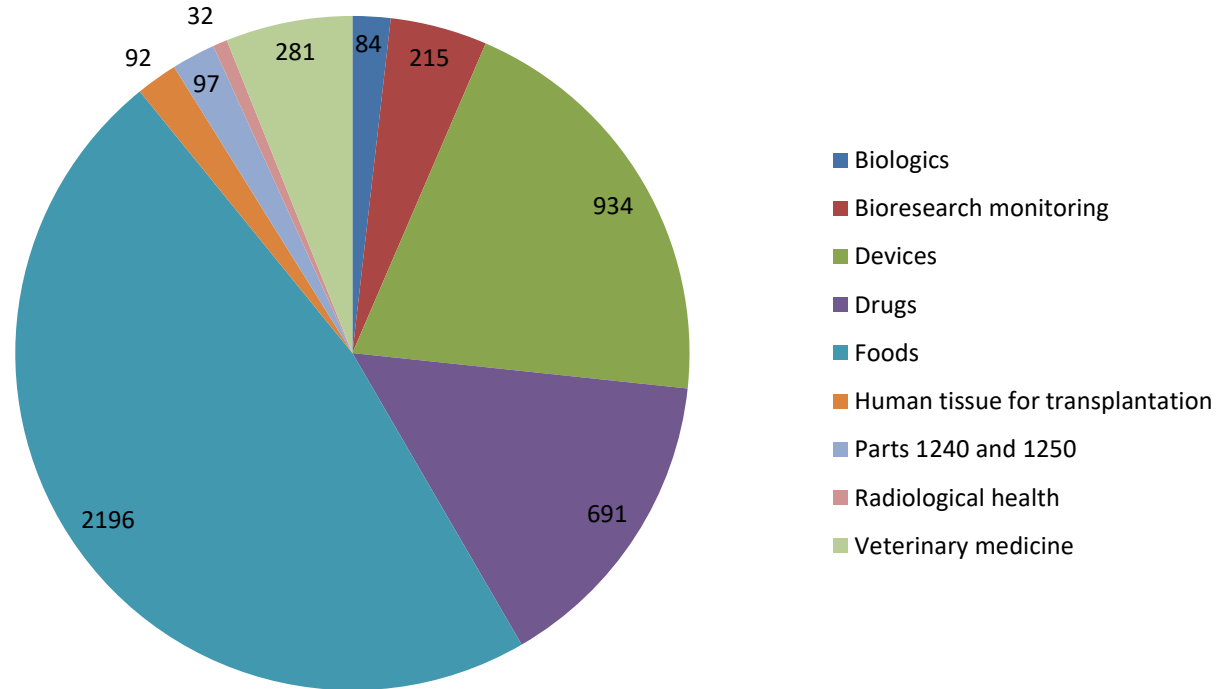


FDA Enforcement Trends: 483 Observations



483 Observations - 10/1/2015 to 9/30/2016

- Approximately 4,500 total 483 observations
- Drugs: ~15%
- Devices: ~21%



483 Observations – Top 5 Observations (2016)

Drugs (691 total)

Short Description	Frequency
Quality control procedures not in writing, fully followed	147
Scientifically sound laboratory controls not established	133
Investigations of discrepancies, failures to adequately review	126
Absence of Written Procedures for production and process controls	85
Environmental Monitoring System deficient	78

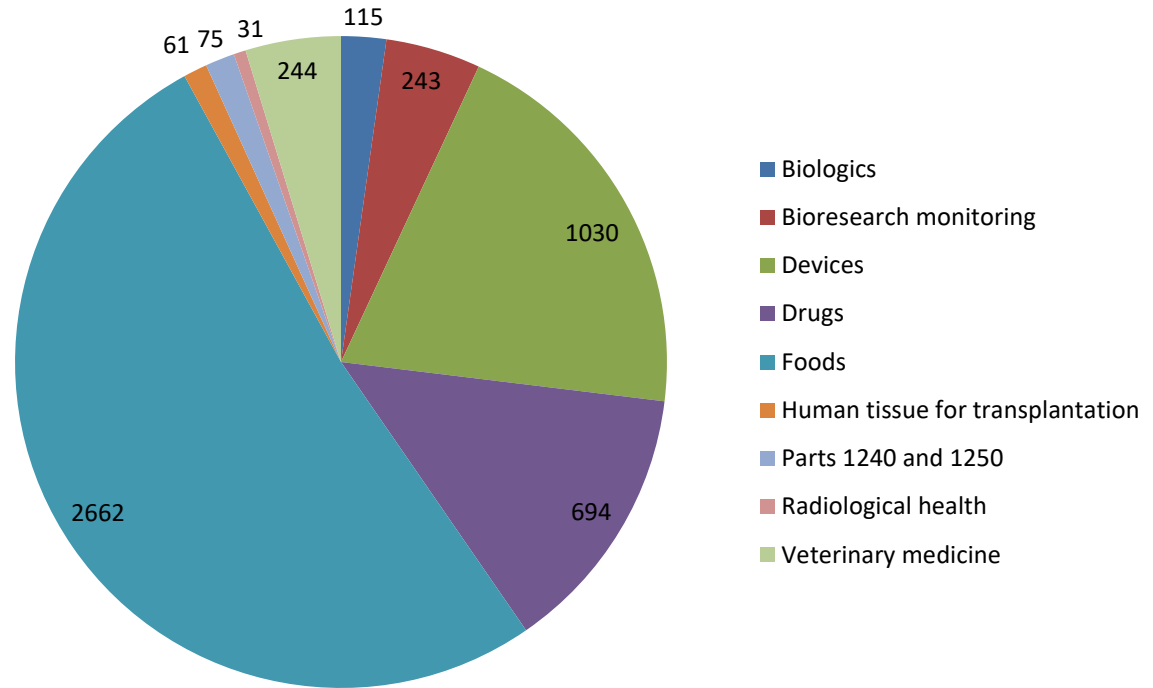
483 Observations – Top 5 Observations (2016)

Devices (934 total)

Short Description	Frequency
Lack of or inadequate procedures (CAPAs)	344
Lack of or inadequate complaint procedures	264
Lack of Written MDR Procedures	146
Nonconforming product, Lack of or inadequate procedures	135
Purchasing controls, Lack of or inadequate procedures to ensure that all purchased product conforms to specifications	122

483 Observations - 10/1/2016 to 9/30/2017

- Approximately 5,000 total 483 observations
- Drugs: ~14%
- Devices: ~20%



483 Observations – Top 5 Observations (2017)

Drugs (694 total)

Short Description	Frequency
Quality control procedures not in writing, fully followed	185
Scientifically sound laboratory controls not established	124
Investigations of discrepancies, failures to adequately review	100
Absence of Written Procedures for production and process controls	91
<i>Written procedures not established/followed for cleaning and maintenance equipment</i>	68

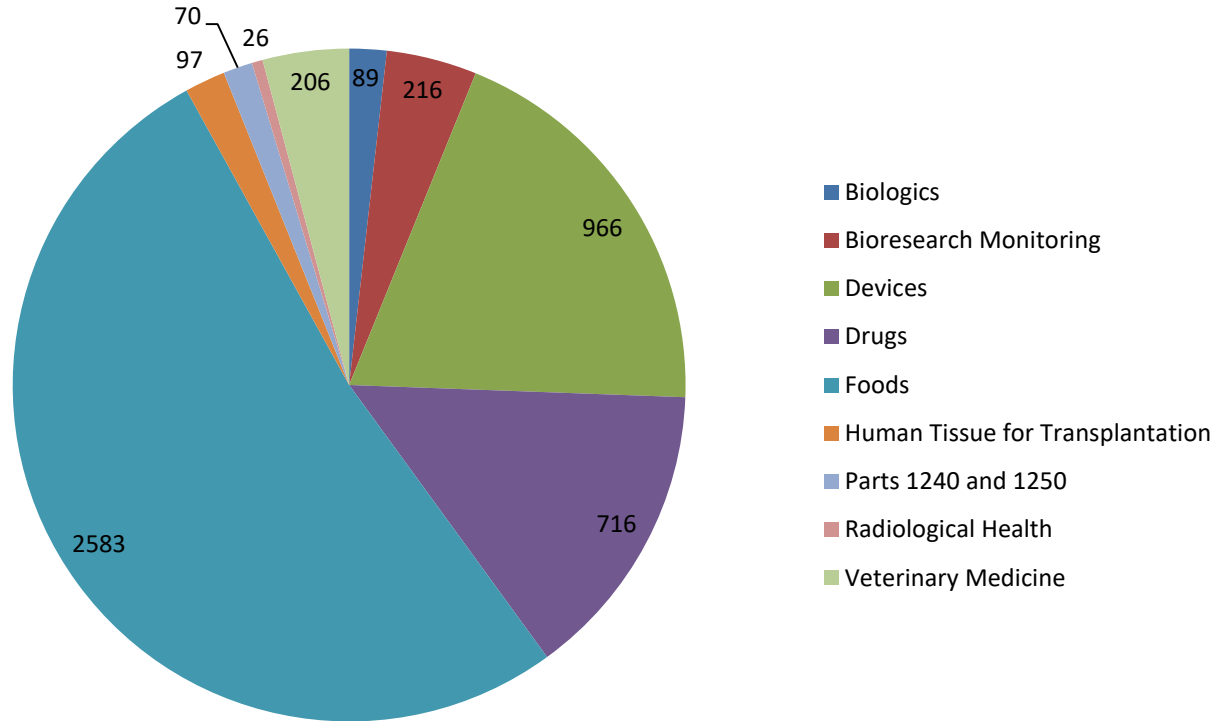
483 Observations – Top 5 Observations (2017)

Devices (1,030 Total)

Short Description	Frequency
Lack of or inadequate procedures (CAPAS)	400
Lack of or inadequate complaint procedures	269
Purchasing controls, Lack of or inadequate procedures to ensure that all purchased product conforms to specifications	138
<i>Lack of or inadequate process validation</i>	137
Lack of Written MDR Procedures	127

483 Observations - 10/1/2017 to 9/30/2018

- Approximately 4,900 total 483 observations
- Drugs: ~14.5%
- Devices: ~19%



483 Observations – Top 5 Observations (2018)

Drugs (716 total)

Short Description	Frequency
Quality control procedures not in writing, fully followed	208
Scientifically sound laboratory controls not established	127
Investigations of discrepancies, failures to adequately review	107
Absence of Written Procedures for production and process controls	86
Written procedures not established/followed for cleaning and maintenance equipment	81

483 Observations – Top 5 Observations (2018)

Devices (966 total)

Short Description	Frequency
Lack of or inadequate procedures (CAPAs)	354
Lack of or inadequate complaint procedures	229
Purchasing controls, Lack of or inadequate procedures to ensure that all purchased product conforms to specifications	142
Lack of Written MDR Procedures	139
Lack of or inadequate process validation	138

Overall Trends in FDA 483s from 2016-2018

What does the data tell us?

- Enforcement activity has been relatively consistent in the past 3 years, with a slight increase in 483 observations in 2016 (4500 total) to 2018 (4900 total) – a total increase of 9% from 2016
- 483 observations related to drugs are consistently 14 to 15% of the total number of 483 observations
- 483 observations related to medical devices have consistently ranged from 19 to 21% of the total number of 483 observations

Overall Trends in FDA 483s from 2016-2018 (cont.)

What does the data tell us?

- The top 4 most common observations for drugs have remained identical from 2016-2018
 1. Quality control procedures not in writing, fully followed
 2. Scientifically sound laboratory controls not established
 3. Investigations of discrepancies, failure to adequately review
 4. Absence of written procedures for production and process controls
- The top 2 most common observations for devices have remained identical from 2016-2018
 1. Lack of or inadequate procedures (CAPAs)
 2. Lack of inadequate complaint procedures
- While not consistently ranked in the same spot, “Lack of Written MDR Procedures” and “Purchasing controls, Lack of or inadequate procedures to ensure that all purchased product conforms to specifications” have made the top 5 each year from 2016-2018.



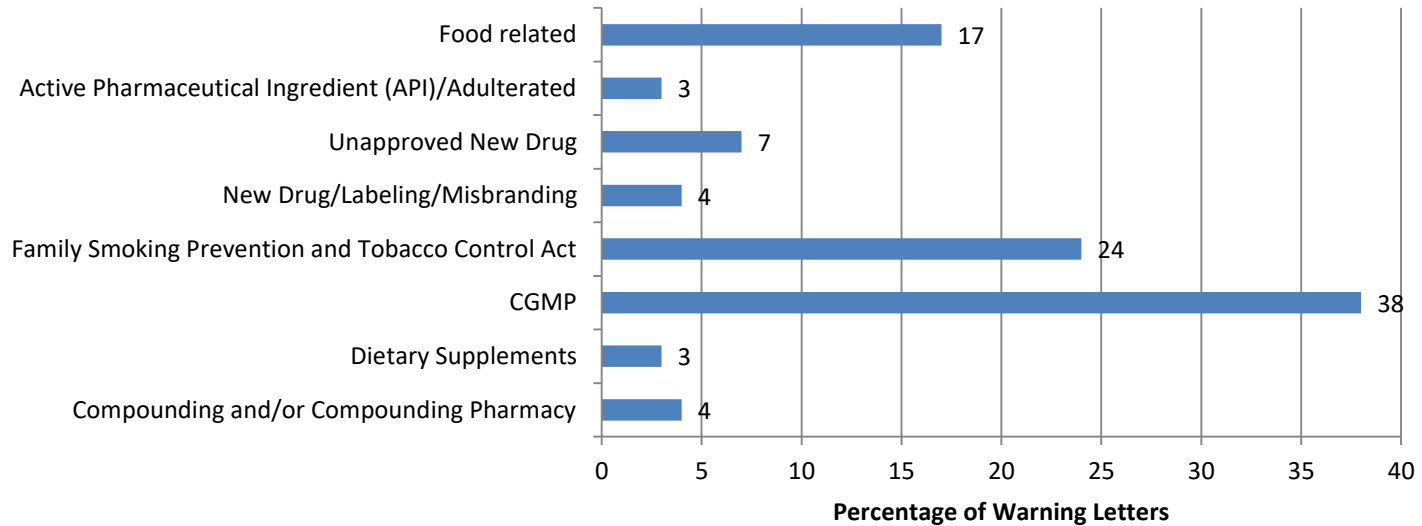
FDA Enforcement Trends: Warning Letters



Warning Letter Trends - 2016

607 total warning letters

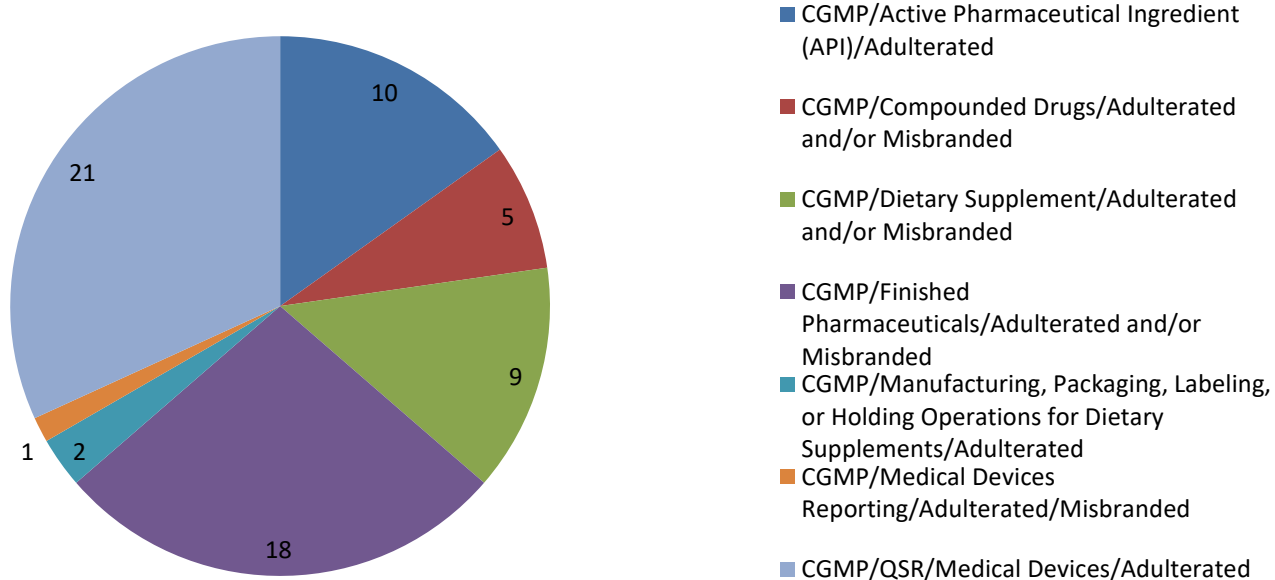
Subject of Warning Letters



2016 CGMP Breakdown

230 total Warning Letters in 2016 based on CGMPs

CGMPs Relevant to Medical Devices and Drugs - Percentage of Total CGMPs in 2016



Examples of CGMP Issues Cited in Warning Letters (2016)

- **CGMP/Dietary Supplement/Adulterated/Misbranded**
 - Warning Letter to HoneyCombs Industries, LLC: HoneyCombs was selling cough syrup, cold and flu medicine, and other products as “dietary supplements” when the products were intended to be used as drugs. HoneyCombs did not have the proper FDA approvals for drug products.
- **CGMP/Compounded Drugs/Misbranding**
 - Warning Letter to the Compounding Pharmacy of America, Inc.: The FDA found that The Compounding Pharmacy of America was not receiving valid prescriptions for portions of the drugs it was producing – further, FDA investigators found that the company’s practices for producing sterile drug products was putting patients at risk, including technicians preparing drugs in street clothes, and in an environment with no HEPA filtration. According to the FDA, these deficiencies posed a “significant contamination risk.”
- **CGMP/Finished Pharmaceuticals/Adulterated**
 - Warning Letter to Sri Krishna Pharmaceuticals, Ltd.: The FDA found that Sri Krishna Pharmaceuticals failed to ensure that its records included complete data from “all tests necessary to assure compliance with established specifications and standards.” FDA inspectors observed that in the testing process, “the first analyst deleted 28 original files due to pressure fluctuations and ghost peaks, while the second analyst deleted original trial injections of working standard and sample testing data due to a problem associated with peak shape.”

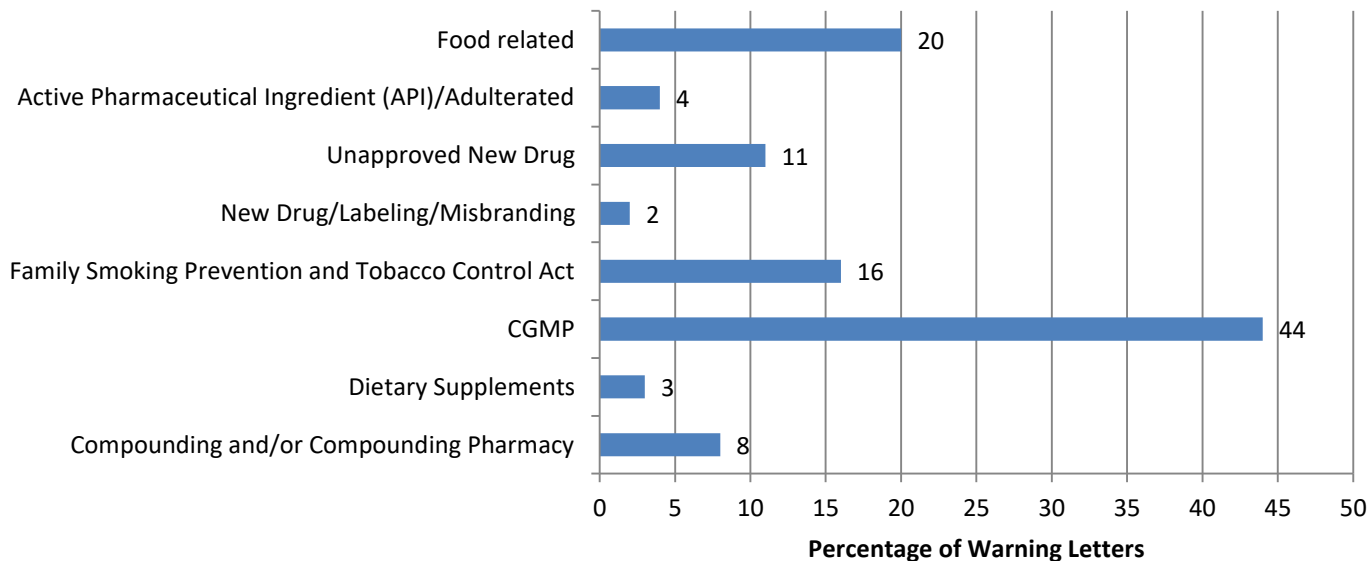
Examples of CGMP Issues Cited in Warning Letters (2016)

- **Lack of controls to prevent contamination of drug products**
 - Warning Letter to Horizon Pharmaceuticals, Inc.: FDA identified conditions at facilities that pose a significant microbial contamination risk. For example, poor facility maintenance, including leaking pipes in the cleaning room ceiling, chipped and cracked floors in the batch tank room, and blue and black particulates as well as dust on tanks next to the ingredient charging ports
- **Failure to thoroughly investigate contamination, and releasing lots without meaningful scientific justification. (A negative retest, alone, is NOT sufficient).**
 - Warning Letter to Horizon Pharmaceuticals, Inc.: FDA noted that the firm identified microbial contamination with a positive test result, yet distributed the lots that tested positive after a “clean” retest without a scientific basis to invalidate positive test results
 - No evidence of lab error
 - Failure to recognize that it is typical for contamination to be distributed non-uniformly in a batch
 - Failure to identify a root cause of the contamination and setting forth a scientific rationale to discount the firm’s production operation was not the source of the microbial contamination

Warning Letter Trends - 2017

514 total warning letters

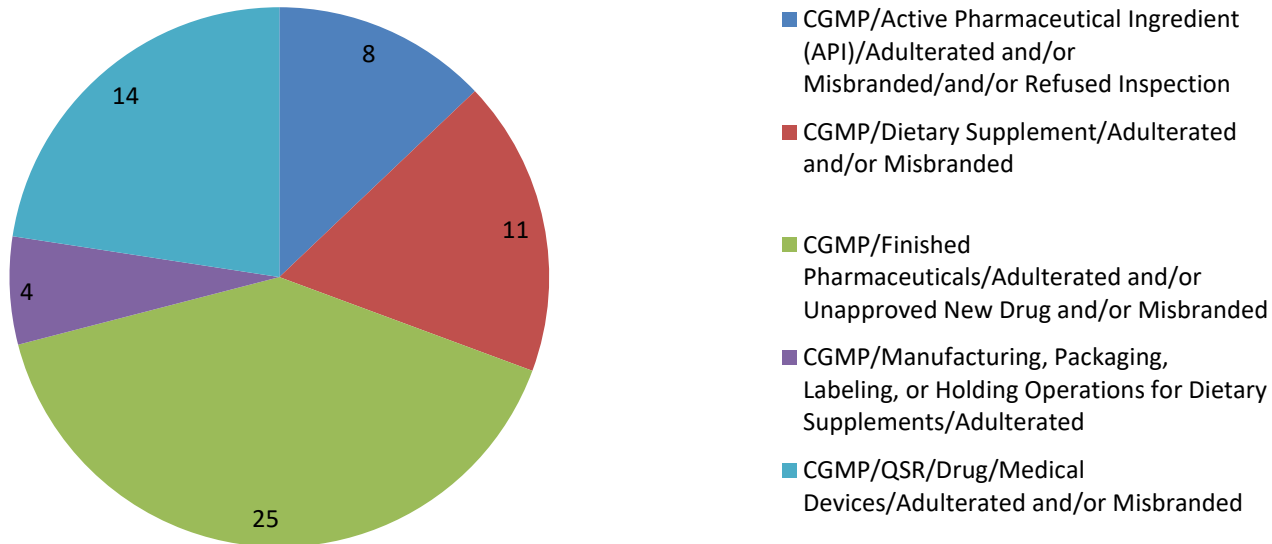
Subject of Warning Letters



2017 CGMP Breakdown

225 total Warning Letters in 2017 based on CGMPs

CGMPs Relevant to Medical Devices and Drugs - Percentage of Total CGMPs in 2017



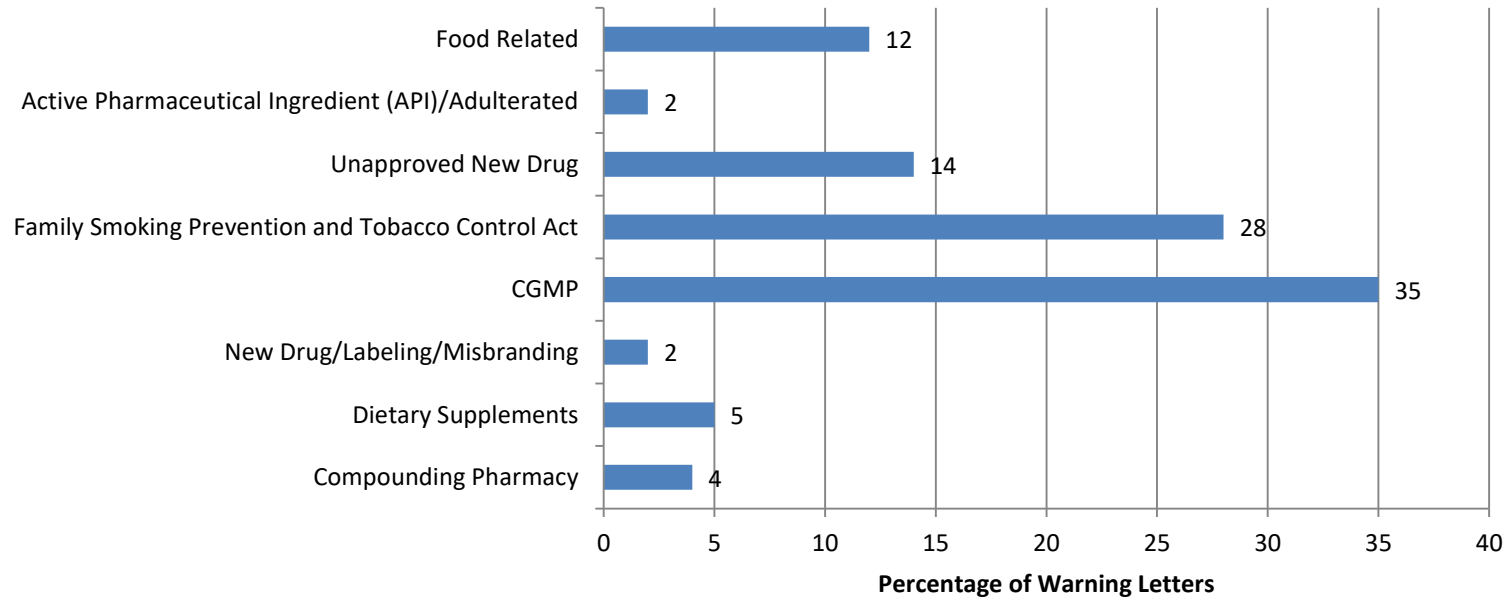
Examples of CGMP Issues Cited in Warning Letters (2017)

- **CGMP/Finished Pharmaceuticals/Adulterated**
 - Warning Letter to Cellex-C International, Inc.: Cellex-C was releasing its drug products without testing *any* of them to ensure conformance with specifications, such as identity and the strength of each active ingredient.
- **CGMP/QSR/Medical Devices/Adulterated**
 - Warning Letter to Oxford Performance Materials, Inc.: The FDA found that Oxford did not perform cleaning validation for its cranial implants, despite labelling the products as “clean and ready to sterilize.” The FDA noted that Oxford had confirmed a complaint regarding a cranial implant with residual powder from inadequate cleaning.
- **CGMP/Dietary Supplement/Adulterated/Misbranded**
 - Warning Letter to Life Rising Corporation: Life Rising was labelling and selling its dietary supplements as drug products without the proper drug approvals. For example, Life rising was selling a “Pancreas Support” product intended to treat “Diabetes, high blood sugar.”

Warning Letter Trends - 2018

421 total warning letters

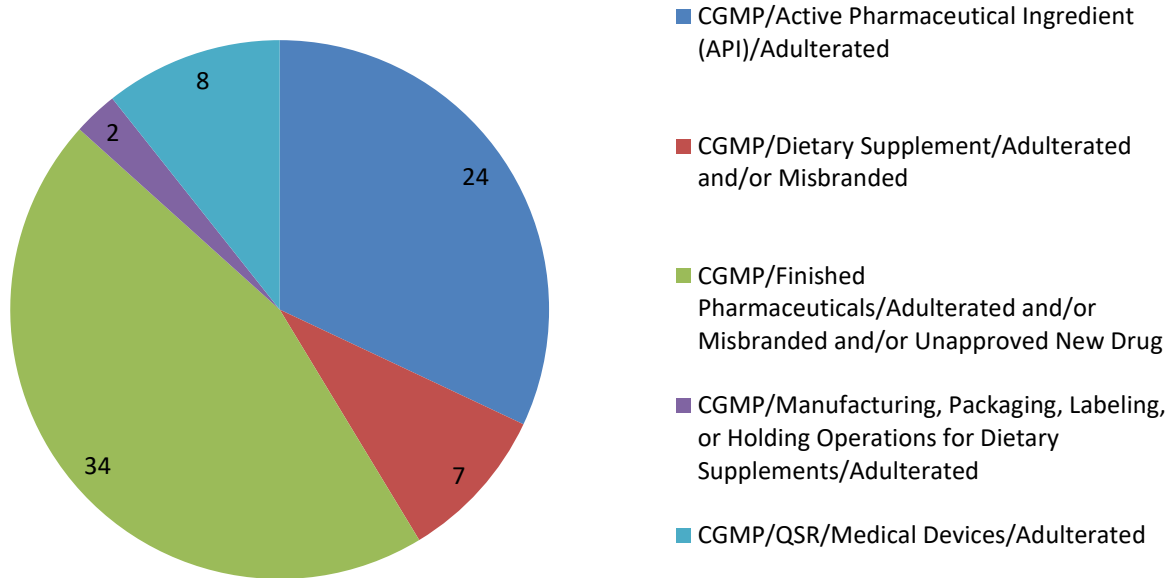
Subject of Warning Letters



2018 CGMP Breakdown

149 total Warning Letters in 2018 based on CGMPs

CGMPs Relevant to Medical Devices and Drugs - Percentage of Total CGMPs in 2018



Examples of CGMP Issues Cited in Warning Letters (2018)

- **CGMP/Finished Pharmaceuticals/Adulterated**

- Warning Letter to Tris Pharma Inc.: Tris Pharma failed to adequately investigate product failures and complaints – for example, in response to 24 complaints that its morphine sulfate oral solution bottles were leaking and/or underfilled, Tris Pharma concluded that the leaks were due to cracked bottle caps, but it let the bottles remain in inventory without retesting. Further, the defective product remained on the market for eight months before Tris Pharma initiated a recall.

- **CGMP/QSR/Medical Devices/Adulterated**

- Letter to Zimmer Biomet, Inc.: Zimmer failed to ensure that its orthopedic implants conformed to specifications, in part due to employees in the production line failing to follow production procedures. For example, one employee was using a nylon brush to remove debris from the devices, when the work instruction required a wire brush to remove debris. Another employee was not able to demonstrate how to measure the package seal using a gauge required by Zimmer's package requirements.

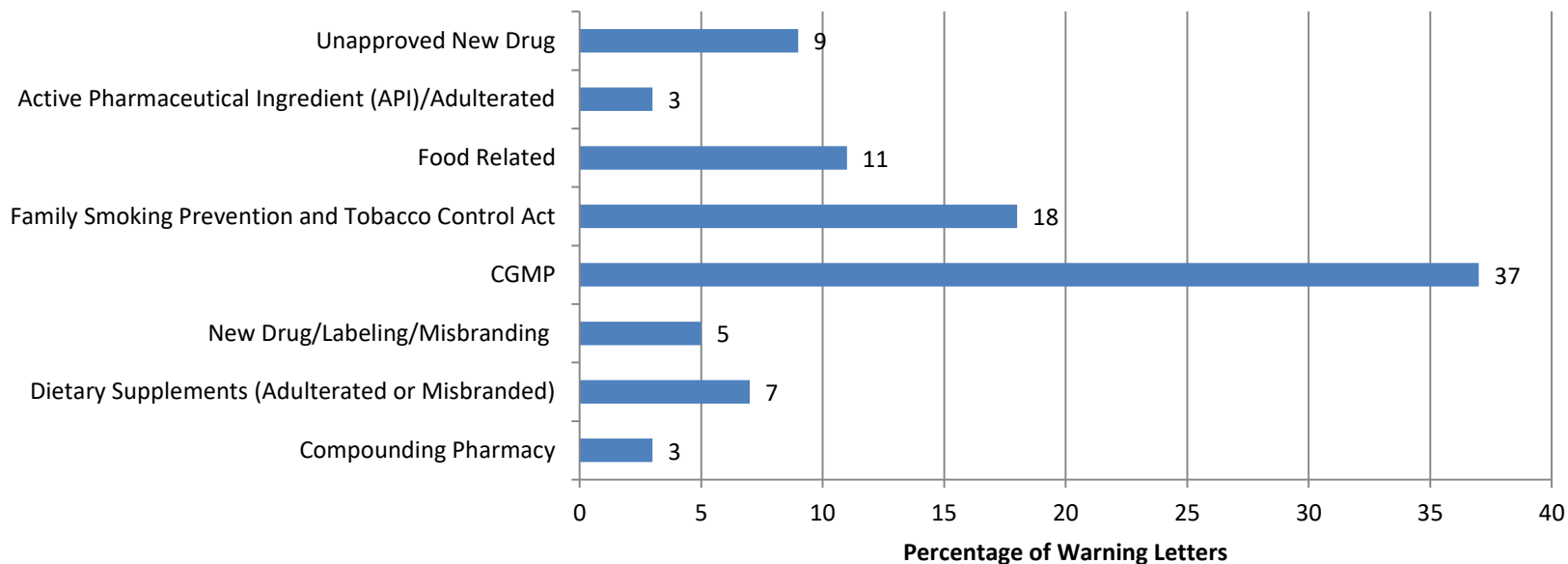
- **CGMP/Active Pharmaceutical Ingredient (API)/Adulterated**

- Warning Letter to Sichuan Friendly Pharmaceutical Co., Ltd.: The FDA found that Sichuan Friendly failed to ensure that its API distributed to the United States conformed to established standards of quality and purity. For example, Sichuan Friendly did not conduct residual solvent testing in its intermediate or finished batches, and manufactured its API on shared equipment, on which inherently toxic solvents were used for other products.

Warning Letter Trends - 2019

284 total warning letters (Limited data available – only current through 9/10/2019)

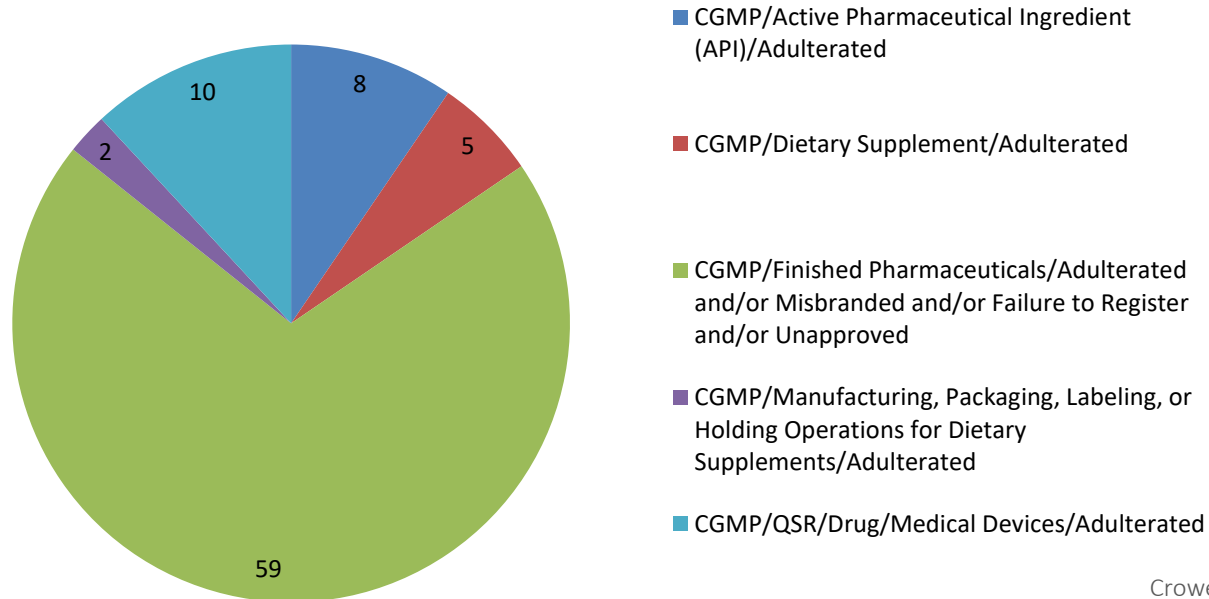
Subject of Warning Letters



2019 CGMP Breakdown

105 total Warning Letters in 2019 based on CGMPs (based on data available through 9/10/19)

CGMPs Relevant to Medical Devices and Drugs - Percentage of Total CGMPs in 2019



Examples of CGMP Issues Cited in Warning Letters (2019)

- **CGMP/Finished Pharmaceuticals/Adulterated**

- Warning Letter to New Era Naturals, LLC: New Era Naturals, a sunscreen manufacturer, did not perform *any* final drug product testing, including testing for the identity and strength of the active ingredient, zinc oxide. New Era Naturals also did not have *any* batch production records for its products to present at its FDA inspection, and had *no* established quality unit.

- **CGMP/QSR/Medical Devices/Adulterated**

- Warning Letter to Datascope Corp.: Datascope failed to provide the FDA with evidence that its Cardiosave device “passed the appropriate dielectric strength and leakage current tests and whether no signs of wetting of uninsulated electrical parts or electrical insulation of parts could result in the loss of basic safety or essential performance”. Datascope also failed to generate new CAPAs after receiving complaints that its Intra-Aortic Balloon Pumps had batteries failing to meet the minimum run time. FDA did not accept Datascope’s response that new CAPAs were not necessary because “new software and instructions for use were being released” for the batteries.

- **CGMP/Active Pharmaceutical Ingredient (API)/Adulterated**

- Warning Letter to Yino, Inc.: Yino Inc., a Chinese company, distributes API products from other manufacturers and ships them to the United States. The FDA found that Yino failed to include the name and address of the original manufacturer on the Certificates of Analysis (COAs) it generated on company letterhead. Further, the COAs lacked a signature from an employee in the quality unit. Yino included the results of testing on its COAs, but the tests were not performed by the original manufacturer, and it could not prove that it actually performed the tests.

Overall Trends in Warning Letters from 2016-2019

What does the data tell us?

- The number of warning letters consistently decreased from 2016 (607) to 2018 (421) – a 31% overall decrease (excluding 2019, as data was only available through 9/10/19).
- Current Good Manufacturing Practices (CGMP) was consistently the subject of the greatest number of warning letters.
 - In categories most relevant to drugs and devices, the top CGMP violations included:
 - CGMP/Finished Pharmaceuticals/Adulterated
 - CGMP/QSR/Medical Devices/Adulterated
 - CGMP/Dietary Supplement/Adulterated/Misbranded
 - CGMP/Active Pharmaceutical Ingredient (API)/Adulterated
- For the subjects specific to the pharmaceutical industry (Compounding Pharmacy, Active Pharmaceutical Ingredient, Dietary Supplement, New Drug/Labeling/Misbranding, Unapproved New Drug), there were no clear trends. With the exception of Unapproved New Drugs, none of these subjects exceeded 10 percent of the total number of warning letters issued.



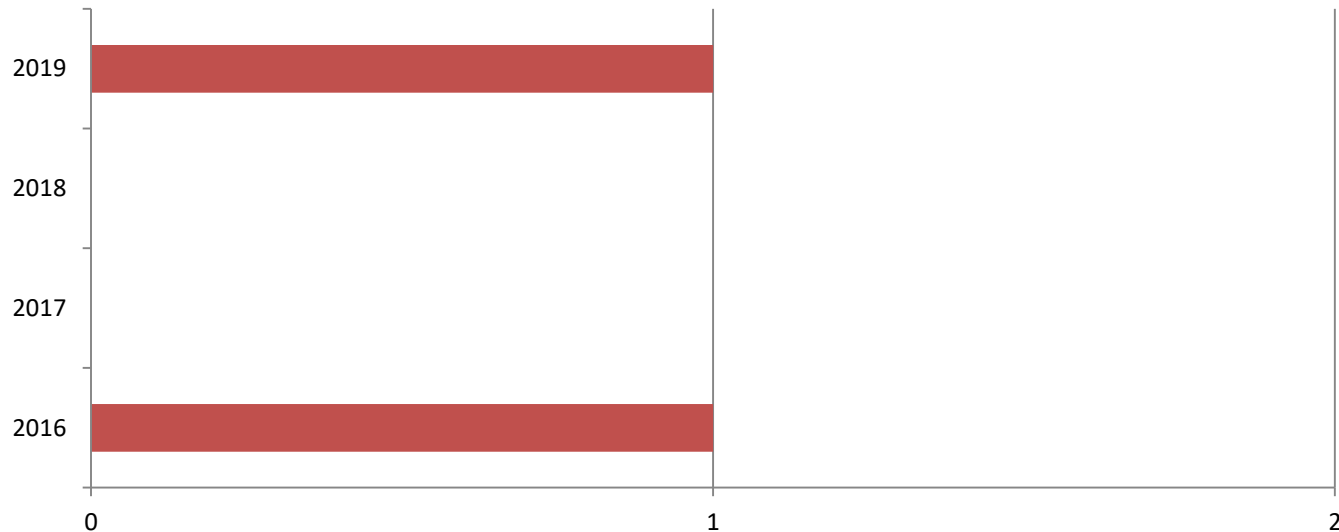
FDA Enforcement Trends: Seizures (Health Fraud)



Seizures Related to Health Fraud

- **According to FDA**, Health fraud scams refer to products that claim to prevent, treat, or cure diseases or other health conditions, but are not proven safe and effective for those uses.

Number of Seizures Related to Health Fraud by Year





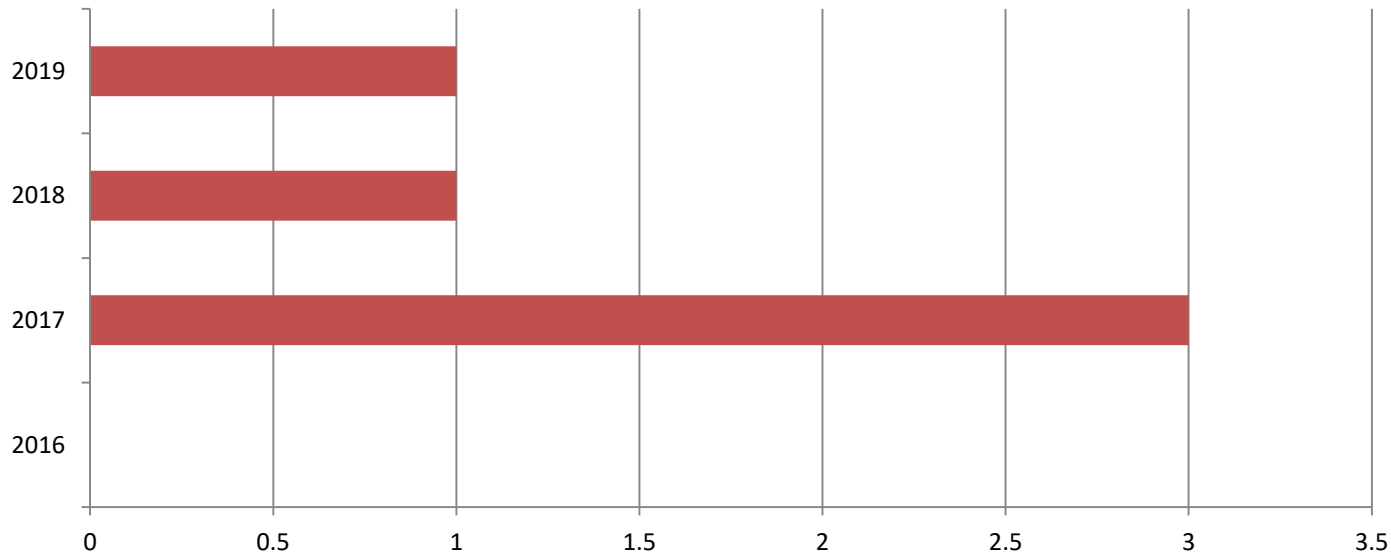
FDA Enforcement Trends: Injunction (Health Fraud)



Injunctions Related to Health Fraud

- **According to FDA**, Health fraud scams refer to products that claim to prevent, treat, or cure diseases or other health conditions, but are not proven safe and effective for those uses.

Number of Injunctions Related to Health Fraud by Year





FDA Enforcement: Litigation Spark



FDA Enforcement: Litigation Spark

- **FDA enforcement actions readily available**
 - FOIA
 - EIR
 - 483's
 - Published by agency
 - Warning letters
 - Seizures
 - Injunctions
- **Admissibility:** 483's and Warning Letters are admissible in many jurisdictions under the public records exceptions to the hearsay rule.
- **Evidence of non-compliance**
 - E.g., warning letters for unsubstantiated claims
- **Legal Landscape**
 - Strict Liability
 - Consumer Protection Statutes



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

Protective apparel is not worn as necessary to protect drug products from contamination.

Specifically,

On 3/19/14 during the set-up of Omnipaque (iohexol) 240mg/ml injectable in Clean Room (b) (4) a technician was observed with exposed skin in the ISO 5 laminar flow hood setting up equipment and supplies. Approximately 1/4 inch of skin was exposed across the length of the technician's forehead above the goggles.

OBSERVATION 2

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established.

Specifically,

It was observed on 3/17/14, a technician unnecessarily handling sterile rubber stoppers. A technician was observed hand stoppering vials (b) (4) vials) of HCG/B12 lot 20141703@3; 10ml CONCENTRATE 10,000 UNITS/1200mcg/ml injectable in the ISO 5 laminar flow hood.