Best Lessons Learned from FDA Warning Letters

Presented by:
Walter Nowocin, ASEM Fellow
IndySoft Corporation, Minneapolis, Minnesota

Hosted-PJLA , Tracy Szerszen, President

January 17, 2023
1:00-2:00 PM EST

PJLA

Presentation Overview

Hosted By-Tracy Szerszen
President
Perry Johnson Laboratory Accreditation (PJLA)

- FDA Database- how to review citations
- Common findings regarding calibration issues and how to prevent
- Questions & Answers

Webinar Housekeeping

- This webinar will be recorded
- All PJLA webinars are made available on our website & YouTube channel

  https://www.pjlabs.com/training/pjla-webinars/past-webinars
- All attendees are muted
- Please utilize the question tool bar to submit questions to be answered at the end of presentation

ISO/IEC 17025:2017-Section 6

- **6.4 Equipment**
- *6.4.3 The laboratory shall have a procedure for handling, transport, storage, use and planned maintenance of equipment in order to ensure proper functioning and to prevent contamination or deterioration.*
- *6.4.5 The equipment used for measurement shall be capable of achieving the measurement accuracy and/or measurement uncertainty required to provide a valid result.*
- *6.4.6 Measuring equipment shall be calibrated when:*
- *— the measurement accuracy or measurement uncertainty affects the validity of the reported results*
- *6.4.13 Records shall be retained for equipment which can influence laboratory activities. The records shall include the following, where applicable:*
- **6.5 Metrological traceability**
- **6.5.1** The laboratory shall establish and maintain metrological traceability of its measurement results by means of a documented unbroken chain of calibrations, each contributing to the measurement uncertainty, linking them to an appropriate reference.
- *6.5.2 The laboratory shall ensure that measurement results are traceable to the International System of Units (SI) through:*
- *a) calibration provided by a competent laboratory; or*
- **6.6 Externally provided products and services**
- *6.6.1 The laboratory shall ensure that only suitable externally provided products and services that affect laboratory activities are used, when such products and services:*

Welcome
Walter Nowocin, IndySoft

- Walter Nowocin is the Life Sciences Product Manager for IndySoft Corporation. He works with development, marketing, and sales to ensure that IndySoft is optimized to support calibration quality systems in regulated industries while being compliant with FDA, GMP, and ISO requirements.
- Walter has over 35 years of calibration and leadership experience with Medtronic, the world's largest medical device manufacturer, and with the United States Marine Corps.
- Walter is Co-Chair of the NCSL International Healthcare Metrology Committee and is the Section Coordinator of the NCSLI Minnesota Section.
- Walter is a Co-Author of the Third Edition of the ASQ Metrology Handbook released in January 2023.
- Walter is the Writing Group Chair for the Fifth Edition of the NCSLI Recommended Practice "Calibration Quality Systems for the Healthcare Industries" (RP-6) released in December 2022.
- Walter has a Masters in Engineering Management degree from St. Cloud State University, Minnesota and is a Fellow of the American Society of Engineering Management.

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Walter Nowocin, ASEM Fellow
IndySoft Corporation, Minneapolis, Minnesota
Perry Johnson Laboratory Accreditation Webinar
17 January 2023

About the Presenter: Walter Nowocin

Experience

- Over 35 years of experience in the field of metrology
  - Medtronic – Senior Engineering Manager, Metrology Department
  - United States Marine Corps – Master Sergeant, Precision Measuring Equipment Laboratory

Education

- Masters in Engineering Management, St. Cloud State University, MN
- Certified Professional Engineering Manager (cPEM)

Other

- Fellow, American Society of Engineering Management
- Co-Chair, NCSLI Healthcare Metrology Committee
- Co-Author, ASQ Metrology Handbook, 3rd Edition
- Vice President,
  NorthStar Camaro Club of Minnesota

1977 Camaro Sports Coupe

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Objectives

- Learn How to Use the FDA Web Site for Searching Regulatory Observations/Findings
- Review the Top 8 calibration related FDA warning letters and 483s recently posted
- Have discussions involving best practices on avoiding similar occurrences
- Pass along lessons learned

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Content

- **Background**

  Review two sources for the FDA Warning Letters and 483 Findings

- **General Observations**

  Share recent trends of FDA Warning Letters and 483 Findings

- **Top Eight FDA Warning Letters**

  Review of the examples with summary comments

- **Key Take A Ways**

  Summarize key points

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Source of FDA Data

- All data in this presentation was taken from the 'FDA Electronic Freedom of Information Reading Room'
  - Warning Letters: https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters
  - 483 Observations: https://www.fda.gov/about-fda/office-regulatory-affairs/ora-foia-electronic-reading-room

★ These web sites have dramatically improved on the ease for searching for particular examples and I would encourage you to perform your own search experiments.

? Don't ask me why there are two different search sites for essentially the same kind of information. Just our great government at work. ☺

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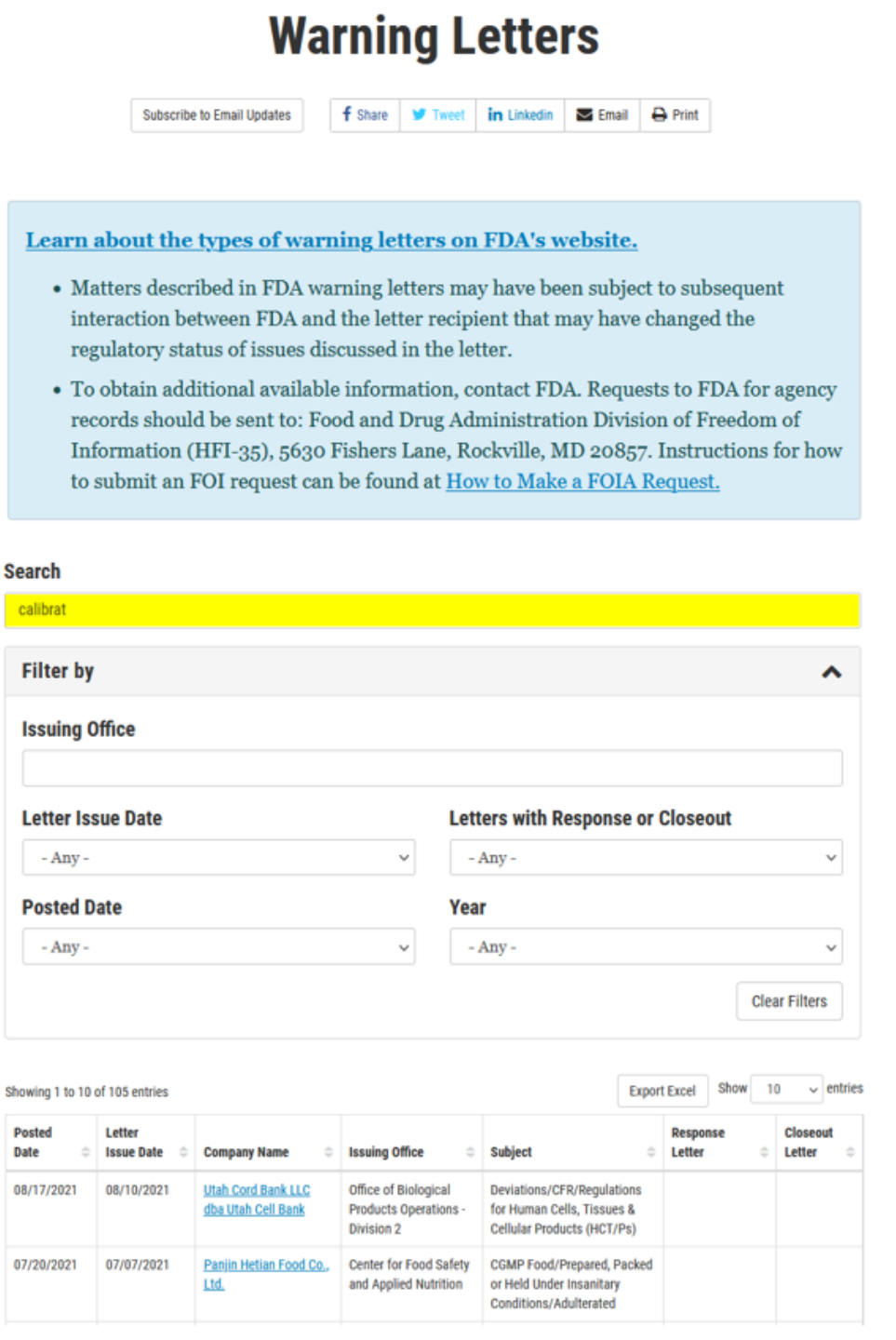
FDA notification levels of violations:

- **Form 483** *Inspectional Observations: FDA* official notification of inspection findings at the conclusion of an on-site inspection.
- **Warning Letter**: sent to the manufacturer for significant violations of FDA regulations.
- **Consent Decree**: an FDA injunction to the manufacturer to halt operations until violations are resolved.

Search Tips:

- Use key words such as 'cleanroom'
  - ✓ Found 'calibrat' best to cover variations of 'calibrate,' calibrated,' and 'calibration.'
  - ✓ Results: 105 out of 2,600 reports (4%)
- Click on 'Company Name' to open each report.



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.

Search: calibrat

Filter by

Issuing Office

Letter Issue Date: - Any -

Letters with Response or Closeout: - Any -

Posted Date: - Any -

Year: - Any -

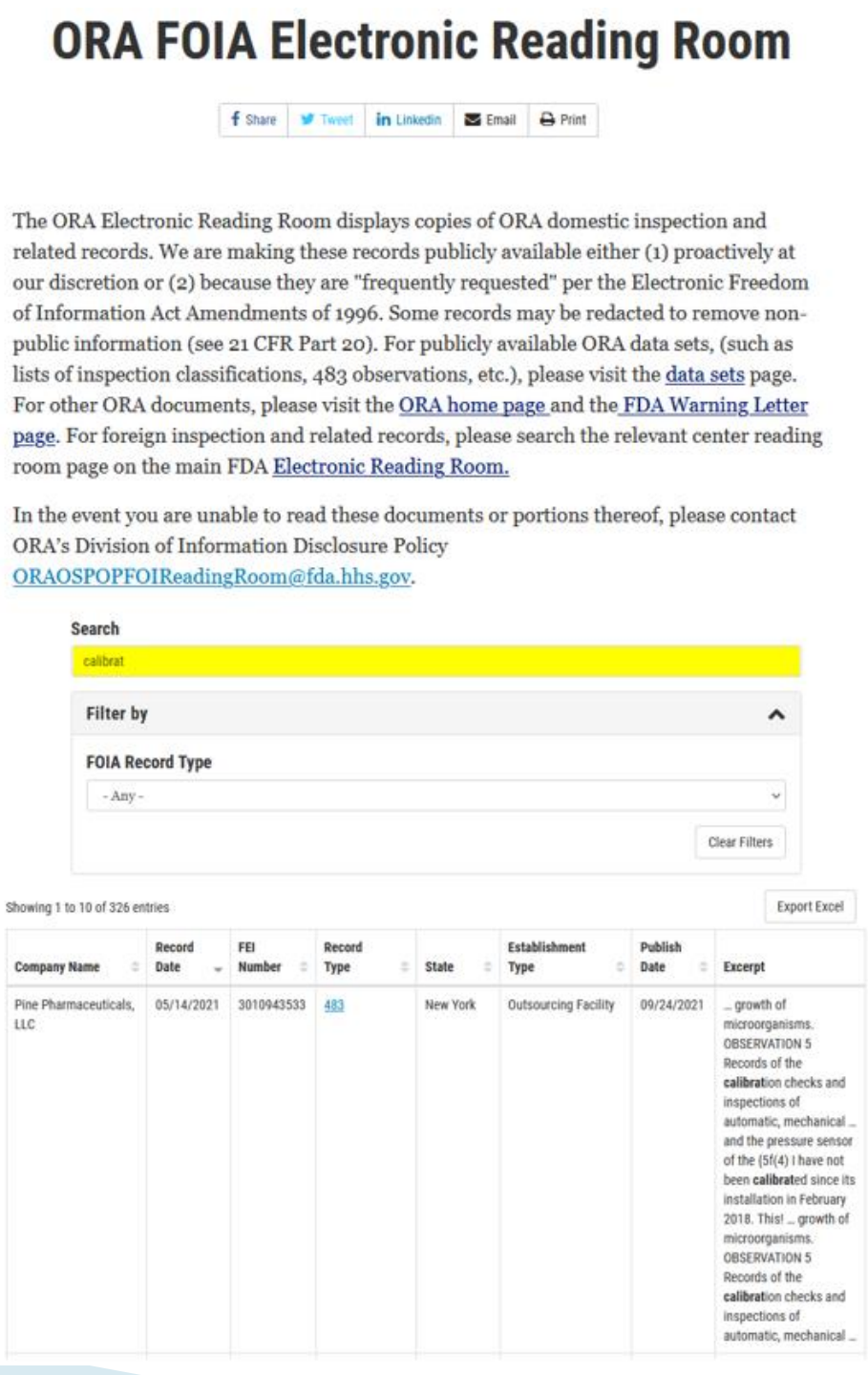
Clear Filters

Showing 1 to 10 of 105 entries | Export Excel | Show 10 entries

Posted Date	Letter Issue Date	Company Name	Issuing Office	Subject	Response Letter	Closeout Letter
08/17/2021	08/10/2021	Utah Cord Bank LLC dba Utah Cell Bank	Office of Biological Products Operations - Division 2	Deviations/CFR/Regulations for Human Cells, Tissues & Cellular Products (HCT/Ps)		
07/20/2021	07/07/2021	Panjin Hetian Food Co., Ltd.	Center for Food Safety and Applied Nutrition	CGMP Food/Prepared, Packed or Held Under Insanitary Conditions/Adulterated		

FORM 483 Inspectional Observations

- Though labeled as ‘ORA FOIA . . .,’ this is the search site for FDA Form 483s.
- Search field works similar to the ‘Warning Letter’ search site. Recommend using key words.
- Click on ‘Record Type’ [483] to open each report.
- A nice improvement is the ‘Excerpt’ field where you can see your highlighted search words. This speeds up your search work by seeing which reports may be of more interest.
- Results for ‘calibrat’: 326 out of 2,237 reports (15%.)



ORA FOIA Electronic Reading Room

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The ORA Electronic Reading Room displays copies of ORA domestic inspection and related records. We are making these records publicly available either (1) proactively at our discretion or (2) because they are "frequently requested" per the Electronic Freedom of Information Act Amendments of 1996. Some records may be redacted to remove non-public information (see 21 CFR Part 20). For publicly available ORA data sets, (such as lists of inspection classifications, 483 observations, etc.), please visit the data sets page. For other ORA documents, please visit the ORA home page and the FDA Warning Letter page. For foreign inspection and related records, please search the relevant center reading room page on the main FDA Electronic Reading Room.

In the event you are unable to read these documents or portions thereof, please contact ORA's Division of Information Disclosure Policy ORAOSPOPFOIReadingRoom@fda.hhs.gov.

Search: calibrat

Filter by

FOIA Record Type: - Any -

Clear Filters

Showing 1 to 10 of 326 entries — Export Excel

Company Name	Record Date	FEI Number	Record Type	State	Establishment Type	Publish Date	Excerpt
Pine Pharmaceuticals, LLC	05/14/2021	3010943533	483	New York	Outsourcing Facility	09/24/2021	... growth of microorganisms. OBSERVATION 5 Records of the **calibrat**ion checks and inspections of automatic, mechanical ... and the pressure sensor of the (5f(4) I have not been **calibrat**ed since its installation in February 2018. This! ... growth of microorganisms. OBSERVATION 5 Records of the **calibrat**ion checks and inspections of automatic, mechanical ...

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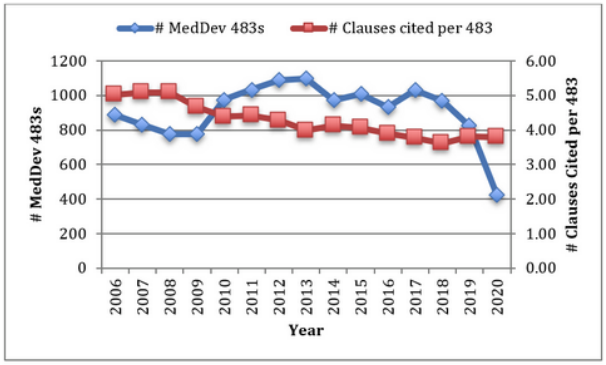
General Observations

- **Form 483 Inspection Findings** have steadily declined from FY17 through FY20; back to FY06 levels.



Med Device Online. 17 March 2021

- **Production and Process Controls (PPC)** continues to be a Top 10 area citied by the FDA for 483 Inspection violations, coming in at #6.

- **Calibration** trends:
  - ✓ Issues tend to be basic; e.g. no calibration schedules, overdue calibrations, or no procedures.
  - ✓ Rare to have a calibration issue alone; usually associated with other quality system issues.
  - ✓ Many findings are non-compliance to the company's own documented requirements. **"Say What You Do and Do What You Say"**

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FDA Warning Letter Categories

- Quality System Regulation for Medical Devices – 21 CFR Part 820
- Current Good Manufacturing Practice for Finished Pharmaceuticals – 21 CFR Part 211
- Good Laboratory Practice for Nonclinical Laboratory Studies – 21 CFR Part 58

Number 8

Environmental Monitoring Alarms – Device Warning Letter – 31 August 2016

"Failure to establish and maintain procedures to adequately control environmental conditions, where environmental conditions could reasonably be expected to have an adverse effect on product quality. **For example**, it was observed that the firm did not inspect its temperature and humidity monitoring system's alarm to verify its function of triggering an audible alert for temperature and/or humidity excursions as part of the environmental control for the manufacturing floor."

"The response is not adequate because your firm did not:

- Provide a copy of the new procedure used to monitor and document the settings of alarm systems/temperature of the different rooms used for manufacturing.
- Provide training records demonstrating employees have been properly trained to conduct and document inspections in the future.
- Provide documentation of a retrospective review of past maintenance records, including transcripts from PC logs to determine whether environmental controls have been maintained during manufacturing and whether further corrective action is needed.
- Conduct a retrospective review of similar environmental control systems to determine compliance with 21 CFR 820.70(c)."

COMMENT: A good example to start with. Environmental controls is an area of particular focus for the FDA. This finding highlights the need to learn how to respond to FDA findings.

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"How to Effectively Respond to FDA 483s," Kristen Grument, Executive Director, NSF Health Sciences. 28 January 2015.

There are three methods to better respond to 483s:

1. Understand the FDA's definition of "**establish**" when revising or creating procedures. Per 21 CFR 820.3(k), "establish" means define, document (in writing or electronically), and implement. **Training** is an integral part of implementation and is therefore expected to be included as part of the response package when submitting new or revised procedures.

2. Address the actual example cited in the 483 observation. It is imperative to correct the cited examples (**immediate correction**), but also the system glitch that allowed the noncompliance to occur to prevent recurrence (**system corrective**). Also, to look beyond the immediate issue to see where else a similar noncompliance could occur (**preventive action**).

3. Evaluate the impact of a long-standing deficiency on past practices, decision, and records. It is also important to evaluate each 483 observation for the need for a ***retrospective review***, especially when the new or revised procedures implement significant changes to the process or decision-making criteria. The FDA will generally accept **two years** as an adequate timeframe for a retrospective review.

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Number 7

OOT Report Effectiveness – FDA Form 483 Finding – 15 April 2014

"Your firm performs corrective actions in the Product Risk Assessment (PRA) system, the Nonconformance (NCR) system and the Equipment/Instrument Calibration (OOT) system; the **corrective** actions taken in these systems do not include:

(1) conducting **verifications of *effectiveness*** to the specific correction to ensure the problem was resolved,
(2) reoccurrence was prevented, and
(3) the action did not negatively affect the finished device.

Your procedures do not include instructions for effectiveness checks of corrective actions taken within the individual reports."

COMMENT:

Remember this tip:
"A **correction** is present tense and does not require an effectiveness check, while a **corrective** action is future tense and does require an effectiveness check."

Ensure that your standard operating procedure (SOP) explains the difference.

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Number 6

Stern FDA Response – Drug Product Warning Letter – 11 June 2019

"Failure to ensure that necessary calibrations are performed and recorded. You failed to appropriately calibrate scales used to weigh API for their intended use. **For example**, scale 5 used to weigh small amounts of estriol API down to (5) grams was calibrated at (10), and (20) grams, which *did not bracket* the precise amount of API to be weighed. Additionally, the (reference) gram weight used for scale verification checks was **last calibrated in 2008**."

"Your response stated the use of the scales was halted and your policies were updated to include yearly weight calibration. However, your response did not indicate how you plan to review equipment calibration.

In response to this letter, provide the following, your:

(1) **Review of product** distributed that may have been affected by inadequate calibration of scales for intended use

(2) **Plan to notify customers** affected by the inadequate scale calibration

(3) **Corrective actions and preventive actions** for routine management oversight of equipment to ensure prompt detection of equipment performance issues, execution of repairs, completion of preventive maintenance, and equipment calibration."

COMMENT:
1. A recent trend where the FDA is getting more stringent on response expectations.
2. This is a good example of why you do not want to get an FDA Warning Letter; A simple finding that will now take a very large effort to resolve.

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Number 5

Monitoring Chambers – Drug Product Warning Letter – 29 August 2018

"Your firm failed to use equipment in the manufacture, processing, packing, or holding of drug products that is of appropriate design, adequate size, and suitably located to facilitate operations for its intended use (21 CFR Part 211.63).

Your microbiological laboratory equipment was not suitable for use. You use unqualified incubators which are intended to grow and maintain microbiological cultures. You have not conducted **mapping studies** to ensure adequate temperature distribution for the incubator. In addition, one incubator did not have an internal thermometer or a **continuous monitoring device** to monitor temperature and ensure it remains within specification."

In response to this letter, provide a detailed plan for qualifying, maintaining, and monitoring all laboratory equipment.

COMMENT: Inspectors know that environmental chambers may not be adequately qualified, maintained, or monitored. Many companies are using older chambers that may not have adequate specifications for chamber stability, linearity, or sufficient data for determining location and number of adequate monitoring devices to **map** hot and cold locations throughout the chamber.
How are your legacy chambers controlled; e.g. ovens, refrigerators, incubators, cleanrooms, etc.?

Number 4

Uncontrolled Spreadsheet – Device Warning Letter – 3 August 2016

"Failure to validate computer software for its intended use according to an established protocol when computers or automated data processing systems are used as part of production or the quality system, as required by 21 CFR 820.70(i). **For example**, your firm was utilizing an uncontrolled spreadsheet to track equipment requalification due dates."

"We reviewed your firm's response and conclude that it is not adequate. Your response did not address this deficiency."

COMMENT:

GAMP 5: ***A Risk-based Approach to Compliant GxP Computerized Systems*** defines five categories of spreadsheets in **Appendix S3** ***End User Applications Including Spreadsheets:***

1. **No Calculations – treat as a text document (no verification)**
2. **Disposable – used as a calculator (spreadsheet software verified for general use)**
3. **Retained as Documents – needs adequate control and storage (verification)**
4. **Used as a Template – efficient reuse with better quality control (verification)**
5. **Used as a Database – not recommended for spreadsheet software; too many FDA 21 CFR Part 11 compliance gaps (audit trails, sign-offs, etc.)**

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Number 3

Data Integrity – Drug Product Warning Letter – 23 December 2019

"Your firm failed to routinely calibrate, inspect, or check according to a written program designed to assure proper performance and to maintain adequate written records of calibration checks and inspections of automatic, mechanical, electronic equipment, or other types of equipment, including computers, used in the manufacture, processing, packing, and holding of a drug product (21 CFR Part 211.68(a).

During a review of an out-of-specification investigation for drug content in your bulk drug lot, our investigator identified multiple discrepancies between the human machine interface (HMI) data, and the entries made by operators into batch records. For example, the operator recorded **(b)(4)** the batch during Step **(b)(4)** for **(b)(4)** at **(b)(4)**. However, HMI data indicated that **(b)(4)** were not operational at that time. "

"Your quality system does not adequately ensure the accuracy and integrity of the data to support the safety, effectiveness and quality of the drugs you manufacture. Without complete and accurate records, you cannot assure appropriate decisions regarding batch release, product stability, and other matters that are fundamental to ongoing assurance of quality."

COMMENT: **Data Integrity** is the latest buzz word in FDA inspections. But this is an area that has been consistently reported on just not using the new buzz word. Companies are vulnerable to data integrity issues as a result of legacy instrumentation lacking robust data entry, data modification, and data record controlled access protocols. How are your legacy software integrated instrumentation being controlled? FDA Guidance Document: *Data Integrity and Compliance with Drug CGMP. www.fda.gov/media/97005/download.*

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Number 2

"Mini–Calibration" – Drug Product Warning Letter – 26 March 2019

Equipment Calibration and Qualification:

"Your firm lacks qualification study records for critical manufacturing equipment. You also lack adequate procedures for calibrating and qualifying the equipment used to manufacture your drug products. Our investigators found that you moved tablet presses, V-shape blenders, fluidized bed granulator, mixers, and packaging line manufacturing equipment between your production rooms and the warehouse (a non-controlled area), depending on the manufacturing schedule. Your firm did not adequately evaluate the impact of relocated equipment would have on the manufacturing process.

In your response, you indicated that your fluid bed granulator, tablet press, and large V-shape blender usually remained in place. You indicated that before every start of a manufacturing process, a "**mini-calibration**" is performed, although the data provided seems to be consistent with routine machine set-up activities. You added that the certain equipment was qualified by the firm's previous owner in 2010, but you were unable to provide qualification documents to our inspection team.

Your response was inadequate. You did not provide evidence of "**mini-calibration**" of equipment after it was moved to demonstrate that it continues to be calibrated and qualified before use.

In response to this letter, include:

- An updated calibration and qualification program for all your manufacturing equipment.
- A revised procedure for the relocation, movement, and calibration of manufacturing equipment. Provide details of appropriate calibration and qualification activities that will be needed and describe which equipment operating parameters are to be evaluated before release of equipment for commercial production.

COMMENT: Just when you think you have heard every type of "calibration" explained, a new one shows up – mini-calibration. Of course, that explains everything. The key concept here is the idea of "before" and "after" qualification for a move of critical equipment in a validated process.

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Number 1

CEO States "No Calibrations Are Needed" Device Warning Letter – 23 March 2017

"Failure to establish and maintain procedures to ensure that equipment is routinely calibrated, inspected, checked, . . . For example:

a. Your firm has not established calibration procedures to ensure that equipment is routinely calibrated . . . In addition, there has been no calibration performed on in-process or final inspection measurement/test equipment because **according to your firm's CEO, "no calibrations are needed**, as the instruments are accurate enough for the firms' purposes."

b. There is no requirement for inspection or measuring tools made in-house to undergo a type of measurement system analysis to confirm suitability of its intended use and ability to provide consistent valid results."

"We reviewed your firm's responses and conclude that they are not adequate. **It is not clear how instruments that were previously calibrated are now accurate enough for your firm's processes, given a lack of design information**. Your firm should provide its calibration procedure for review; a calibration schedule for all of its inspection, test and measuring equipment, including the air gun and molding machine pressure gages; and evidence that calibration has been performed for all of its inspection, test and measuring equipment."

COMMENT: My New Favorite Finding! ☺

1. Unfortunately, this is not an isolated case. ☹
2. How are you ensuring that in-house built tooling is checked periodically for wear?

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Key Takeaways

- ✓ **Remember**: The FDA has two very useful web sites to search for Warning Letters and Form 483 Inspection Findings using key words.
  You can learn a lot from these FDA documents.
- ✓ Follow Kristen Grumet's three methods for submitting FDA responses.
- ✓ Calibration findings are typically very basic in nature and usually associated with many other quality system issues.
- ✓ The latest trends continue to be related to data integrity, environmental monitoring/mapping, legacy equipment issues, and training.

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Thank You For Attending

For more information feel free to contact me:

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Time for Questions and Answers

Join us for future Webinars

February 21, 2023– 1:00pm EST
Section 7.6 “Evaluation of measurement uncertainty” for testing laboratories, Matt Sica, Testing Program Manager

March 29, 2023- 1:00 EST
Section 8.5 “Actions to Address Risks and Opportunities, Mike Kramer, Calibration and Inspection Program Manager

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Thank You!