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Comparing and Analyzing US, UK, and Russian "Top Ten" Drug GMP Inspection Findings FY 2019

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Agenda

- FDA 483s vs. warning letters: what is the difference?
- 483 observations over the years – what has changed?
- **FDA's "Top 10"** warning letter citations for FY 2019
- Compare to 483 findings from FY2019
- **Russian State Institute of Drugs and Good Practices – "Top 10"**
- Compare to "Top 10" to FDA citations
- Go through the SID&GP findings in detail
- **MHRA's top "Top Ten"** inspection findings FY2019
- MHRA citation frequency, how MHRA presents its data
- **Common themes** across the three agencies
- Q&A

What is the difference between a 483 and a Warning Letter?

FDA 483 vs. Warning letter

- A 483 **observation**: FDA investigator's best judgment.

  FDA Form 483 language: "This form lists inspectional observations and does not represent a final agency determination regarding your compliance."

- An FDA warning letter **citation** confirms it is a significant violation

  FDA warning letter: "This summarizes significant violations of current good manufacturing practices and the failure to properly correct these violations may result in legal action."

- Observation vs. citation

483 Macro Data FY 2019 vs. FY2018

- In FY2019 there were 779 drug GMP 483s issued (716 in FY2018)
- With 385 different citations (391 in FY2018)
- Resulting in a total of 3,730 observations (3,344) in FY2018
- The “Top 10” were issued 1,124 times (924 in FY2018)
- The “Top 10” accounted for 30% of the observations issued (28% in FY2018)
- There were 40 drug GMP warning letters issued in FY 2019 = 5.1%

Drug GMP 483 Observations FY2019

	21 CFR Reference	Short Description	Frequency
1	211.22(d)	Procedures not in writing, fully followed	215
2	211.192	Investigations of discrepancies, failures	167
3	211.160(b)	Scientifically sound laboratory controls	145
4	211.100(a)	Absence of written procedures	108
5	211.167(a)	Cleaning / Sanitizing / Maintenance	99
6	211.165(a)	Testing and release for distribution	90
7	211.110(a)	Control procedures to monitor/validate performance	82
8	211.113(b)	Procedures for sterile drug products	79
9	211.68(b)	Computer control of master formula records	73
10	211.166(a)	Lack of written stability program	67

Drug GMP 483 Observations, FY 2018 and FY2019

	21 CFR Reference (FY2019)	Short Description	21 CFR Reference (FY2018)	Short Description
1	211.22(d)	Procedures not in writing, fully followed	211.22(d)	Procedures not in writing, fully followed
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FDA 483 Observations Over Time

FY06	FY015	FY016	FY017	FY018	FY019
211.22(d)	211.22(d)	211.22(d)	211.22(d)	211.22(d)	211.22(d)
211.110(a)	211.160(b)	211.160(b)	211.160(b)	211.160(b)	211.192
211.192	211.192	211.192	211.192	211.192	211.160(b)
211.160(b)	211.100(a)	211.113(b)	211.100(a)	211.100(a)	211.100(a)
211.100(a)	211.100(a)	211.42(c)(10)(iv)	211.67(b)	211.67(a)	211.67(a)

Why does FDA keep citing the same deficiencies year after year?

- Shared responsibility – agency categorization and industry issues

- Look at the repeat citations:

  211.22(d): Procedures not in writing, fully followed
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- Broad areas, Q Unit used as a catch-all

- Quality Unit expectations, training (https://www.pathway4ph.org/)

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- Broad areas, Q Unit used as a catch-all

- Quality Unit expectations, training (https://www.pathway4ph.org/)

- Quality mindset in the organization

Which do we want to pay attention to? 483s or Warning Letters?

FDA Investigators > Peter Baker

Go to Inspections | CSV

Peter Baker beta

CONSUMER SAFETY OFFICER (OV

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Alameda CA 94502

156 Total Inspections

111 Total 483s Issued

71.2% Total 483s Issue Rate

32 Total WLs Issued

Synopsis

Peter Baker has been inspecting for the FDA as far back as 2008 and has inspected facilities in:

China India United States .

Download all 467 Observations

Download all **76** of Peter Baker's 483s

Inspection Record	Overall	This Year (2019)	Last Year (2018)
# of Inspections	156	0	2
# of 483s Issued	111	0	1
# of Resulting Warning Letters	32	0	0
Average Length of Inspection	6.9 days	NaN days	6 days
Longest Inspection	40		9
Shortest Inspection	1		3

# Inspections w/ key words	Observation Area	# Times
72	Data Integrity	673
59	Investigations	241
54	Process Validation	148
32	EM	122
57	Procedures	111
52	Lab Controls	98
44	Cleaning validation	93
35	Contamination	89
26	OOS	74
30	Facilities, D&C	74

Co-Inspector	Number of Inspections	Year of Last Inspection
Millar, William V	11	2012
Shah, Dipesh K	10	2014
Middendorf, Christopher T	9	2017
Agrawal, Atul	7	2013
Patel, Parul M	5	2013
Roberts, Daniel J	5	2014
Foley, Kevin P	4	2010
Johnson, Jennifer L	4	2011
Karapetyan, Arsen	3	2017
Arista, Thomas J	2	2014
Boyd, Justin A	2	2016

FDA Top 10 Warning Letter Citations FY 2019

Top 10 FDA Warning Letter Citations FY2019

Number	CFR citation	Short Description
1	211.100(a)	Validated production and process controls
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4	211.22(a)	Responsibilities of quality unit
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6	211.84(d)(1), (d)(2)	Components tested for identity and conformity with specifications
7	211.22(a), (d)	Responsibilities of quality unit; written procedures
8	211.67(a)	Equipment cleaning and maintenance
9	211.160(b)	Lack of established lab controls
10	211.194(a)	Laboratory records include complete data

Top 10 FDA Warning Letter Citations FY2019

Number	CFR citation	Short Description	FY2019 483 rank
1	211.100(a)	Validated production and process controls	4
2	211.192	Investigations of discrepancies and OOS results	2
3	211.166(a)	Inadequate stability testing	10
4	211.22(a)	Responsibilities of quality unit	NA*
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MINPROMTORG RUSSIA

SID& GP

Russian State Institute of Drugs and Good Practices (SID&GP) Top Ten GMP Inspection Findings FY 2019

Russian State Institute of Drugs and Good Practices (SID&GP) Top Ten GMP Inspection Findings FY 2019

#1	Laboratory records do not include complete data
#2	Data integrity lapses in the laboratory
#3	Lack of established laboratory controls
#4	Inadequate stability program
#5	Inadequate justification for storage conditions
#6	Failure to test finished products
#7	Incorrect finished product testing
#8	Failure to test finished products following official "Normative Documents" (specifications)
#9	Cleaning and maintenance of equipment
#10	Manual cleaning procedures not verified

Russian State Institute of Drugs and Good Practices (SID&GP) Top Ten GMP Inspection Findings FY 2019

	Citation	FDA WL #
#1	Laboratory records do not include complete data	10
#2	Data integrity lapses in the laboratory	10?
#3	Lack of established laboratory controls	9
#4	Inadequate stability program	3
#5	Inadequate justification for storage conditions	NA
#6	Failure to test finished products	5
#7	Incorrect finished product testing	NA
#8	Failure to test finished products following official "Normative Documents" (specifications)	NA
#9	Cleaning and maintenance of equipment	8
#10	Manual cleaning procedures not verified	NA

SID&GP Top 10 FY2019

#1 Laboratory records do not include complete data

- **No records were kept** on the preparation of investigational and reference samples during quality control of a product with a spectrofluorimetric method. No prescribed preparations for spectrofluorometers were recorded, i.e. 30 minutes “heating”. The device is not equipped with a computerized system for recording all activities associated with its use.

- **No comments on variations in raw data** on the results of NDEA and NDMA contents in candesartan API. Overall, there were 31 report versions in Empower 3.

- In the chemical lab, logbook **records** of received raw material samples were written down **in pencil**.

SID&GP Top 10 FY2019

#2 Data Integrity Lapses in the Laboratory

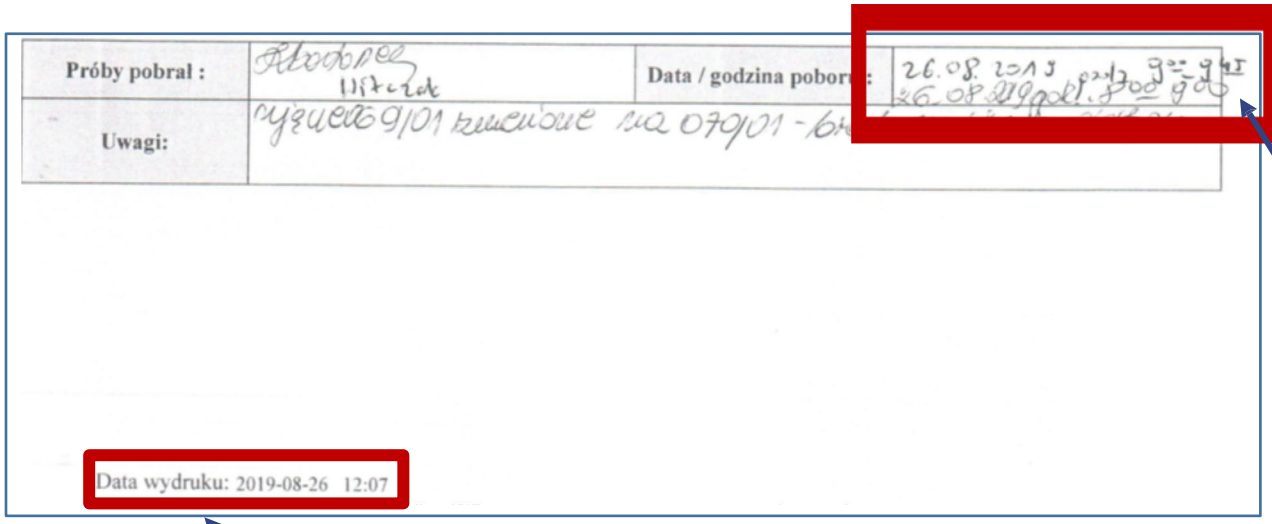
- Bioburden testing records **do not include data** about the media used and about sample preparation.

- **No real time records** on purified water sampling were made.

According to the company's SOP, the sampling protocol must be printed in advance to be filled in during the sampling. In reality, some protocols were printed and filled in 3 hours later, after the actual sampling:

SID&GP Top 10 FY2019

#2 Data Integrity Lapses in the Laboratory *(continued)*



Actual sampling date and time

Protocol printing date and time

SID&GP Top 10 FY2019

#3 Lack of Established Laboratory Controls

- **Manual integration of chromatograms** was used without the proper procedure and double checking.

The analytical method transfer procedure does not contain step-by-step description and responsibilities of the parties. The whole description of the process **fits in a single page** instead of the usual at least 10-15 pages.

Analytical method description for the API does not specify which exact piece of lab equipment should be used for testing. The company method description contains only general information such as “use a scale”, “use an oven”, etc.

SID&GP Top 10 FY2019

#4 Inadequate Stability Program

- **Reduced follow-up stability study protocol.** For instance, for an oral suspension, one of the required parameters, namely "sedimentation" is omitted with no justification.

Sterile product packed in semi-permeable vials: In 2013, during follow-up stability study of the product, some **negative trends** were detected: weight loss and impurities concentration growth. In 2015, the company made the decision to reduce shelf-life of product from 3 years to 2 years. However, in Russia the 3-year shelf-life batches were being marketed for sale until 2018. The company **failed to inform the Russian Regulator** about the change.

SID&GP Top 10 FY2019

#4 Inadequate Stability Program *(continued)*

- The kit of sterile dissolvent (Water for Injection, or WFI) and freeze-dried product. During follow-up stability study, **multiple Out of Specification (OOS) results** of oxidizable substances were detected in the dissolvent at the points of 6, 12, 24 months. The company informed their local Regulator about the OOS and it was decided not to reduce 3-year shelf-life of dissolvent. **The Russian Regulator had not been informed** about the findings. In Russia, the product was being marketed as it was until the revelation of the Russian inspection.

SID&GP Top 10 FY2019

#5 Inadequate Justification for Storage Conditions

- Approved **storage conditions** for final product (tablets) are up to **30 °C.** The company provided **follow-up stability study** conditions within **(25 ± 2) °C.**

SID&GP Top 10 FY2019

#6 Failure to Test Finished Products

- There is no quality control of finished product for soft gel capsules. Assay is tested on the intermediate with subsequent calculation for the final dosage form. No justification was provided.

SID&GP Top 10 FY2019

#7 Incorrect Finished Product Testing

- Inadequate testing for the presence of ***E. coli*** **in finished product.** Incubation of MacConkey broth is done at **30-35 °C, instead of 42-44 °C.** Subculture on MacConkey agar is incubated at **20-25 °C, instead of 30-35 °C.** No 42-44 °C incubator was presented during the inspection.

SID&GP Top 10 FY2019

#8 Failure to Test Finished Products as Described by Normative Documents

Quality control of finished products for the Russian Federation **not done in line with** Normative Document **(**ND = **approved specification):**

- according to the ND assay maximum must be **11.00** mg/ampoule, the company spec is **13.75** mg/ampoule

- according to the ND **impurities must be tested.** In fact, this control is **not done** and not included in the company's specification.

SID&GP Top 10 FY2019C

#9 Cleaning and Maintenance of Equipment

- Inadequate maintenance of the Fluid Bed Dryer (FBD), i.e. **the gasket check-ups failed.** Powder deposit was found in technical area. Charging and discharging of FBD are done under negative pressure inside the machine. Drying is done under positive pressure inside. As a result, failed maintenance can lead to **cross-contamination**.

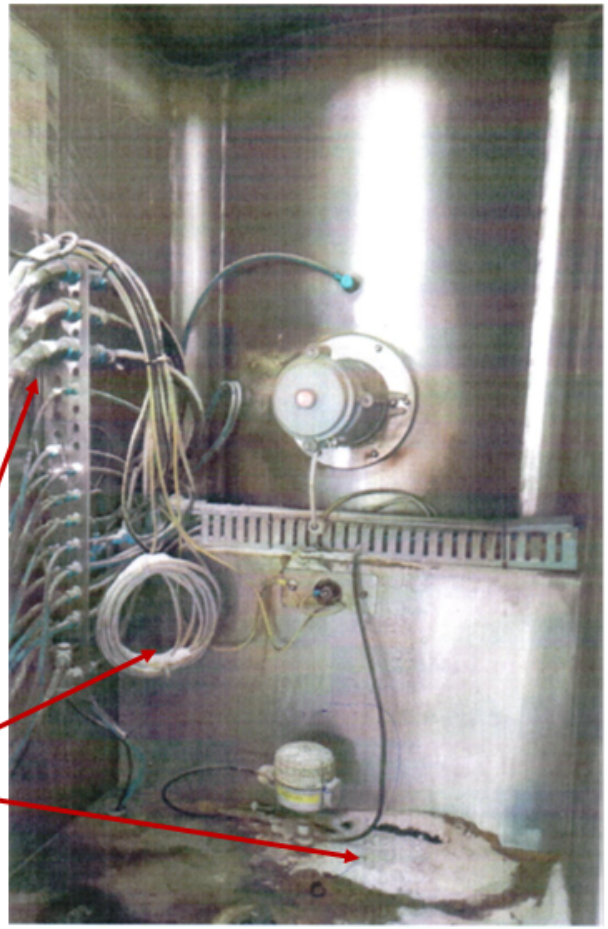
- Limits for the **carryover of product residues are based on OEL** (Occupational Exposure Limits) instead of a toxicological evaluation (Permitted Daily Exposure or PDE).

SID&GP Top 10 FY2019C

#9 Cleaning and Maintenance of Equipment *(continued)*

Cleaning and Maintenance of Equipment (#9) Photographic Example:

"This is a picture showing equipment cleaning and maintenance issues," Arkhipova explained. "This is what we found in the technical area, where the Fluid Bed Dryer is installed. This machine is used for manufacturing of all solid dose products from tablets to pellets. There are big deposits of powders, and they were not fresh. I think it has been collecting for months. You can see some dust, some machine oil, and something else. There is risk of cross contamination, because company has just failed two gasket check-ups."



Mix of products, dust, machine oil and something else

SID&GP Top 10 FY2019

#10 Manual Cleaning Procedures Not Verified

- **Manual cleaning** procedures of the compactor and the capsule machine **have never been verified** after their validation. Full cleaning of the machines is done manually.

MHRA Top 10 Inspection Findings FY 2019

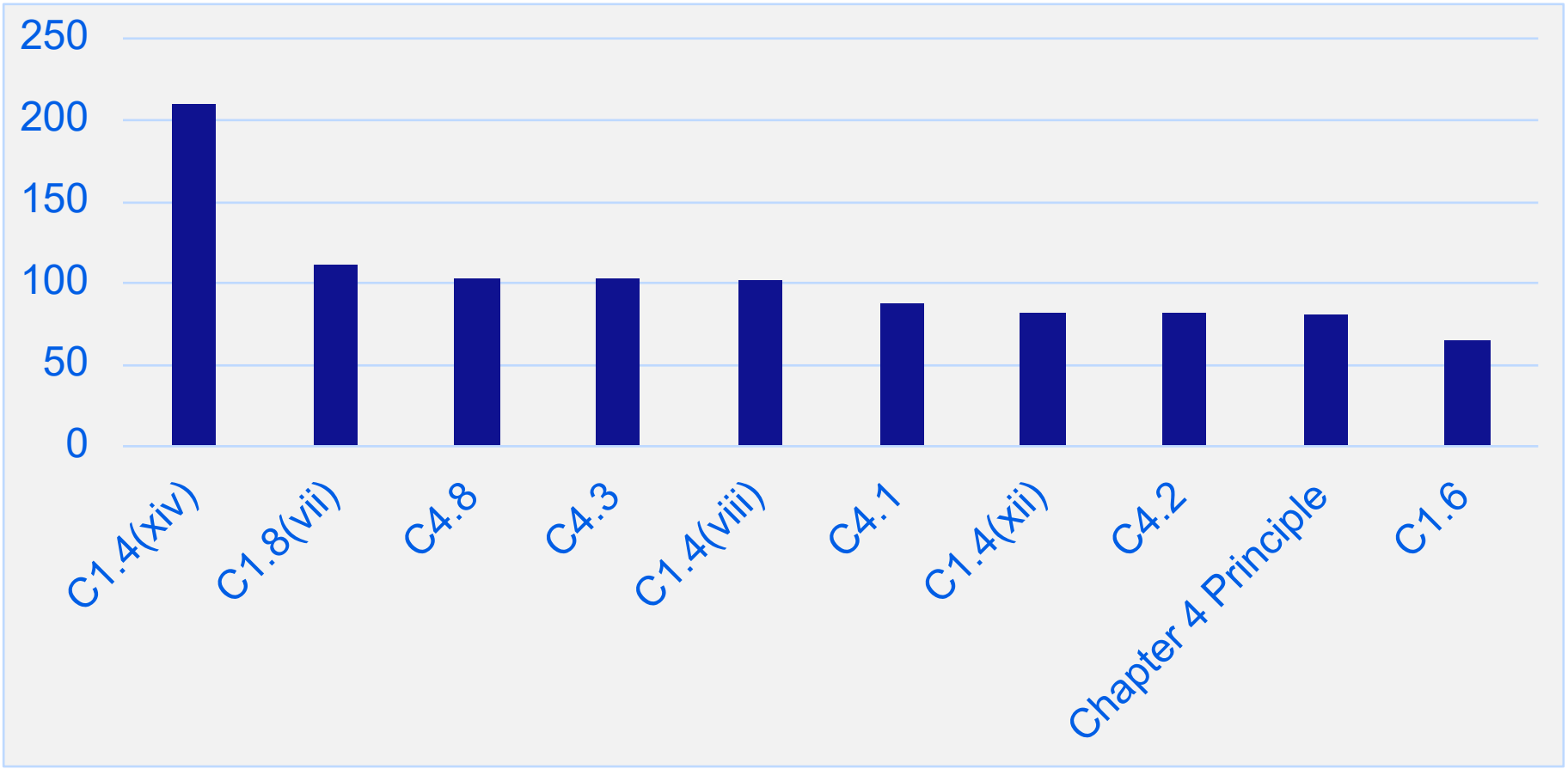
Top 10 MHRA deficiencies 2019

#	Ref	Detail
1	C1.4(xiv)	Investigations, root cause analysis, human error, CAPA
2	C1.8(vii)	Significant deviations recorded and investigated
3	C4.8	Contemporaneous records
4	C4.3	Documents approved, signed and dated by appropriate and authorised persons, unambiguous, identifiable, effective date defined
5	C1.4(viii)	State of control (e.g. timeliness of investigations)
6	C4.1	Appropriate controls to ensure the integrity of the record throughout retention period etc.
7	C1.4(xii)	Prospective evaluation of planned changes
8	C4.2	Documents designed, prepared, reviewed and distributed with care.
9	C4P	Suitable controls to ensure the accuracy, integrity, availability and legibility of documents
10	C1.6	Periodic management review

Top 10 MHRA deficiencies 2019

#	Ref	Detail	FDA WL #
1	C1.4(xiv)	Investigations, root cause analysis, human error, CAPA	2
2	C1.8(vii)	Significant deviations recorded and investigated	2
3	C4.8	Contemporaneous records	NA
4	C4.3	Documents approved, signed and dated by appropriate and authorised persons, unambiguous, identifiable, effective date defined	7
5	C1.4(viii)	State of control (e.g. timeliness of investigations)	2
6	C4.1	Appropriate controls to ensure the integrity of the record throughout retention period etc.	NA
7	C1.4(xii)	Prospective evaluation of planned changes	NA
8	C4.2	Documents designed, prepared, reviewed and distributed with care.	7
9	C4P	Suitable controls to ensure the accuracy, integrity, availability and legibility of documents	NA
10	C1.6	Periodic management review	NA

Top 10 MHRA Deficiency References 2019



Comparing Inspection Findings Across the Three Agencies

Common Themes Across Citations from FDA, MHRA, and Russia's SID&GP

Issue / Theme	U. S. FDA	U. K. MHRA	Russia SID&GP
Data integrity	#10 Lab records do not include complete data	#3 Contemporaneous records #4 Documents approved and signed by appropriate persons, unambiguous #6 Controls to ensure integrity of the record #8 Documents designed, prepared, reviewed with care #9 Suitable controls to ensure the accuracy, integrity, availability, and legibility of docs	#2 Data integrity lapses in the laboratory
Deviation and failure investigations	#2 Investigations of discrepancies and OOS results	#1 Investigations, root cause analysis, human error, CAPA #2 Significant deviations recorded and investigated	N/A
Lack of established lab controls	#9 Lack of established lab controls	N/A	#1 Lab records do not include complete data #3 Lack of established laboratory controls
Finished product testing	#5 Failure to test finished products	N/A	#6 Failure to test finished products #7 Incorrect finished product testing #8 Failure to test finished products as described by Normative Documents
Stability program	#3 Inadequate stability testing	N/A	#4 Inadequate stability program
Equipment cleaning and maintenance	#8 Equipment cleaning and maintenance	N/A	#9 Cleaning and maintenance of equipment

Resource Links

Read conference coverage on key presentations by regulators and industry leaders here.

Read about the latest GMP trends and analysis here.

Read the latest on GMP enforcement actions here.

Learn what data integrity issues are, why are they important, how to find them, here.

Interested in the FDA investigator profiles mentioned earlier? Click here.

Read a CGMP inspection case study on cross-contamination in a fluid bed dryer here.

Former FDA Official David Doleski On Agency Hot Button Issues And Developing A Positive Relationship, read here

After the inspection, how do FDA, MHRA, and SID&GP determine if inspection findings are escalated to be considered for compliance actions? *Article coming soon – we will email you.*

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