



**Search Less, Know More**

The essential tool for regulatory,  
compliance, & quality professionals

[www.govzilla.com](http://www.govzilla.com)

[help@govzilla.com](mailto:help@govzilla.com)

(844) 332-3320

## **Impact of the Global Pandemic on Recent Data Integrity and Regulatory Noncompliance Trends**

**Presented by:**

**Paul Smith  
Global Compliance Specialist at  
Agilent Technologies**

# Impact of the Global Pandemic on Recent Data Integrity and Regulatory Noncompliance Data

Paul Smith  
26<sup>th</sup> August 2020



# Why Review Regulatory Noncompliance Data ?



- **cGMP and Regulations** – *Typically Only Provide a Framework – That must be Satisfied*
- **Interpretation** - *Typically Interpretation is Required*
- **How are Regulators “Applying” (Interpreting)?**
- **Nonconformance Data and Guidance Documents** – *Show Regulatory Focus*

## Why Focus on Data FDA ?

- **Quality and Volume of Data** – *e.g. Warning Letters, 483's, Citations, Actions...etc.*
  - **Influence** – *Other Regulators can “Follow” The FDA....*
  - **At Least 10 x** - *More FDA Data – Than All Other Regulators in the World Combined (at the moment)*
-

# How do Companies Approach to Regulatory Trends?

**Lowest Risk**

Strategy:

**Implement  
Improvements  
(risk / trend)**

*Longer Term....*

**Proactive  
- Plan Risk Reduction**

**Data – to Analyse**



Regulatory Trends



**Specific Information**



Regulatory Answers



*Shorter Term....*

**Reactive  
- React to Problems**

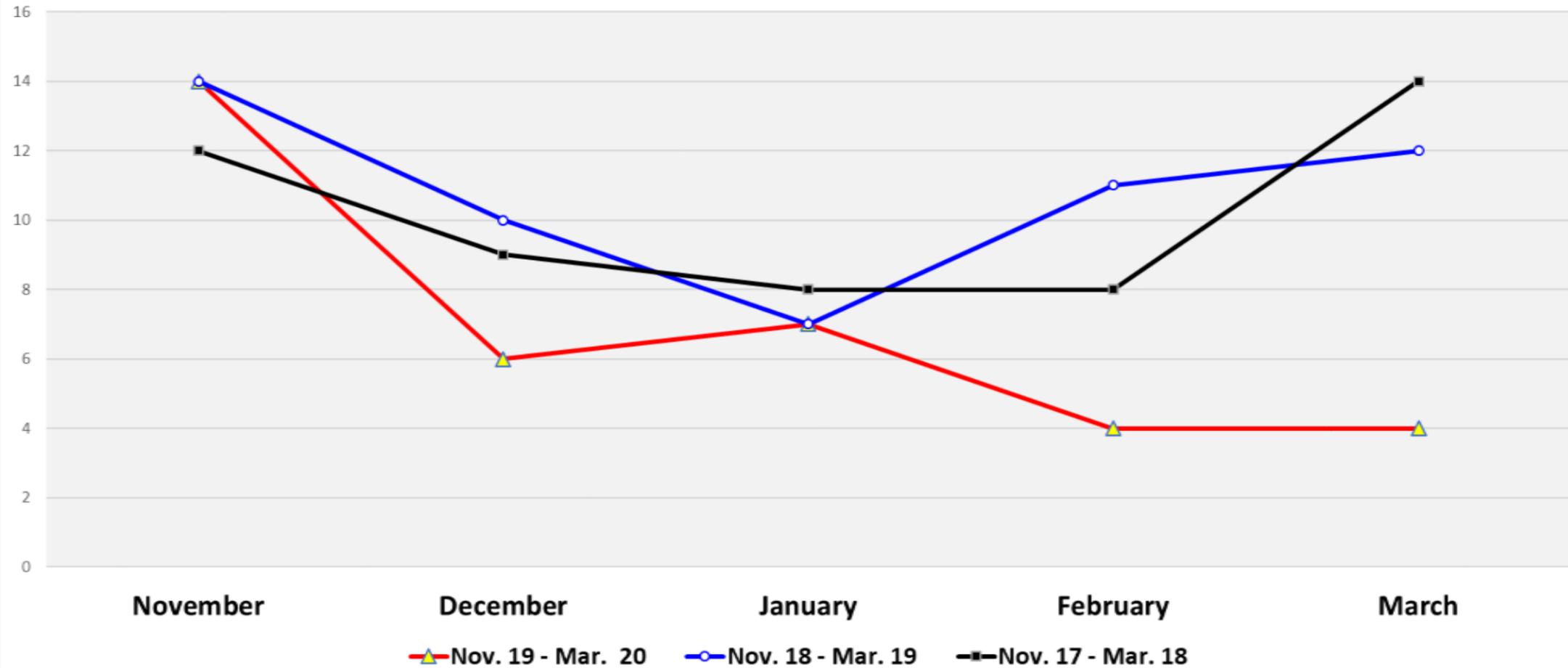
Strategy:

**React to  
Audit Findings**

**Lowest “Apparent” Cost**

# FDA – 3 Years Trend - Drug Audit Inspection

### Number of FDA Drug Audits Per Month - Access FDA



Data Source – Access FDA 



# Limitations of FDA Warning Letter Search Page.....

**FDA Website – Can be Slow – Right Mouse “Click”  
(Use Open Link in New Tab.....)**

**From table on website – if use the filters...**

*Redacted*

Issuing Office	Regulated Product	Subject	Letter Type
Center for Drug Evaluation and Research			Warning Letter
Center for Drug Evaluation and Research			Warning Letter
Center for Drug Evaluation and Research			Warning Letter
Center for Drug Evaluation and Research			Warning Letter
Center for Drug Evaluation and Research			Warning Letter
Center for Drug Evaluation and Research			Warning Letter
Center for Drug Evaluation and Research			Warning Letter

**Example Format of FDA Excel Download..... *No Hyperlinks!***

**Example Cut and Paste FDA Data into Excel..... *(Hyperlinks)***

Letter Issue Date	Company Name	Issuing Office	Regulated Product	Subject	Letter Type
4/18/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter
4/18/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter
3/21/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter
3/18/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter
3/11/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter
2/26/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter
2/25/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter
2/13/2019	<i>Redacted</i>	Center for Drug Evaluation and Research			Warning Letter

# Example FDA Warning Letter.....

To Search  
For  
Individual  
Warning Letter  
Content

“Ctrl F”

FDA Finding or  
Information in the  
“Boiler Plate”  
(WL Template) ?

validation 1/2 ^ v X

More Warning Letters

Warning Letters

About Warning and Close-Out Letters

## WARNING LETTER

MARCS-CMS 606700 – AUGUST 13, 2020

Share Tweet LinkedIn Email Print

Delivery Method: Via Email  
Reference #: 320-20-43  
Product: Drugs

Recipient:

Issuing Office:

Center for Drug Evaluation and Research | CDER  
United States

13<sup>th</sup> August 2020

Content current as of:  
08/25/2020

Regulated Product(s)  
Drugs

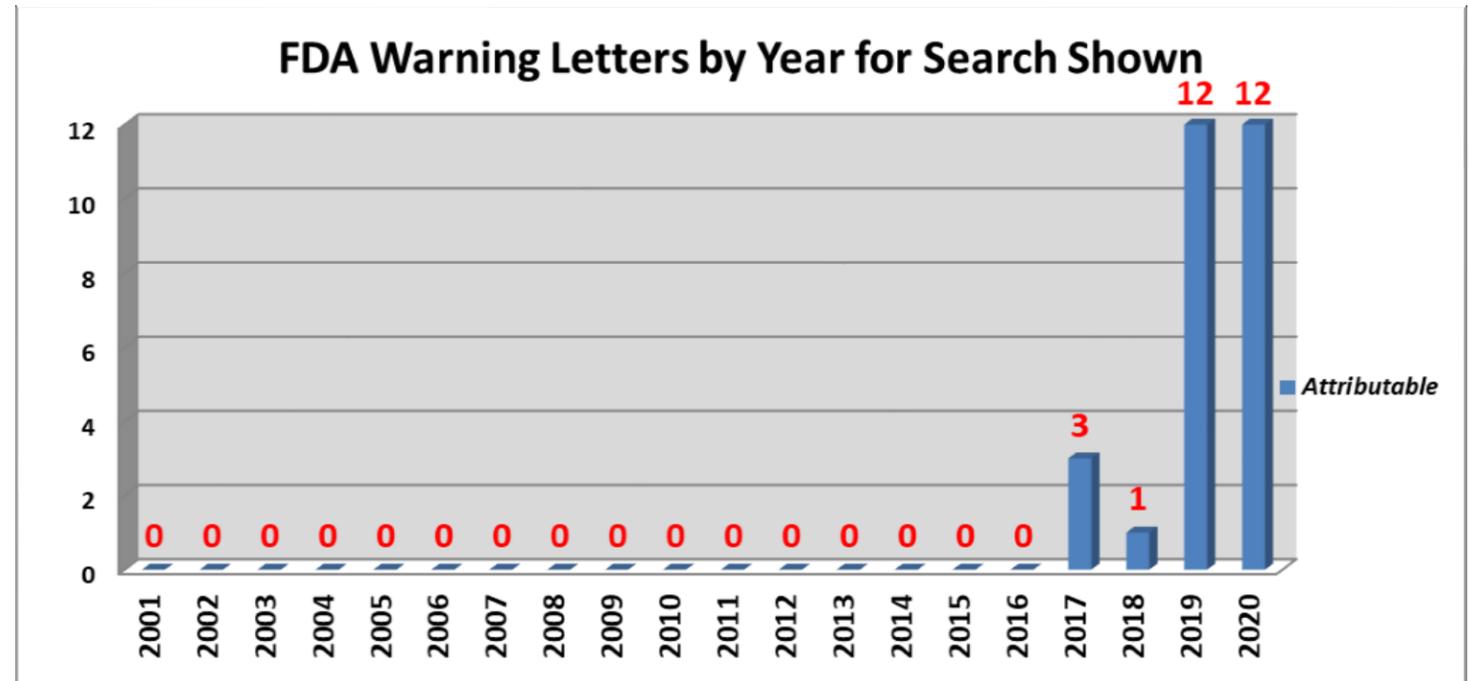
### Warning Letter 320-20-43

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include **validation** of all aseptic and sterilization processes (21 CFR 211.113(b)).

# Data Integrity – ALCOA – Warning Letters

Indicates that **“Attributable”**  
Is a recent FDA trend

What Does it Mean ?



**Attributable** – is associated with the standard wording used by the FDA – the **“trend”** is associated  
With the **“change”** in the standard wording – **NOT BECAUSE THE** companies were cited for **“Attributable”**

• A complete assessment of documentation systems used throughout your manufacturing and laboratory operations to determine where documentation practices are insufficient. Include a detailed CAPA plan that comprehensively remediates your firm's documentation practices to ensure you retain attributable, legible, complete, original, accurate, and contemporaneous records throughout your operation.

# How to “Content Search” FDA Warning Letters

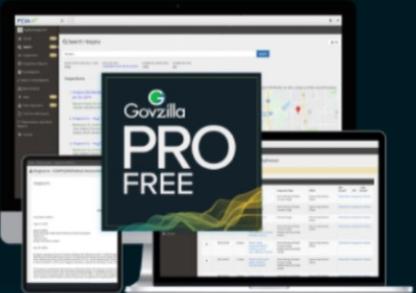
<https://govzilla.com/>



**EXPERIENCE  
THE POWER OF  
GOVZILLA**

Sign up for your FREE account today and get instant access to:

- SEARCH**  
Find the inspection records you want by inspector's name, company name, site, city, country, etc.
- WARNING LETTERS**  
Easily search the largest database of FDA Warning Letters by date, company, FDA office, or subject
- SITES**  
Quickly assess inspection records including dates and inspectors across all of your sites
- INSPECTIONS**  
Complete list of FDA inspections by date, company, category, and country



Work Email\*  
If you use a work email provider for your work, please contact sales@govzilla.com for help with registration.

Please complete this required field.

Industry\*  
Pharma / BioPharma

Govzilla, Inc offers and provides a Pro Free account to users at its sole discretion. The intention of the Pro Free account is to provide complimentary compliance assistance to users, who are employed by a legitimate company, and who have legitimate compliance business needs. Govzilla, Inc. reserves the right to define a legitimate company and legitimate compliance business needs. Pro Free users agree that they may be contacted by Govzilla and offered paid subscription services that may better suit their business needs. For more information, see our [Terms](#) and [Privacy Policy](#).

**SUBMIT**

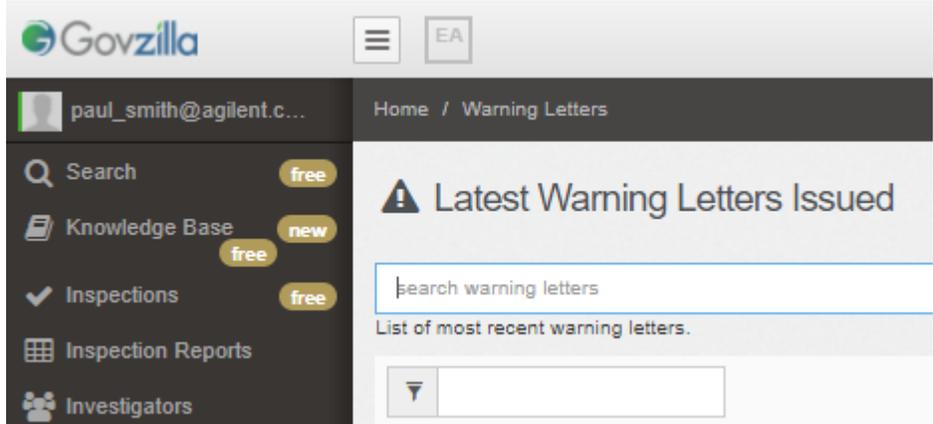
**Work email**  
(e.g. no yahoo mail... etc.)

Log In to:

Search

FDA

Warning Letters



Govzilla

Home / Warning Letters

Latest Warning Letters Issued

Search warning letters

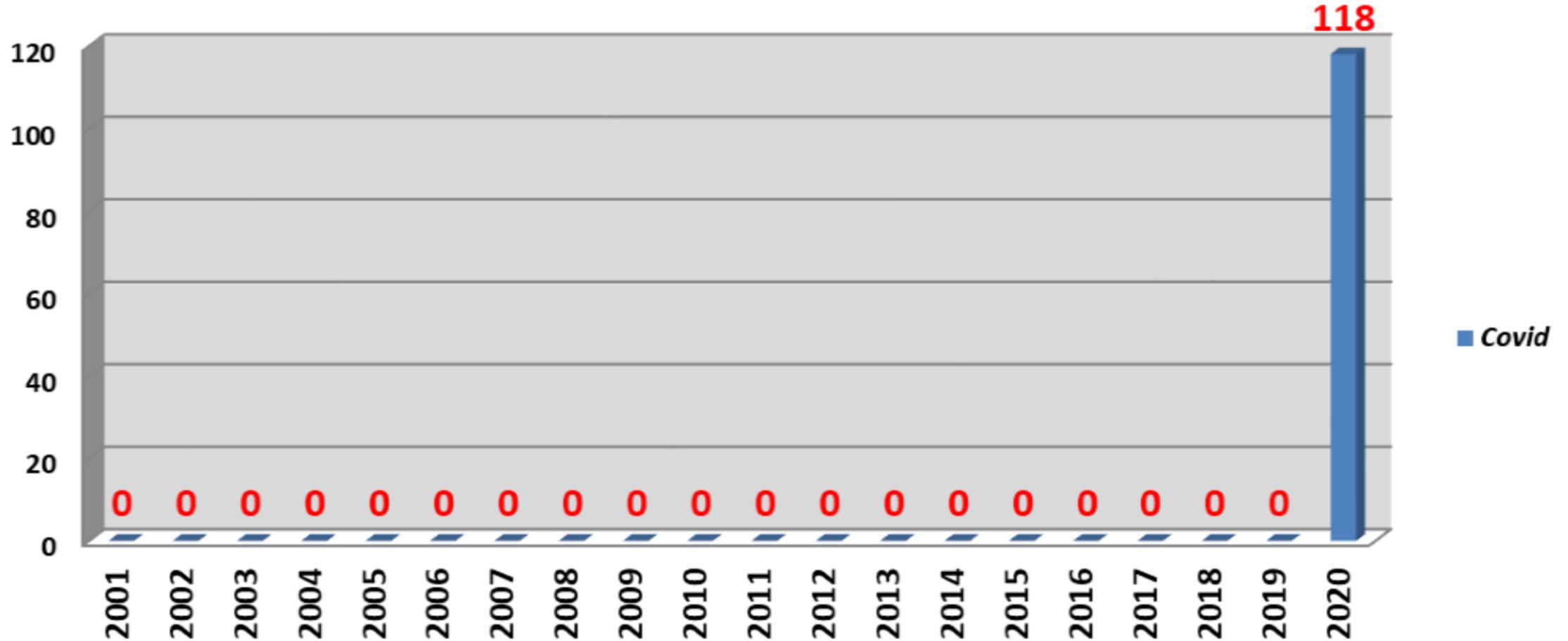
List of most recent warning letters.

- Search free
- Knowledge Base new
- Inspections free
- Inspection Reports
- Investigators

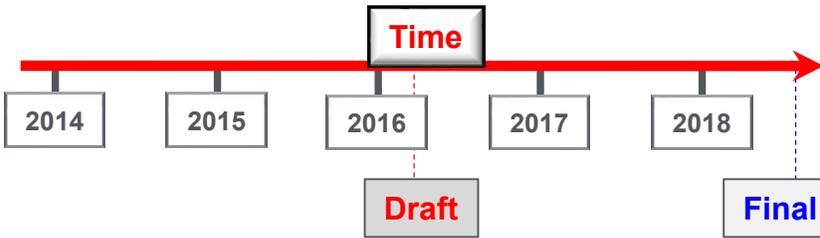
# Example Trend Data – “Covid”



## FDA Warning Letters by Year for Search Shown



# Data Integrity Guidance – Simplified Example of Analysis



**Was:** ucm495891  
(*Final*)  
(Dec. 2018)

Data Integrity and Compliance  
With Drug CGMP  
Questions and Answers  
Guidance for Industry

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
Center for Veterinary Medicine (CVM)

December 2018  
Pharmaceutical Quality/Manufacturing Standards (CGMP)

**Attributable**.....

**Legible**.....

**Contemporaneous**.....

**Original**.....

**Accurate**.....

A  
L  
C  
O  
A



**Footer – Page 4 – CFR / ALOCA**

<https://www.fda.gov/media/119267/download>

<sup>5</sup> These characteristics are important to ensuring data integrity and are addressed throughout the CGMP regulations for drugs. For *attributable*, see §§ 211.101(d), 211.122, 211.186, 211.188(b)(11), and 212.50(c)(10); for *legible*, see §§ 211.180(e) and 212.110(b); for *contemporaneously recorded* (at the time of performance), see §§ 211.100(b) and 211.160(a); for *original or a true copy*, see §§ 211.180 and 211.194(a); and for *accurate*, see §§ 211.22(a), 211.68, 211.188, and 212.60(g).

# Changes to FDA Data Integrity Guidance - Questions

Q & A Format – 18 Questions....

- Changes to Content
- Changes to References

Overall Increase = + 24 %  
(pages & words)

## Word Count Example

Q17 Answers

Q17 - 41 words (2016)

Q17 - 110 words (2018)

% Change =

$$\left( \frac{110 - 41}{41} \right) \times 100 = 168 \%$$

Comparison of 2016 and 2018 Answers in FDA DI Guidance - % Change - Word Count

1a. What is Data Integrity

8. How often should audit trails be reviewed ?



17. Is FDA allowed to look at electronic records ?

FDA Data Integrity Section

# Changes to FDA Data Integrity Guidance – CFR Changes

(Federal Regulations).....

Q & A Format – 18 Questions....

- Changes to Content
- **Changes to References**

## Q13 Answers

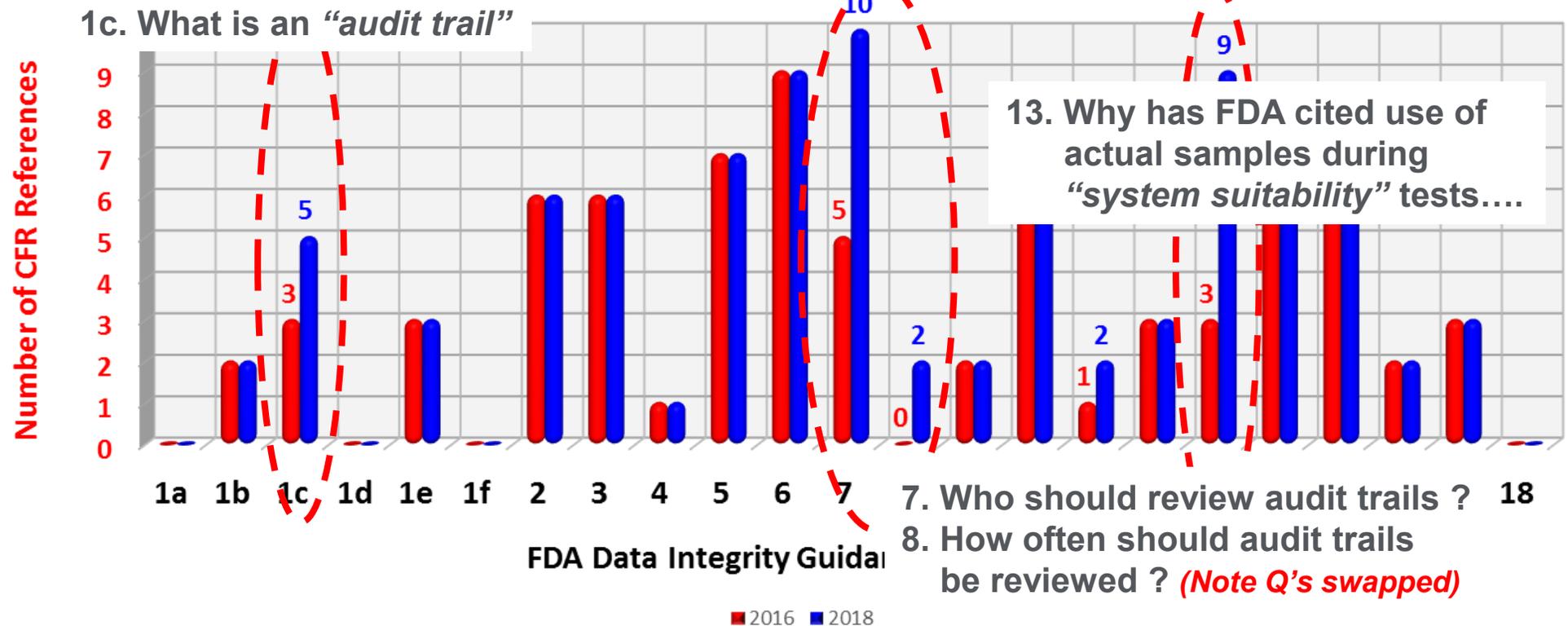
2016 (3) 2018 (9 *new*)

	211.68(b)
	211.160
	211.165
211.160	211.186(a)
211.165	211.188
212.60	211.192
	211.194
	211.194(a)(8)
	212.60

CFR References....

CFR   
(Keyword Search)

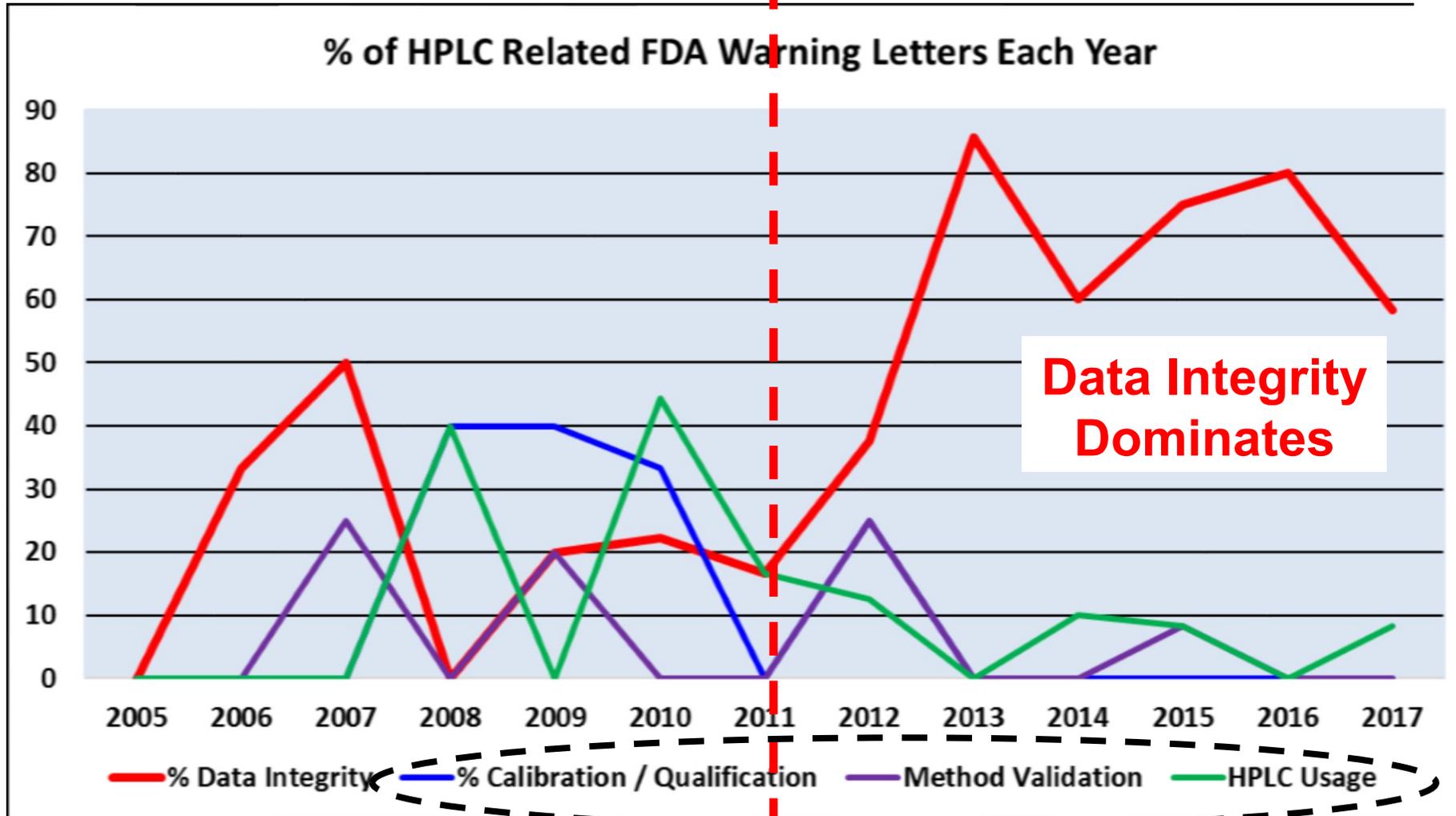
## Comparison of 2016 and 2018 FDA Data Integrity Guidance - CFR References



# Historical Warning Letter Data

## Impact of Data Integrity Focus – on Warning Letters

## Historical Analysis of FDA Warning Letters - HPLC



Prior to  
Data Integrity  
Focus:

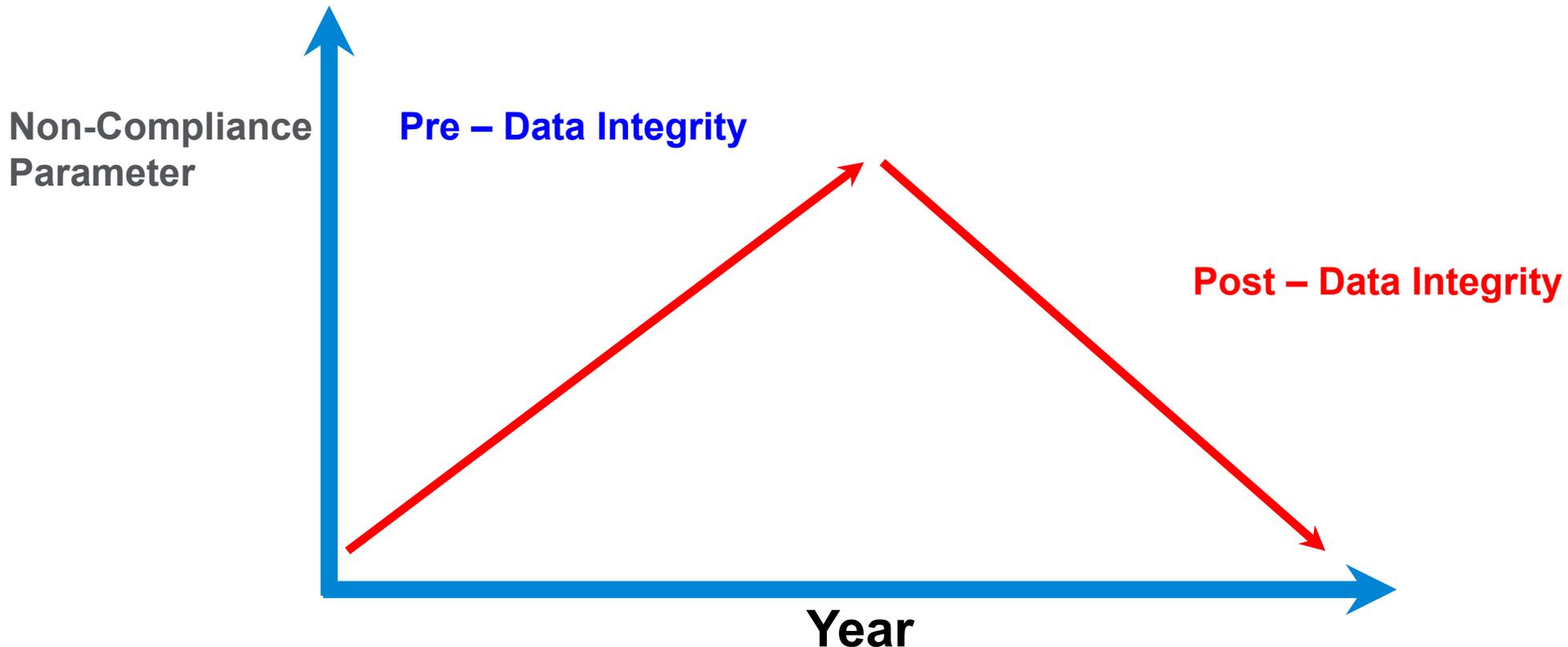
Many TECHNICAL  
HPLC Related  
Warning Letters

- Calibration
- Method Validation
- HPLC Procedures

# FDA Data Integrity Trends / Observation Patterns

## General Observations

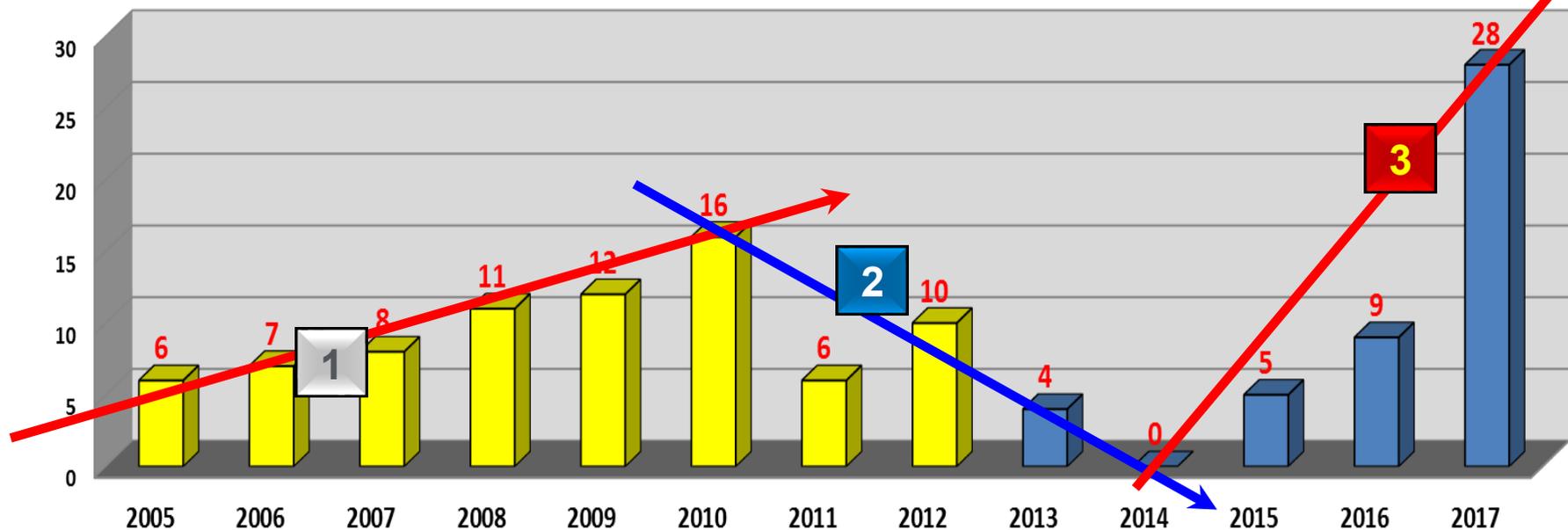
- **Longer Data Review Period (time) – Different Trends**
- **Change in Warning Letter Content**
- **Critical Thinking Skills – Need to Look at the Data**



# FDA Warning Letter Search – “Old FDA Warning Letters Page”

## Patterns of FDA Warning Letter Reporting

FDA Warning Letter Bar Graph for: 21 CFR 211.22(d)



“Procedures not in writing, fully followed....”

Always number 1 in 483s

### FDA Warning Letters Years 2005-2017

1

2005-2010 *Linear Increase in FDA Warning Letters Referencing 21 CFR 211.22(d)*

2

2010-2014 *Downward decline in Warning Letters Referencing 21 CFR 211.22(d)*

3

2014-2017 *From Zero to Highest EVER Referencing of 21 CFR 211.22(d)*

- **VARIABLE !**
- **3 Patterns**
- **FDA Warning Letters becoming more detailed!**

# What are The Implications of the Non-Conformance ?

**“Validated for Intended use...”**

2. Your firm failed to establish and follow appropriate written procedures that are designed to prevent microbiological contamination of drug products purporting to be sterile, and that include **validation** of all aseptic and sterilization processes (21 CFR 211.113(b)).

**“Software Validation”**

***Frequently Cited in Medical Device  
Warning Letters.....***

*(so “direct evidence” of WL’s).*

***However – Rarely Mentioned in  
Laboratory Software Related  
Warning Letters.....***

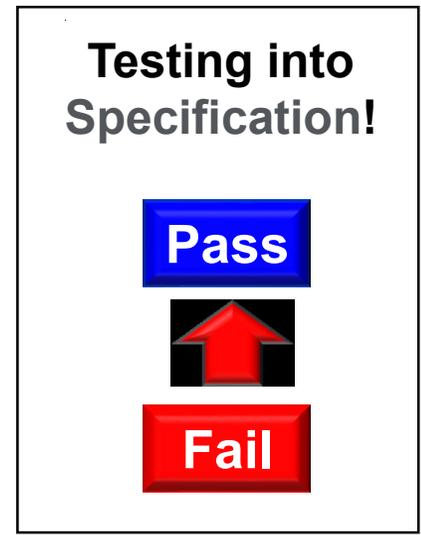
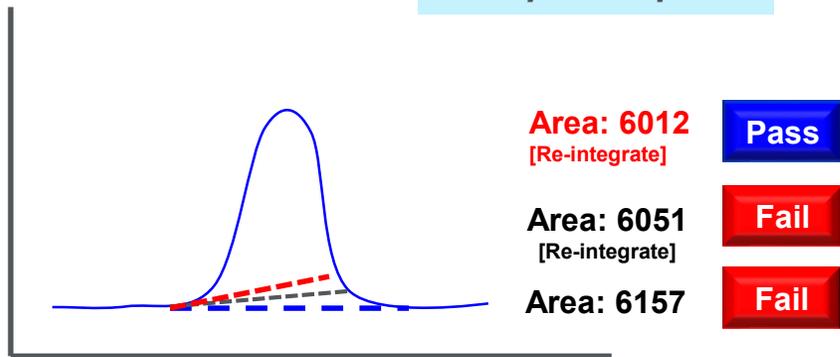
*(so little “direct evidence” of WL’s).*

**“If Software was  
Validated for Intended use...”**

**Deficiencies in “Laboratory Controls”  
– Would be Identified...**

# Data Integrity Example: Chromatographic Data Flow

## Workflow Mapping Identifies Risk



**Manual and / or “Uncontrolled”  
Calculation (e.g. Excel)  
have the Highest Risk**

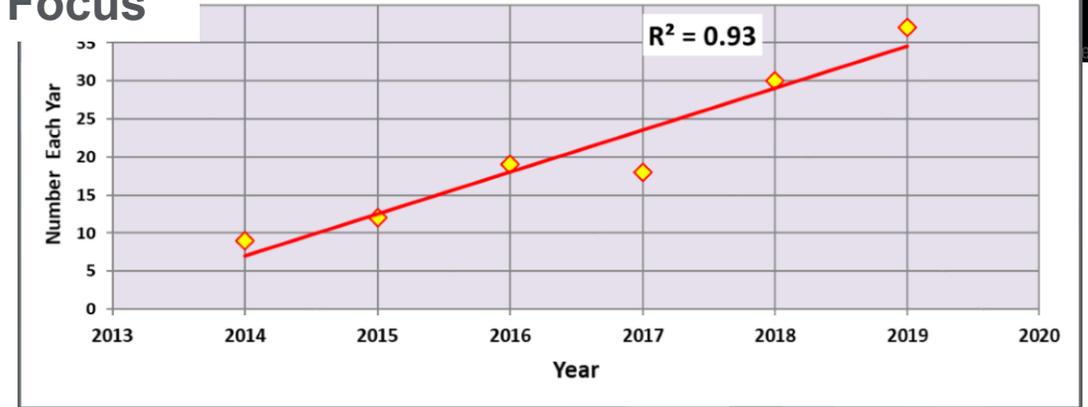
# FDA – OOS Investigations

## Recent FDA Out of Specification Focus

### FDA OOS Focus:

- Testing Into Compliance
- Incomplete Investigations
- Incomplete Data
- Unsound Scientific Decisions

FDA Warning Letters - Out of Specification (OOS)



### FDA WARNING LETTER EXAMPLE:

MARCS-CMS 535014 —NOV. 06, 2017

### FDA – Warning Letter

*“...you invalidated nearly all (134 out of 139) initial OOS results and attributed them to laboratory error.”*

### FDA WARNING LETTER EXAMPLE:

MARCS-CMS 597629 — APR. 15, 2020

### FDA

*“Your head of Quality Assurance informed our investigator during the inspection that failures are investigated **only upon customer request.**”*

### FDA – 483 – FEI 3004819820, 7<sup>th</sup> APR., 2017

Area	No. Investigations	No. Invalidated	% Overturned
Product	89	67	75
Stability	31	30	97
Raw Mats.	48	34	71

# Regulatory Agency Trends - Transparency & Modernisation

## FDA Dashboards....., Example – Health Canada, MHRA “Blog Posts”

### Examples:

- Health Canada Risk Assessment
  - Audit of Health Canada....
- Health Canada may “Share” data from Audits Performed by other Agencies.....

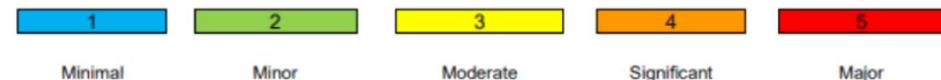
### Is Driving:

- “Real Time” Data Sharing (*Analytics*)
- Fast Upload / Visibility of Information (*No where to “Hide”*)
- Need to “Pull” Data from Multiple Sources (*Impractical to manually search multiple platforms*)

Appendix A – Scorecard

Audit of Inspection Activities			
Criteria	Risk Rating <sup>3</sup>	Risk to the Compliance and Enforcement program without Implementing Recommendation	Rec #
A comprehensive plan is in place to support Compliance and Enforcement (C&E) modernization.	4	The C&E plan did not cover all aspects of C&E modernization for ROEB’s inspection programs. Without a comprehensive plan that clearly identifies all aspects of C&E modernization, as well as the resource requirements, milestones, and deliverables, there is a risk that some aspects of the C&E modernization are being missed or not being considered by management.	1
Oversight of the implementation of C&E modernization is in place.	3	While elements of a governance structure were in place, overall responsibility for oversight of compliance and enforcement modernization initiatives was not clear due to oversight committees having broad and overlapping mandates.  Due to the complexity and magnitude of the initiatives, oversight is required to ensure timely and appropriate implementation. Otherwise, successful implementation of modernization efforts may be at risk.	2
Plans related to C&E modernization are monitored and reported on to ensure their implementation.	2	Dashboards presented to management did not contain sufficient information to provide senior management with a complete picture of the overall status of modernization initiatives. There is a risk that management does not have sufficient information to support decision making, which can negatively affect its ability to exercise effective oversight and ensure consistent implementation of the key elements of compliance and enforcement modernization.	2
Plans related to C&E modernization have sufficient funding and resources to achieve their objectives.	3	Current funding levels have enabled some investments to address certain identified gaps. However, other levels of funding will need to be identified to complete implementation of key elements of compliance and enforcement modernization programs. Gaps in implementation exist consistently across all inspection programs.	1
Plans for inspection activities consider risk in inspection planning, IM/IT, operating procedures, and training.	3	Action plans for key elements of compliance and enforcement modernization are required to ensure that they do not affect the implementation of the key elements of compliance and enforcement modernization.	3
Sex- and Gender-Based Analysis Plus (SGBA+) is considered in the C&E approach.	2	The compliance and enforcement activities might not sufficiently mitigate risks to vulnerable segments of the population.	4

**“Audit of Inspection Activities of Health Canada”**



# Traditional – Regulatory Analysis – *Document Focus*

**Need  
Multiple  
Data  
Sources !**

**Quality  
Professionals  
Would:**

- **Get a copy of the document** *(historical approach)*
- **Review / write a publication / blog / presentation.....** *(or trend based on many documents)*

**Valuable insight, based on expertise, many excellent examples from:**

- Bob McDowall
- Barbara Unger
- Jamie Colgin
- Paul Smith
- FDA (e.g. Sarah Barkow) and Ex FDA (e.g. Paula Katz) .....Etc.

## Warning Letter



Typically – *High Level*

**“Your firm failed to establish an adequate quality control unit....”**

## FDA 483

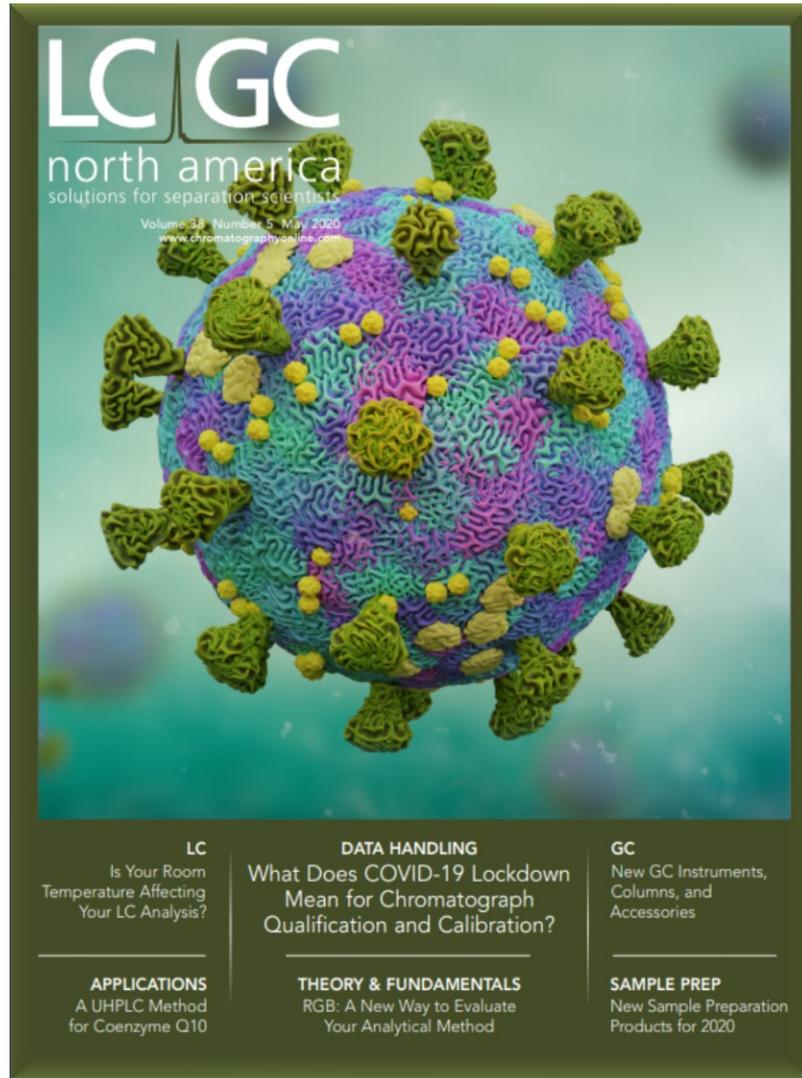


Typically – *More Detail*

**“The .... audit trail revealed that.....(run) was aborted after injection #6 during system suitability.....”**

**no incident report was generated....”**

# Covid 19 and Laboratory Compliance



LCGC North  
America Vol. 38  
Number 5 May 2020

## Covid-19 and Data Integrity: What Does Lockdown Mean for Chromatograph Qualification and Calibration?

The manufacture of pharmaceutical products is classed as critical work, and thus is continuing during the Covid-19 pandemic. With limitations of travel and requirements for social distancing, how should you maintain the calibration and qualification of chromatographs to ensure data integrity of results during this pandemic?

R.D. McDowall

Over the past three months, as coronavirus or Covid-19 has spread from China around the world, many countries have engaged in various forms of lockdown, social distancing, or travel restrictions to prevent the spread of the virus. The focus in the news has naturally been on the number of infections identified, the number of patients in hospitals, and, sadly, on the number of deaths. In the background, the pharmaceutical and medical device industries are still working to produce medicines such as acetaminophen (paracetamol) to alleviate the fever caused by the virus, developing potential vaccines, and conducting research to see if any existing medicines can combat the disease.

During this pandemic, it can be easy to forget that we are a regulated industry and, in the laboratory, chromatographs must be qualified, calibrated, and maintained. To ensure that this is the case, inspections are carried out to ensure that laboratories are complying with regulatory requirements. However, the direct impact of the pandemic on regulated laboratories is an important subject that needs to be considered. In some instances, facilities are restricting access to sites to try to minimize potential risk of exposure for critical employees, while, in others, restrictions may prevent service engineers from traveling. Both issues have the potential to affect compliance in a laboratory. In the absence of inspections and service engineers, how will you keep your chromatographs operating reliably and ensuring data integrity?

### Why Are Qualification and Calibration Important to Data Integrity?

A data integrity model has been presented and discussed in an earlier "Data Integrity Focus" article (1), and also in my book, *Data Integrity and Data Governance* (2).

The model consists of four layers. The foundation layers consist of management leadership, quality culture and ethics, procedures, and training. Level 1 requires the right analytical instrument for the job. The importance of Level 1 to data integrity is if you don't know how an instrument performs, how can you trust the results it generates? Therefore, at Level 1, analytical instruments must be qualified under USP chapter <1058> on Analytical Instrument Qualification (3), and comply with the requirements of 21 CFR 211.63 and 160(b)(4) (4) and EU GMP Chapter 3 clauses 3.34 and 3.35 (5). As the FDA issued 17 (211.63) and 37 (160(b)(4)) 483 observations against these two CFR codes in 2019, these areas are on an inspector's radar (6). We discuss two of these regulations later in this article.

### What Happens Now? Inspections

Let us have a look at what is happening with two regulatory agencies: the Food and Drug Administration (FDA) in the United States, and the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom.

In a press statement issued on March 10th of this year, the FDA announced

that they were postponing all foreign inspections due to travel advice from the State Department that prohibits foreign travel by U.S. government employees. In addition, there are actions by non-U.S. governments that require overseas travelers to self-isolate for 14 days on arrival, or prohibit any foreign travelers arriving at all. Therefore, given that FDA are unable to physically inspect foreign companies, they will gather information under Mutual Recognition Agreements with other regulatory authorities, and revert to physical inspection and possible testing at the U.S. border, as they have done since the start of the outbreak in China when inspections were halted there (7).

Later, FDA announced on March 18th that domestic routine surveillance inspections were being postponed for the safety of the inspectors, and also due to industry concerns about visitors. However, for-cause inspections would be risk assessed, and only critical ones would be carried out (8).

In the United Kingdom, the MHRA posted a statement on the web site on March 20th, stating that they are only conducting essential GXP inspections associated with the UK's response to Covid-19, and all other inspections will be deferred to a later date (9). The same post noted that:

We are expecting organizations to maintain GxP compliance, and will support the industry and NHS to focus on service continuity by using alternative

# FDA Guidance For Industry – June 2020

*Contains Nonbinding Recommendations*

## Good Manufacturing Practice Considerations for Responding to COVID-19 Infection in Employees in Drug and Biological Products Manufacturing

### Guidance for Industry

June 2020

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Center for Biologics Evaluation and Research  
Center for Veterinary Medicine

#### Manufacturing Controls (p3)

***“Drug manufacturers are expected to prevent or mitigate potential adverse effects on the safety and quality of drugs....”***

**Review 21 CFR 211.28(d) “Personnel responsibilities”**

#### Impact on Quality (p7)

##### **Risk Assessment....**

***“...drug manufacturers are expected to evaluate whether it poses new risks in the context of their drugs, facilities, processes, and manufacturing controls.”***

#### Employee.....

- Exposed to COVID-19
- Symptoms of COVID-19
- Tested Positive for COVID-19

# Laboratory Instrument Compliance – During a Pandemic

Many options exist for laboratories

Options:	Comments:
1. Continue ( <i>vendor services</i> )	<ul style="list-style-type: none"><li>• ✓ Business as usual</li><li>• ✗ If corporate/local policies allow</li></ul>
2. Substitution ( <i>of equipment</i> )	<ul style="list-style-type: none"><li>• ✓ Lockdown conformance</li><li>• ✗ Requires equipment redundancy on site</li><li>• ✗ May need method validation</li></ul>
3. Vendor remote services	<ul style="list-style-type: none"><li>• ✓ Lockdown conformance</li><li>• ✗ Vendor dependent</li><li>• ✗ Requires a certified executing employee</li></ul>
4. Vendor exchange services	<ul style="list-style-type: none"><li>• ✓ Lockdown conformance</li><li>• ✗ Vendor and equipment dependent</li><li>• ✗ Need to address qualifications about re-installation</li></ul>
5. Use “expired” equipment	<ul style="list-style-type: none"><li>• ✓ Lockdown conformance</li><li>• ✗ Address Policy Requirements + detailed risk assessment</li><li>• ✗ Increased dependency on equipment’s PQ</li></ul>

# Risks of Using “Expired” Equipment ?

	<b>No Preventative Maintenance (PM)</b>	<b>No Operational Qualification (OQ)</b>	<b>No Performance Qualification (PQ)</b>	<b>Poor System Suitability Tests</b>
<b>Catastrophic Failure</b>	Increased risk of catastrophic failure	No impact	No impact	No impact
<b>Performance Drift</b>	Increased risk of performance drift	Reduces likelihood of detecting failures / “drift” Increases audit risk*	Reduces likelihood of detecting failures / “drift” Increases audit risk*	Inability of detecting failures / “drift” Increases audit risk*

\* Based on the challenge of justifying the scientific validity of actions

# Data Integrity Findings – Have Implications for All Regulated Laboratories.....

**Attributable**.....

**A**

- Clause: 7.5.1

*(“...technical records shall include the data and identity of personnel responsible for each activity and for checking data and results”)*

**Legible**.....

**L**

- Clause: 7.5.2

*(“...ensure that amendments to technical records can be traced to previous versions or to original observations”)*

**Contemporaneous**.....

**C**

- Clause: 7.5.1

*(“Original observations, date and calculations should be recorded at the time they are made...”)*

**Original**.....

**O**

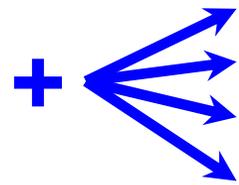
- Clause: 7.5.2

*(“...original and amended data shall be retained”)*

**Accurate**.....

**A**

- Clause: 7.11.3 c) *(“...provides conditions which safeguard the accuracy of manual recording and transcriptions”)*

- +** 
- Complete - 7.11.3 e)
  - Consistent - 7.11.6
  - Enduring - 7.11.3 b)
  - Available - 8.4.2

**ISO 17025 Accredited Laboratories**

