Analysis Of
CY2018 FDA WARNING LETTERS THAT CITE DATA INTEGRITY FAILURES

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IN THIS SUMMARY WE IDENTIFY:

- CY2018 warning letters that cite data integrity deficiencies
- The number of warning letters citing this topic in the past 11 years and the countries where these sites are located
- The regulations identified most frequently in CY2018 drug GMP warning letters citing data integrity failures

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This article represents the fourth year we have published an evaluation of warning letters associated with data governance and data integrity deficiencies. Articles for 2016 and 2017 and 2018 may be found here:

- Data Integrity: Surveying The Current Regulatory Landscape (2016)
- An Analysis Of FDA Warning Letters On Data Governance & Data Integrity (2017)
- Drug GMP Warning Letters Data Governance and Data Integrity (2018)

Enforcement for failures in data integrity and data governance began almost 20 years ago. This year however, we may have turned the corner, which we'll address below. Although, the FDA is not the only health authority that identifies these issues in inspections and enforcement actions, but their transparency ensures the data is readily available. In this summary, we identify:

- CY2018 warning letters that cite data integrity deficiencies
- The number of warning letters citing this topic in the past 11 years and the countries where these sites are located
- The regulations identified most frequently in CY2018 drug GMP warning letters citing data integrity failures

As in past years, all data integrity deficiencies identified in Form 483s and warning letters are failures to follow CGMPs as specified in the predicate rules. The FDA has not implemented novel interpretations or requirements applicable to data governance. The use of computer systems and other electronic systems require different approaches to ensure compliant practices, but these are all based on the existing regulations in 21 CFR211.

Data Integrity GMP Warning Letters And Trends From The Past 11 Years

Figure 1 lists the warning letters issued to drug manufacturers in CY2018 that include data integrity deficiencies. The list includes the date of issuance and the country where the facility is located. Rows are color-coded.

The FDA issued 85 drug GMP warning letters in CY2018, excluding those issued to compounding

FIGURE 1: CY2018 Drug Warning Letters with Data Integrity Deficiencies

DATE	COUNTRY	COMPANY
1/2/2018	China	Yicheng Chemical Corp
1/9/2018	China	Hunan Norchem Pharmaceutical Co. Ltd.
1/18/2018	Japan	Daito Kasei Kogyo Co., LTD
2/2/2018	South Korea	Cosmecca Korea Co., Ltd
2/7/2018	China	Shanghai Weierya Daily Chemicals Factory
2/18/2018	India	Alchymars ICM SM Private Limited
2/23/2018	China	Zhejiang Ludao Technology Co., Ltd
2/23/2018	Hong Kong China	Nan San (HK) Pharmaceutical Factory Limited
3/9/2018	Dominican Republic	Labocont Industrial SRL

FIGURE 1 CONTINUED: CY2018 Drug Warning Letters with Data Integrity Deficiencies		
DATE	**COUNTRY**	**COMPANY**
3/15/2018	India	Keshava Organics Pvt. Ltd.
3/29/2018	South Korea	Hanbul Co., Ltd dba Hanbul Cosmetics Co Ltd.
4/18/2018	Mexico	Degasa S.A. De C.V.
4/19/2018	China	Lijiang Yinghua Biochemical and Pharmaceutical Co. Ltd.
5/9/2018	India	Reine Lifescience
5/9/2018	US	Cerno Pharmaceutical
5/9/2018	China	Nox Bellcow Cosmetics Lo. Ltd.
5/14/2018	China	Jilin Shulan Synthetic Pharmaceutical Co Ltd
5/18/2018	South Korea	Kolmar Korea Co Ltd
5/23/2018	Australia	ITD Australia Ltd
5/31/2018	Taiwan	Taiwan Biotech Company Ltd
6/21/2018	China	Henan Lihua Pharmaceutical Co. Ltd.
6/22/2018	China	Sichuan Friendly Pharmaceutical Co., Ltd
6/26/2018	China	Foshan Jinxiong Technology Co. Ltd.
6/27/2018	China	Zhuhai United Laboratories Co. Ltd.
7/5/2018	India	Baxter (Claris Injectables Ltd)
7/23/2018	US	Milbar Laboratories Inc.
7/17/2018	Japan	Yuki Gosei Kogyo Co., Ltd.
7/24/2018	Canada	Les Produits Chimiques B.G.R., Inc.
7/26/2018	China	Yicheng Goto Pharmaceuticals Co.,Ltd
7/27/2018	India	JT Cosmetics & Chemicals Pvt Ltd
7/31/2018	US	Signature Formulations, LLC
8/9/2018	India	Apotex Research Private Limited
8/10/2018	Japan	Kyowa Hakko Bio Co., Ltd
8/27/2018	China	Longood Medicine (Beijing) Co. Ltd.
8/29/2018	US	Pharmaceutical Laboratories and Consultants
8/29/2018	Netherlands	Fagron BV
10/3/2018	South Korea	Hanlim Pharm Co., Ltd
10/29/2018	US	I Shay Cosmetics
11/2/2018	US	Product Packaging West, Inc
11/6/2018	US	Surmasis Pharmaceutical
11/27/2018	China	Hangzhou Zhongbo Industrial Co., Ltd.
11/2/2018	US	Genetech Inc

FIGURE 2: Number of Data Integrity Associated Warning Letters by Country CY2008-CY2018

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	TOTAL
China	1	1	3	1			2	2	14	19	15	58
USA	1	2	1	1	1			0	7	15	8	36
India	1	1		2		6	7	10	9	12	6	54
Europe		1					1	2	6	3	1	14
Brazil									3			3
Japan	1								2	1	3	7
Thailand								1				1
Canada			1		1					2	1	5
Mexico					2					1	1	4
UAE					1							1
Jamaica					1							1
South Korea										2	4	6
Singapore										1		1
Australia											1	1
Taiwan											1	1
Dominican Republic											1	1
TOTAL	4	5	5	4	6	6	10	15	41	56	42	194

pharmacies and outsourcing facilities. Forty-two included a data integrity component for a total of 49 percent of the warning letters. In December no warning letters were posted due to the partial government shutdown.

Figures 2 and **3** present data over the last 11 years, CY2008 through CY2018, along with a cumulative total.

- The number of warning letters including this topic ranged from four to six from 2008 through 2013, doubled in CY2014 to 10.
- The number of warning letters increased from 15 in 2015 to 41 in 2016 and 56 in 2017.
- In 2018 the number decreased substantially to 42.

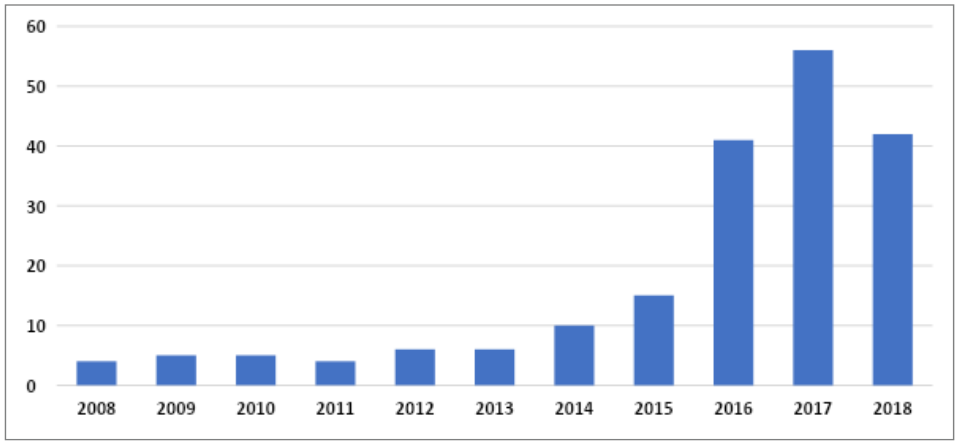

FIGURE 3: Data Integrity Associated Warning Letters, CY2008-CY2018

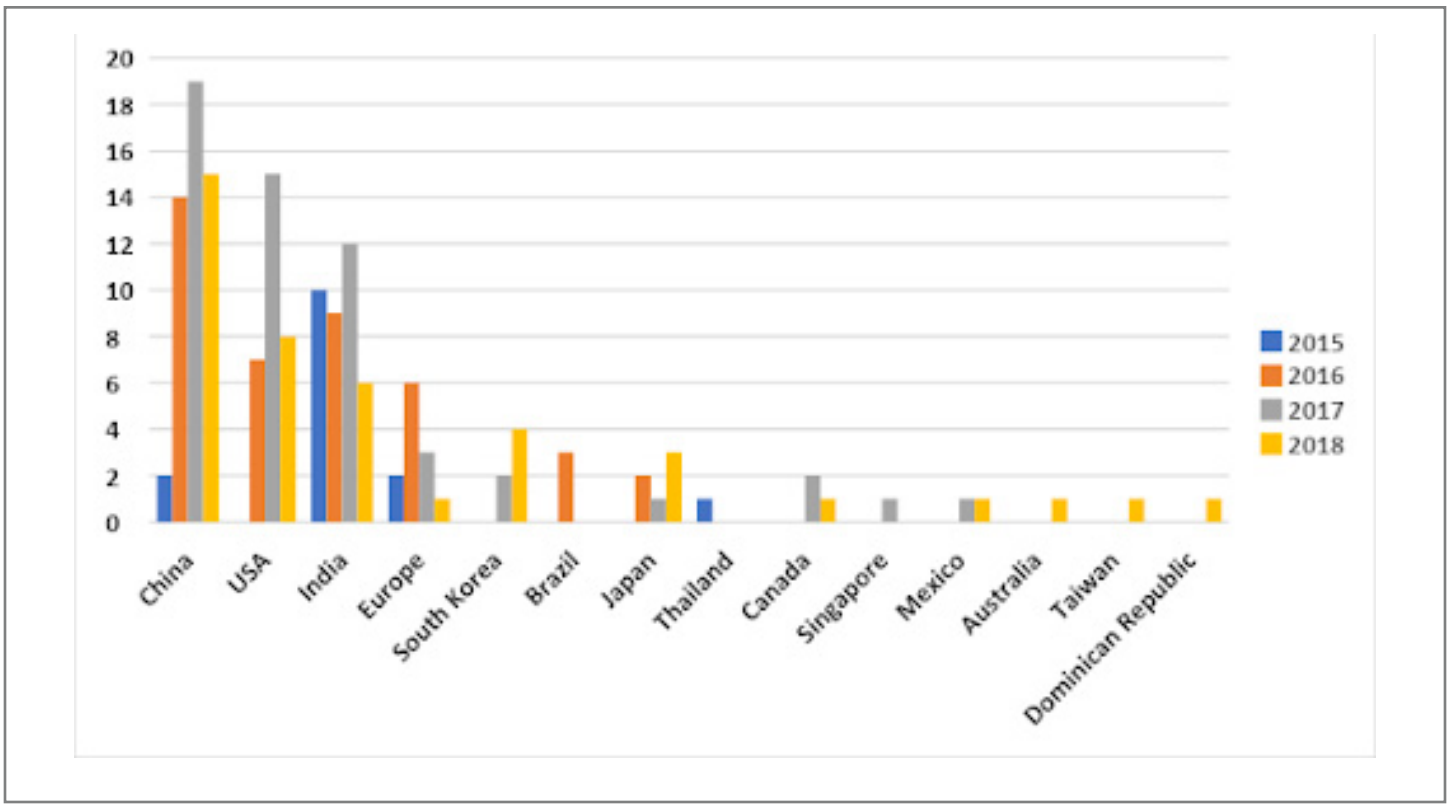

FIGURE 4: Data Integrity Warning Letters by Country

- The number of countries associated with these warning letters continues to increase.
- In 2018 eleven countries were associated with the sites that were the subject of warning letters.

Figure 3 also shows that nearly 80% of warning letters with data integrity components were issued in the past four calendar years. Even though this enforcement actions started almost 20 years ago, the past four years shows a dramatic uptick in number, peaking in CY2017. It will be interesting to monitor CY2019 warning letters and determine whether their number continues to decrease.

Figure 4 shows the data integrity associated warning letters by country from CY2015 through CY2018. South Korea is newly represented in this group of countries in the past two years. Canada and Mexico have been members of the

FIGURE 5: Geographic Totals and Percentage, 2015-2018 and 2008-2018

COUNTRY	TOTAL NUMBER 2015-2018	% of TOTAL 2015-2018	TOTAL NUMBER 2008-2018	% of Total 2008-2018
China	50	32%	58	30%
India	37	24%	54	28%
United States	30	19%	36	19%
Europe	12	8%	14	7%
Rest of World	25	16%	32	16%

group since 2011 and 2012 respectively. Singapore is new in 2017 and Australia, Taiwan and the Dominican Republic are new to the group in 2018.

Figure 5 compares the number and percentage of warning letters citing data governance and data integrity in both the past 11 years and the most recent four years.

- China tops the list in both the last four years and the last eleven years.
- In the past four years China significantly outperforms India in this area and the US comes in third.
- Europe remains constant at 9% of the total for both periods and the rest of the world (ROW) is constant at approximately 20% of the totals.

Figure 6 shows the regulations most frequently cited in the warning letters in CY2018. Many of the deficiencies did not identify a regulation or are provided by the FDA as "conclusions" or "data integrity remediation" instructions to which the firms must respond. Warning letters issued to API manufacturers do not identify 211. The citation of regulations continues the FDAs stated goal of focusing on the evaluation of predicate rule requirements.

Actions Firms Can Take To Prevent, Identify, And Remediate Issues

The number of data integrity associated warning letters decreased significantly between CY2017 and CY2018, though the percentage in 2018 remains slightly above that for CY2016. We will follow the trends for CY2019 to see if this continues to decrease.

So, what is a firm to do to prevent, detect, and remediate these problems before the health authorities become involved? This section remains virtually unchanged from last year.

We divide these actions into ones that may be taken by executive management and functional areas. We include a focus on management of contract services among the actions for firms to consider.

Additional detail on contract manufacture and data governance is provided in two articles published in 2017. Find them here:

- Data Integrity & Your Contract Manufacturer — Common Pitfalls To Avoid
- Best Practices For Data Integrity Oversight At Your Contract Manufacturer

FIGURE 6: Regulations Most Frequently Cited in CY2018 Data Integrity Associated Drug Warning Letters

21 CFR Reference	Number of Times Cited	Title of CFR Section
211.194	10	Laboratory Records, Review of All Data
211.188	6	Batch Production and Control Records
211.165 (a) and (b)	5	Testing and Release for Distribution
211.192	5	Production Record Review, Deviations, and Investigations
211.68	2	Automatic, Mechanical, and Electronic Equipment

EXECUTIVE MANAGEMENT OWNERSHIP

- Executive management must develop and reinforce a **culture of Quality**.
- Executive management must establish and maintain a **corporate culture of openness** where employees may report problems and failures without fear of retribution. In fact, reporting of problems should be encouraged and rewarded.
- Executive management must own the gap assessment process and remediation efforts. **Remediation may be costly and time-consuming.** Firms often uncover additional problems along the way. Don't expect to complete remediation quickly; it's often a multiyear process.

TECHNICAL AREA ACTIONS

- Cross-functional teams should perform **gap assessments** for both paper and computer systems against predicate rule requirements and specific data governance/integrity guidance from health authorities. The team should identify corrective actions and a timeline for their implementation. Firms should implement interim corrective actions until they can put fully compliant solutions in place.
- Firms should **map data and process flows** and identify and remediate risk areas. Results from this exercise can contribute to the gap assessments described above.
- Firms should **validate systems for their intended purpose** and ensure that adequate controls are in place to ensure that deleted or altered data can be detected.
- **Monitor enforcement actions** including Form 483s, warning letters, import alerts, EU reports of GMP noncompliance, and WHO Notices of Concern. All of these, except for the Form 483s, are available without cost on the internet, and Form 483s are available from commercial sources.
- Ensure that the data governance processes at **suppliers and contract service providers** are adequate to ensure that data is valid and trustworthy. This effort begins with rigorous due diligence evaluations, periodic on-site oversight, and appropriately detailed quality agreements.

Conclusion

Data integrity and data governance remain initiatives of global health authorities. The U.K.'s Medicines and Healthcare Products Regulatory Agency (MHRA) was the earliest to enter the area, in 2015, with its guidance and a published revision in 2018. The European Medicines Agency (EMA), World Health Organization (WHO), Pharmaceutical Inspection Co-operation Scheme (PIC/S), Australia, Canada, and China followed in 2016.

Further, enforcement is not limited to the GMP area but includes good clinical practice (GCP), with the most impactful cases at sites that perform bioavailability and bioequivalence studies.

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For these firms, the data for hundreds of products is impacted. Sponsors must frequently repeat the studies at different sites. Among the more significant failures in this area were identified at GVK and Semler Research. Consequences at Semler included a three-page Form 483, untitled letter, WHO notice of concern, and EMA recommendation of suspension.

I expect this type of problem to expand in scope to more OTC manufacturers because actions in this area is a clear trend that began in 2017. I also watch for this topic to be cited more frequently in enforcement actions taken against compounding pharmacies and outsourcing facilities.

GMP enforcement citing data governance and data integrity has not diminished, expanding both the number of warning letters and their geographic distribution. Although the number of warning letters has increased markedly over the past three years, the percentage has decreased slightly. In CY2017 an increasing number of countries were home to sites that were the subject of these warning letters.

Deficiencies in data governance and data integrity have remained markedly consistent over the 10 years addressed in this report, with a few new areas identified each year. Newer focus areas that appeared in 2017 continue in 2018 and include:

- Firms that repackage APIs were transferring analytical results onto Certificates of Analysis on their own letterhead, making it appear that they generated the results. The practice obscures the supply chain from the company that purchases and uses the material in the manufacture of drug products.
- Firms aborted an excessive number of analytical of runs.
- Firms manipulated "integration suppression" parameters within chromatography data systems, intending to obscure or minimize impurity peaks.

I expect this type of problem to expand in scope to more OTC manufacturers because actions in this area is a clear trend that began in 2017. I also watch for this topic to be cited more frequently in enforcement actions taken against compounding pharmacies and outsourcing facilities. Previously, most of the problems in this area addressed failures in aseptic processing, including facilities and equipment issues. I look for data integrity to be cited more frequently in both Form 483s and warning letters issued to these firms.

Note: Readers who want the complete text of the warning letter deficiencies on this topic can find them on my website for 2015 (starting on page 4), 2016 (starting on page 5), 2017 (starting on page 8) and 2018 (starting on page 1).