Review of CCS Based on FDA Warning Letters

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Agenda

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02 FDA Citations vs Warning Letters

03 Trends and COVID Pandemic Impact

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Pharmaceutical regulatory warning letters: What can we learn post-COVID?

16-Nov-2022

Regulatory | *Pharmaceutical*

A looks at how the COVID-19 pandemic impacted FDA inspections and the trends that have now cropped up reflecting industry changes. Mirna Vazquez and Jessica Rayser from Charles River discuss

FDA Inspections

Evaluations during Inspections and Relevant Regulations

The manufacturing environment, contamination control strategy, environmental monitoring, risk management, and data integrity are all evaluated and checked for compliance with relevant regulations.

- Annex 1
- USP <1085>
- USP <1116>
- USP <797>
- FDA Code of Federal Regulations 21 CFR 211

Contamination Control Strategy

Why is CCS important to the FDA?

- Formally **documented strategies** with multiple elements implemented site-wide.
- Designed for manufacturers **to identify and resolve risk.**
- To collect all the **precautions to put in place to ensure manufacturing environments remain under control.**
- Should be put in place **across all sterile manufacturing sites.**

CCS should "***define all critical control point and assess the effectiveness of all the controls and monitoring measures to manage risks associated with contamination***" through:

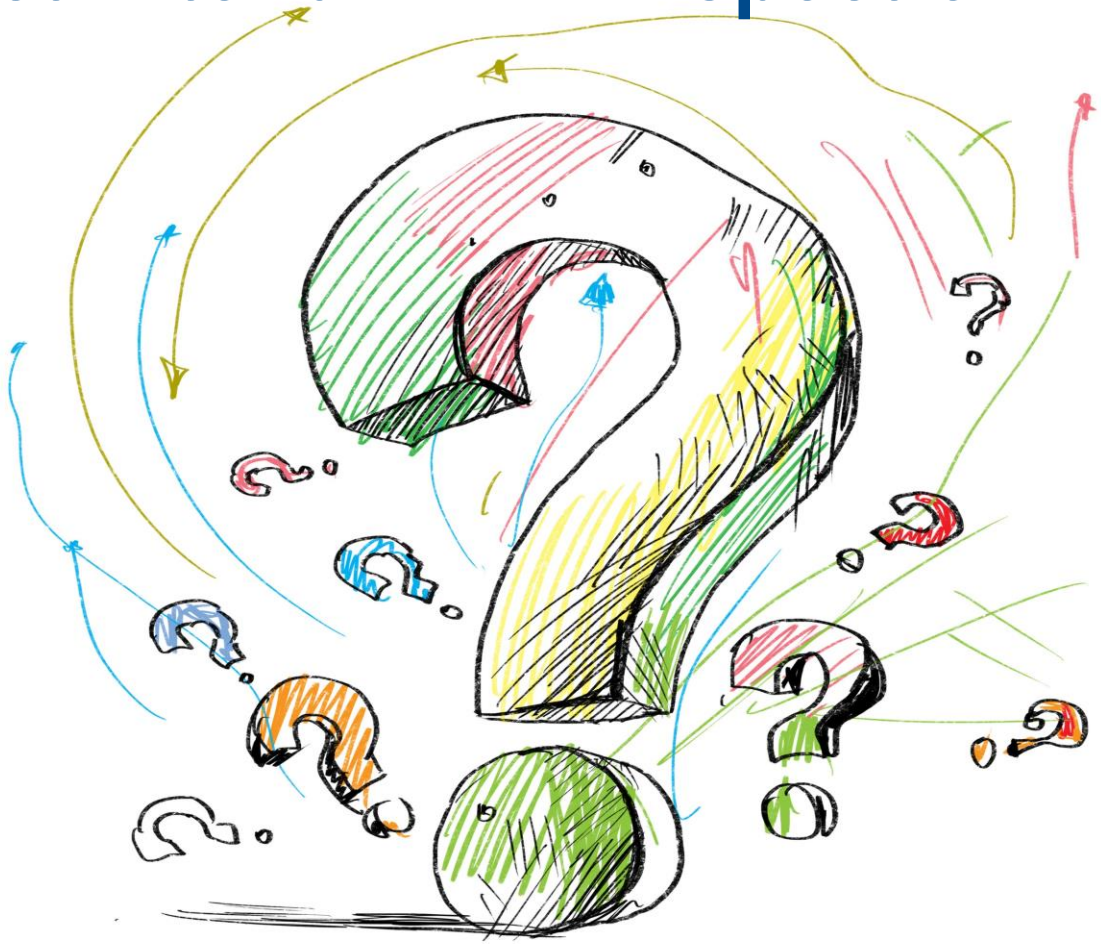
- Continuous updates
- Regular assessment of Environment

} **Tracking & Trending**

What to Expect After an FDA Inspection?

483 Form

Consent Decree



Warning Letter

Facility Closure

FDA Citations vs FDA Warning Letters

483

- Observation after an inspection
- Notice of non-compliance where FDA regulations have not been followed
- Does not imply a warning letter is to follow
- Not an all-inclusive list of every deviation

Warning Letter

- FDA determines a manufacturer has made a significant violation of FDA regulations
- Manufacturers must take immediate corrective action
- Escalation from 483 Form

Can I view 483s and Warning Letters?

FDA U.S. FOOD & DRUG ADMINISTRATION

← Home / Inspections, Compliance, Enforcement, and Criminal Investigations / Compliance Actions and Activities / Warning Letters

- How beneficial can reviewing past Warning Letters help me?

- Freedom of Information Act (FOIA) states the public has the right to request access to records from any federal agency.

Warning Letters

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Learn about the types of warning letters on FDA's website.

- Matters described in FDA warning letters may have been subject to subsequent interaction between FDA and the letter recipient that may have changed the regulatory status of issues discussed in the letter.
- To obtain additional available information, contact FDA. Requests to FDA for agency records should be sent to: Food and Drug Administration Division of Freedom of Information (HFI-35), 5630 Fishers Lane, Rockville, MD 20857. Instructions for how to submit an FOI request can be found at How to Make a FOIA Request.

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Clear Filters

www.fda.gov/regulatory-information/freedom-information

FDA Warning Letter Process

- Notification from the FDA to manufacturer when FDA regulations have been violated during an inspection
- FDA states the company must correct the problem along with directions and timeframe
- Companies must inform FDA of their plans for correction
- FDA verifies corrections are acceptable

Case: 614278

WARNING LETTER

[redacted]

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing [redacted]

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See Title 21 Code of Federal Regulations (CFR), parts 210 and 211 (21 CFR parts 210 and 211).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your response to our Form FDA 483 in detail.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

Your firm's quality control unit failed to exercise its responsibility to ensure drug products manufactured are in compliance with CGMP, and meet established specifications for identity, strength, quality, and purity (21 CFR 211.22).

Lack of quality control over batch release

You manufactured and distributed over the counter (OTC) drug products labeled as Durisan Hand Sanitizer, Alcohol-Free. Your quality unit (QU) approved and released Durisan Hand Sanitizer, Alcohol-Free into the market that failed its finished product specifications for total aerobic microbial count for bacteria (TAMC) and yeast/molds (Y/M) from at least March through December 2020. Furthermore, your firm identified *Burkholderia cepacia*, an opportunistic pathogen, in the drug product Hand Sanitizer Kidney lot# DHS030920A1-S, Hand Sanitizer lot # DHS030920A2-S and Sanitizer Wipes lot# DHS031020A4-S. You released these lots for distribution in April, July, and December of 2020.

In the affidavit dated March 5, 2021, and signed by you, the Chief Executive Officer, you stated that products manufactured from March 1 to June 30, 2020 were shipped in "contaminated form."

These topical products could be applied to broken skin or used by vulnerable populations. Objectionable microbiological contamination of these products can pose a serious hazard to consumers. Moreover, you stated to our investigator that one of your top three customers is a school system that includes infant, toddler, and pre-k programs.

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How did the COVID-19 Pandemic Impact FDA Regulators and Manufacturers?

Impact on Inspections by COVID-19 Pandemic

- Guidance on Remote Interactive Evaluations for Oversight of Drug Facilities During COVID-19 released April 14, 2021
- The FDA adapted, by implementing remote evaluations to aid in their regulatory decision-making
- “The FDA conducts mission-critical inspections to ensure FDA-regulated pharmaceutical products are meeting applicable FDA requirements”
- Manufacturers were prompted to acclimate to this new version of inspections

Remote Regulatory Assessments (RRAs)

Set of Tools used during pandemic by FDA

- *RRAs are an examination of an FDA regulated establishment and/or its records, conducted entirely remotely, to evaluate compliance with applicable FDA requirements*

- Assess establishments and their compliance with applicable FDA requirements

- Applied both domestically and abroad

- RRAs assisted the FDA **conduct oversight, mitigate risk, and meet critical public health needs**

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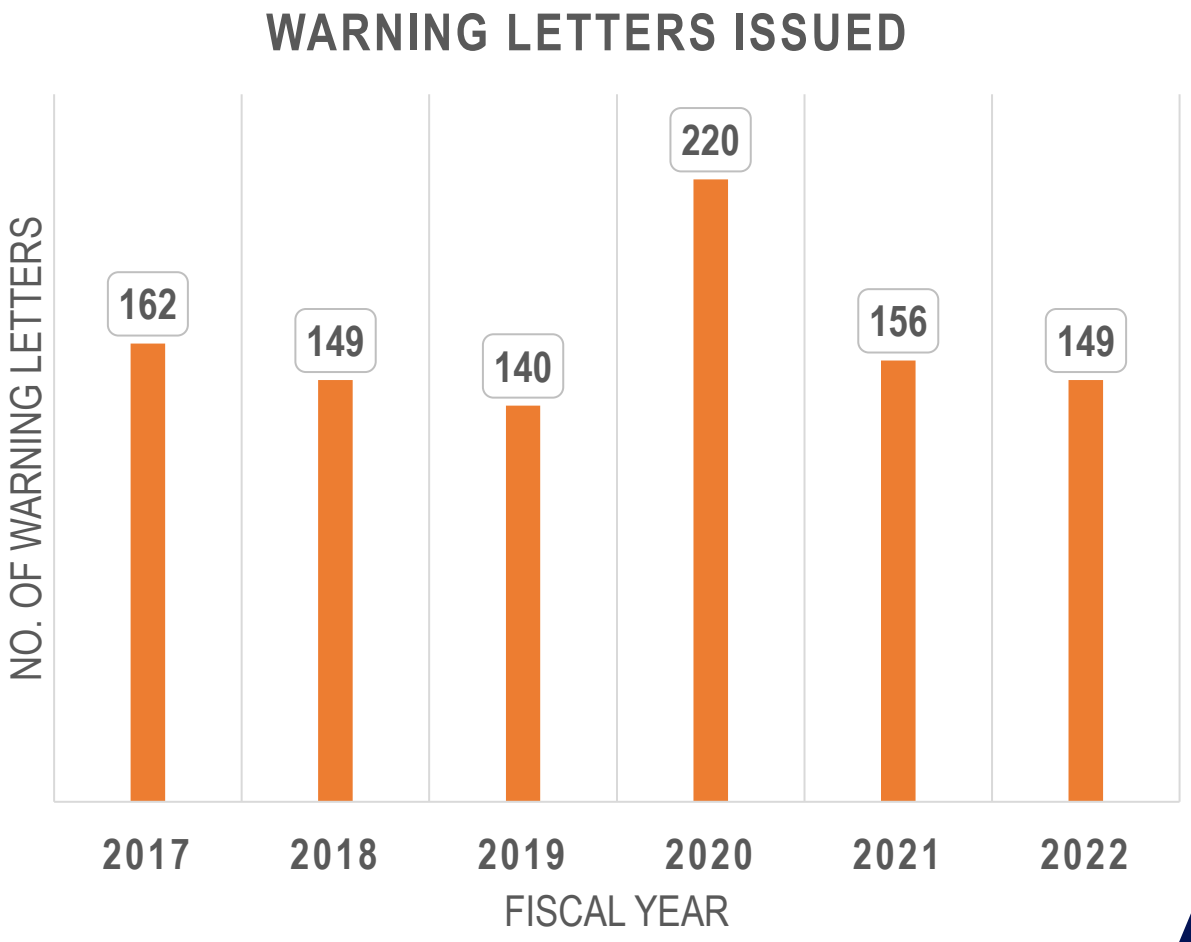

FDA Trends

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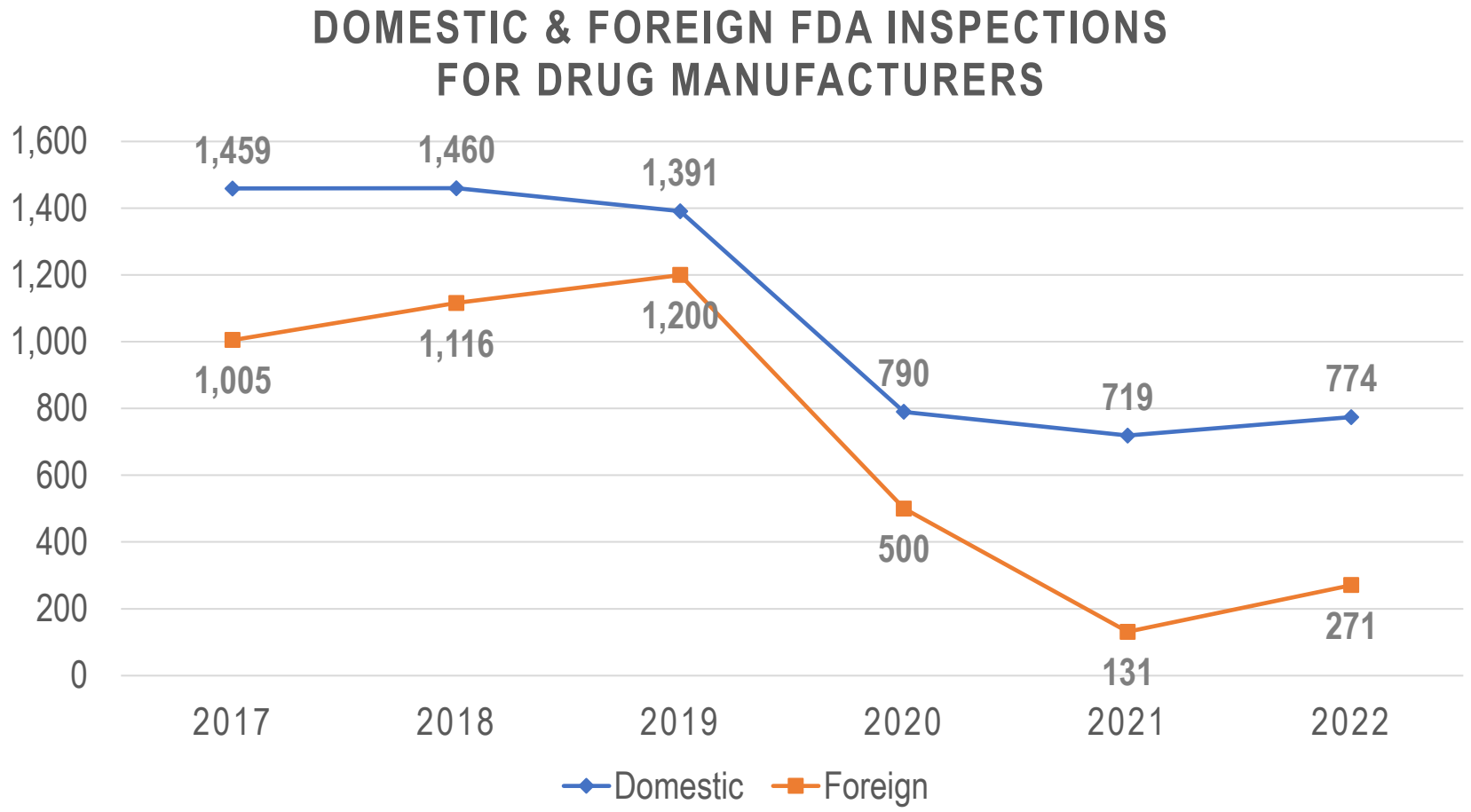
FDA Inspections (Past 6 Years)

- Inspections over time pre/post COVID pandemic and impact from remote evaluations.



https://datadashboard.fda.gov/ora/cd/index.htm

FDA Citations issued pre-pandemic

FDA Citations for Drug Manufacturers - 2017, 2018, 2019			
Rank	Program Area-Citation	Count	Percentage
1	Drugs-21 CFR 211.22(d)-Procedures not in writing, fully followed	438	19%
2	Bioresearch Monitoring-21 CFR 312.60-FD-1572, protocol compliance	338	15%
3	Drugs-21 CFR 211.160(b)-Scientifically sound laboratory controls	268	12%
4	Drugs-21 CFR 211.192-Investigations of discrepancies, failures	241	11%
5	Drugs-21 CFR 211.100(a)-Absence of Written Procedures	196	9%
6	Bioresearch Monitoring-21 CFR 312.62(b)-Case history records- inadequate or inadequate	183	8%
7	Drugs-21 CFR 211.67(a)-Cleaning / Sanitizing / Maintenance	169	7%
8	Drugs-21 CFR 211.165(a)-Testing and release for distribution	160	7%
9	Drugs-21 CFR 211.110(a)-Control procedures to monitor and validate performance	144	6%
10	Drugs-21 CFR 211.67(b)-Written procedures not established/followed	143	6%

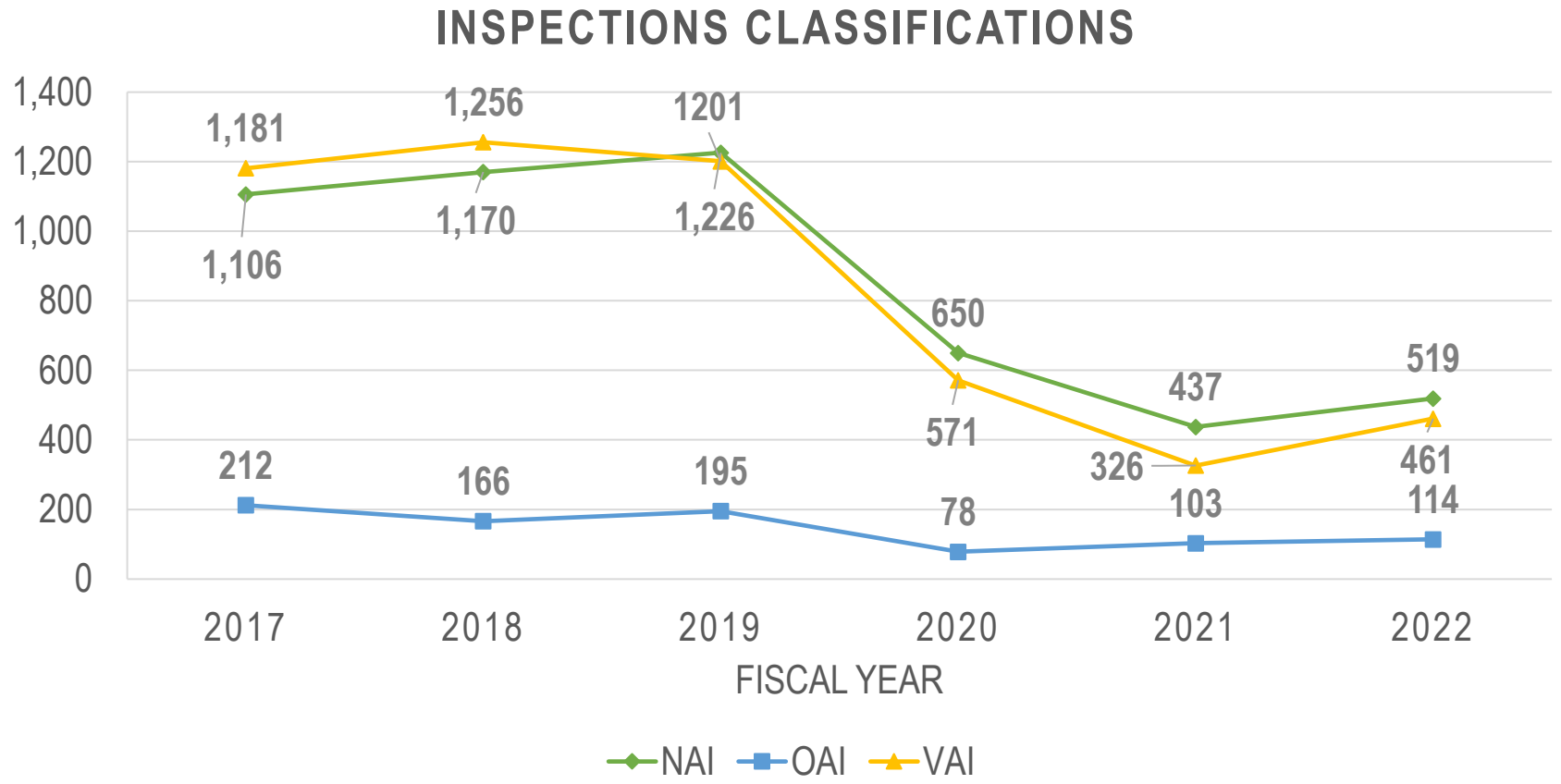
FDA Citations issued post-pandemic

	Rank	FDA Citations for Drug Manufacturers - 2020, 2021, 2022 Program Area-Citation	Count	Percentage
	1	Drugs-21 CFR 211.22(d)-Procedures not in writing, fully followed	228	21%
	2	Bioresearch Monitoring-21 CFR 312.60-FD-1572, protocol compliance	131	12%
▲	3	Drugs-21 CFR 211.192-Investigations of discrepancies, failures	129	12%
▼	4	Drugs-21 CFR 211.160(b)-Scientifically sound laboratory controls	117	11%
	5	Drugs-21 CFR 211.100(a)-Absence of Written Procedures	106	10%
▲	6	Drugs-21 CFR 211.67(a)-Cleaning / Sanitizing / Maintenance	85	8%
▲	7	Drugs-21 CFR 211.63-Equipment Design, Size and Location	77	7%
▲	8	Drugs-21 CFR 211.68(b)-Computer control of master formula records	77	7%
▼	9	Bioresearch Monitoring-21 CFR 312.62(b)-Case history records- inadequate or inadequate	75	7%
	10	Drugs-21 CFR 211.67(b)-Written procedures not established/followed	57	5%

NAI, VAI, and OAI (Past 6 Years)

No Action Indicated (NAI), Voluntary Action Indicated (VAI), Official Action Indicated (OAI)

- Inspections Classified over time pre/post COVID pandemic.

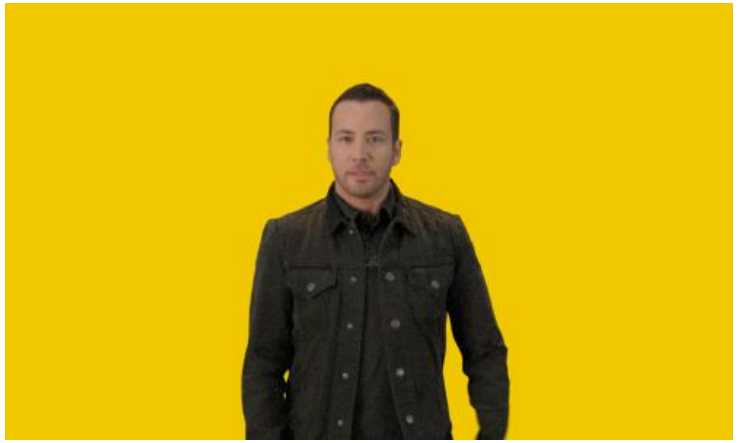


https://datadashboard.fda.gov/ora/cd/index.htm

Warning Letter issued March 2021

21 CFR 211.22(d)-Procedures not in writing, fully followed

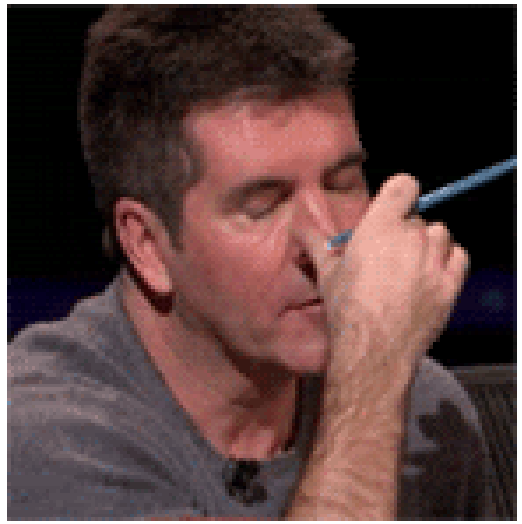
Evaluate product quality before batch release. Your firm obtained out-of-specification (OOS) **(b)(4)** assay release testing results and then sent additional samples from these batches to your contract testing laboratory until passing results were obtained. You reported the passing results and released these batches to the market without investigating release testing assay failures.



Warning Letter issued Nov 2022

21 CFR 211.192-Investigations of discrepancies, failures

Your firm failed to adequately investigate a customer complaint of **(b)(4)** irritation from the use of your **(b)(4)**, lot **(b)(4)**. Your investigation consisted of conducting a "panel test" involving four "participants," who were all your employees, who used the **(b)(4)**. You then determined that further investigation was not required after concluding that your employees exhibited no allergic reactions after using the **(b)(4)**. No additional testing or evaluation of the lot was conducted.



Electronic Batch Records and Equipment Designs

FDA Citations for Drug Manufacturers - 2020, 2021, 2022

FDA Citations for Drug Manufacturers - 2020, 2021, 2022			
Rank	Program Area-Citation	Count	Percentage
7	Drugs-21 CFR 211.63-Equipment Design, Size and Location	77	7%
8	Drugs-21 CFR 211.68(b)-Computer control of master formula records	77	7%

These citations did not make the top 10 from 2017 to 2019!

What changed?

Warning Letter issued July 2021

21 CFR 211.63-Equipment Design, Size and Location

Ensuring your water system, used to manufacture your OTC drug products was suitable for use. The water system produced water contaminated with microorganisms recorded at a level of TNTC on March 23, 2020. Despite these findings, your quality unit (QU) did not exercise its authority to reject drug components made from this system and instead your firm **continued to manufacture and release OTC drug products with objectionable microbiological contamination.** (21 CFR 211.63)

Releasing more product faster does not justify a disregard for quality & safety!

Warning Letter issued August 2022

21 CFR 211.68(b)-Computer control of master formula records

Your firm lacked sufficient controls over your HPLC data acquisition systems used in the testing of drugs for release. For example, your (b)(4) Series HPLC instrument **did not have sufficient controls to prevent deletion and alteration of raw data files.** During the inspection, our investigators observed laboratory personnel performing drug testing and analyses. Personnel had administrative privileges to the (b)(4) operating software for the HPLC equipment. These privileges included, but were not limited to, the ability to delete data sequences and change method parameters.

FDA Stats Overtime

How many citations turn into Warning Letters?

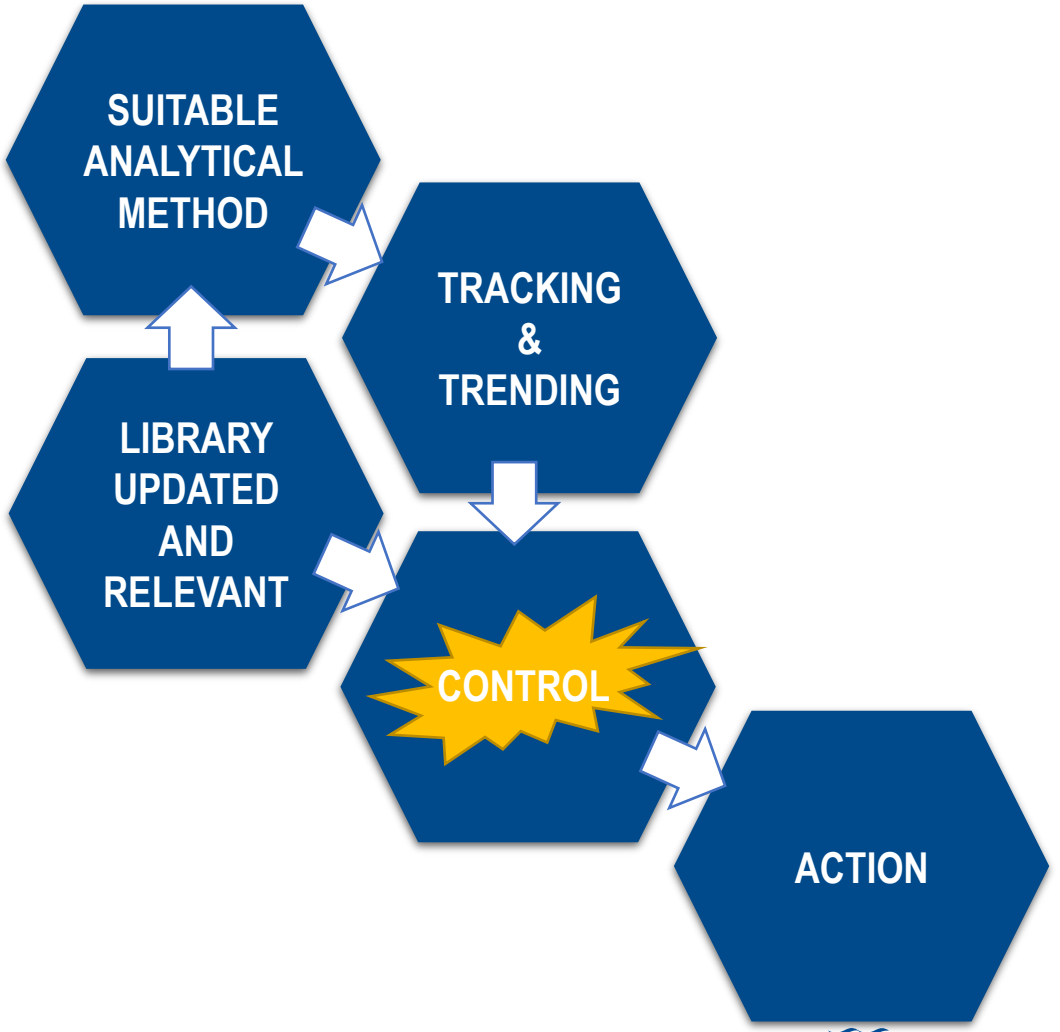
FDA Data (2017 to 2022)	
Inspections	10816
Citations	3362
Warning Letter	976

- On average, **31% of inspections have received a citation or 483.**
- On average, **9% of inspections have received a Warning Letter!**
- What does that mean to you as a manufacturer, microbiologist or quality personnel?

Annex 1

Continuous Improvement Concept

A Contamination Control Strategy (CCS) should be implemented across the facility in order to **define all critical control points and assess the effectiveness of all the controls** (design, procedural, technical and organizational) **and monitoring measures employed to manage risks associated with contamination.** The CCS should be actively updated and should drive continuous improvement of the manufacturing and control methods.



Summary

- Imperative to always be ‘inspection ready’ because an FDA inspector can show up anytime without any prior notice.
- Prioritize a form 483, communicate with FDA on how you can improve.
- Stay up to date with regulations!
- Continuously challenge your CCS, update continuously.
- **Learning from FDA warning letters is just one way demonstrate a commitment to quality, safety, and excellence.**

Knowing the FDA is half the battle!

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Thank You!

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