Review of CCS Based on FDA Warning Letters

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Charles River Laboratories Accugenix®
Agenda

01  FDA Inspections
02  FDA Citations vs Warning Letters
03  Trends and COVID Pandemic Impact
04  Warning Letters Excerpts
05  Summary
Pharmaceutical regulatory warning letters: What can we learn post-COVID?

16-Nov-2022

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.
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:
  
  o Continuous updates
  o 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?

- 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.

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
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
FDA Trends

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>No. of Warning Letters</th>
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<tbody>
<tr>
<td>2017</td>
<td>162</td>
</tr>
<tr>
<td>2018</td>
<td>149</td>
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<td>2019</td>
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<td>2021</td>
<td>156</td>
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<td>2022</td>
<td>149</td>
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FDA Inspections (Past 6 Years)

- Inspections over time pre/post COVID pandemic and impact from remote evaluations.
# FDA Citations issued pre-pandemic

<table>
<thead>
<tr>
<th>Rank</th>
<th>Program Area-Citation</th>
<th>Count</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>1</td>
<td>Drugs-21 CFR 211.22(d)-Procedures not in writing, fully followed</td>
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<td>Bioresearch Monitoring-21 CFR 312.60-FD-1572, protocol compliance</td>
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<td>4</td>
<td>Drugs-21 CFR 211.192-Investigations of discrepancies, failures</td>
<td>241</td>
<td>11%</td>
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<td>Drugs-21 CFR 211.100(a)-Absence of Written Procedures</td>
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<td>Bioresearch Monitoring-21 CFR 312.62(b)-Case history records- inadequate or inadequate</td>
<td>183</td>
<td>8%</td>
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<tr>
<td>7</td>
<td>Drugs-21 CFR 211.67(a)-Cleaning / Sanitizing / Maintenance</td>
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<td>Drugs-21 CFR 211.165(a)-Testing and release for distribution</td>
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<td>Drugs-21 CFR 211.67(b)-Written procedures not established/followed</td>
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### FDA Citations issued post-pandemic

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<th>Rank</th>
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<td>4</td>
<td>Drugs-21 CFR 211.160(b)-Scientifically sound laboratory controls</td>
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<td>7</td>
<td>Drugs-21 CFR 211.63-Equipment Design, Size and Location</td>
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<td>8</td>
<td>Drugs-21 CFR 211.68(b)-Computer control of master formula records</td>
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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

<table>
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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!
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?

<table>
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<th>FDA Data (2017 to 2022)</th>
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<tbody>
<tr>
<td>Inspections</td>
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<td>Citations</td>
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<td>Warning Letter</td>
<td>976</td>
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• 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!
Thank You!

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