AN ANALYSIS OF FDA FY2018 DRUG GMP WARNING LETTERS

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A detailed summary of the drug GMP warning letters issued in FY2018, as well as a comparison of trends since fiscal year 2013.

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This article presents a detailed summary of the drug GMP warning letters issued in FY2018, as well as a comparison of trends since fiscal year 2013. A comprehensive GMP intelligence program includes evaluation of health authority enforcement actions, including FDA Forms 483, warning letters, seizures, recalls, and consent decree agreements. This allows manufacturers and sponsors to identify new trends in the focus of FDA inspectors and act to address or justify similar situations at their own firms.

Section 4.2 of ICH Q10, Pharmaceutical Quality System, specifies the "Monitoring of Internal and External Factors Impacting the Pharmaceutical Quality System" including "Emerging regulations, guidance and quality issues...". Enforcement actions should be monitored as a component of quality issues mentioned in the Q10 guidance.

Although the FDA is more transparent than other health authorities regarding enforcement actions, readers are encouraged to follow information published by Health Canada (HERE and HERE), Eudra GMDP reports of noncompliance (HERE), and WHO Notices of Concern (HERE).

The data presented here for FY2018, ending Sept. 31, 2018, is based on drug GMP warning letters posted by the FDA no later than Jan. 1, 2019. The data for over-the-counter (OTC) products represent CY2018 effective also January 1, 2019. The number will likely increase

TERMS

COMPOUNDING PHARMACY used here includes outsourcing facilities and is considered as a category separate from drug manufacturers based on their legal foundation. These sites are all located in the United States, but they are not combined with data from U.S. drug manufacturing sites in this article.

OUTSOURCING FACILITIES were established by the FDA as entities under an amendment to the Food Drug & Cosmetic Act in November of 2013. FDA published draft guidance describing how outsourcing facilities might comply with GMP regulations in December 2018. These firms are not considered in the data for import alerts, data integrity and OTC manufacture.

as FDA resumes publication of warning letters after the partial government shutdown is resolved. Thus, the OTC numbers we present here are likely an underestimate.

The narrative, tables, and figures address three broad areas:

- **Type of manufacture** (API, dosage form, API and dosage form, compounding pharmacy/outsourcing facility), and country associated with the warning letter.
- **Particular targets of warning letters issued this year**, including over the counter (OTC) drug products, drug product manufacturers, data integrity and contracted operations.
- **Interval between the inspection and enforcement actions**, including issuance of a warning letter or import alert.

SUMMARY

Following are brief highlights of noteworthy findings and trends, followed by a more detailed analysis in subsequent sections.

The number of drug GMP warning letters continues to increase over the previous years from 42 in FY2015, to 102 in FY2016, to 114 in FY2017, and 127 in FY2018 (See **Table 1** and **Figure 1**).

Manufacturers in China received the most warning letters issued to sites in a single country. Firms in China received 24 warning letters, firms in the US received 22 (see **Table 2** and **Table 1,** respectively).

The breakaway category of manufacturers in FY2018 that received warning letters are manufacturers of **over the counter (OTC), non-prescription drugs**. 53 percent of warning letters to drug product manufacturers were issued to OTC manufacturers. This is similar to the seemingly disproportionate enforcement focus that FDA placed on compounding pharmacies and outsourcing facilities several years ago. (see **Table 3** and **Figure 4**).

The number of warning letters issued to OTC manufacturers more than doubled between CY2017 and CY2018 from 17 to 39 respectively. More countries, ten vs seven, were associated with these warning letters in CY2018 (see **Table 3** and **Figure 4**).

Continuing a pattern from last year, **drug product manufacturing sites** more

than doubled the number of warning letters received from the previous year. This is likely associated with the dramatic increase in OTC drug product manufacturers who received warning letters (see **Table 1** and **Figure 2**).

The **compounding pharmacy/outsourcing facility** segment continues to receive enforcement attention from the FDA. We have, however, turned the corner on these warning letters and they have decreased for two consecutive years in both absolute number and percentage of the total (see **Table 1** and **Figure 1**).

Excluding the compounding pharmacies and outsourcing facilities, the FDA continues to focus its **enforcement actions outside the U.S.** Over three times as many warning letters were issued to firms outside the U.S. compared with those issued to domestic firms (see **Table 1** and **Table 2**).

At least twenty warning letters were issued to firms who were **contract manufacturers/laboratories** or to firms that did not exercise appropriate controls over their contracted operations. This continues a focus that began last year.

Import alerts were associated with 48 of the 73 warning letters issued to sites outside the U.S. in FY2018. Firms in China, India and Korea that received warning letters were the subject of 32 of the 48 import alerts associated with warning letters. China was also in first place here with 21 of the 24 firms who received warning letters being subject to import alerts.

The percentage of warning letters that cite deficiencies in data governance/data integrity decreased from the high point of 81 percent in FY2016 to 60 percent for firms outside the U.S in FY2018.

The percentage of warning letters that cite deficiencies in **data governance/data integrity** decreased from the high point of 81 percent in FY2016 to 60 percent for firms outside the U.S in FY2018. Those issued to U.S. firms decreased from 73 percent in FY2016 to 45 percent in FY2018. Data integrity deficiencies are cited in 57 percent of all warning letters, excluding those issued to compounding pharmacies, down from a high of 79 percent in FY2016 (see **Table 4** and **Figure 5**).

The **interval between inspection and issuance of warning letters** continues to

decrease for all categories, though the most dramatic decrease has been for warning letters issued to sites outside the U.S. Warning letters issued to compounding pharmacies and outsourcing facilities continue to take the longest time to issue after inspections are completed.

The interval between inspection and issuance of import alerts continues to be just under 50 percent of the time between inspection and warning letter issuance (see **Tables 5** and **6**, and **Figures 6** and **7**).

WARNING LETTER DATA

Table 1 shows that drug GMP warning letters more than doubled from FY2015 to FY2016 and increased again in 2017 and 2018 though not by as large a percentage.

Table 1 also shows that while the FDA continues an intense focus on compounding pharmacies, the warning letters to these entities have decreased significantly for two years in a row. I doubt this is because they have become more

TABLE 1: DRUG GMP WARNING LETTERS

	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018
TOTAL	41*	49**	42	102	114***	127****
Compounding pharmacies	3 (7%)	27 (55%)	24 (57%)	56 (55%)	45 (39%)	32 (25%)
U.S. (non-compounders)	13 (32%)	4 (8%)	3 (7%)	11 (11%)	20 (17.5%)	22 (17%)
OUS	25 (61%)	18 (37%)	16 (38%)	35 (34%)	49 (43%)	73 (57%)
Breakdown by Facility Type (U.S. & OUS), Excluding Compounding Pharmacies						
API sites	5	8	9	19	19	17
Drug product (non-compounders)	29	12	9	23	46	73
API and drug product	3	2	1	4	3	2

*Includes one repackager not counted as either API or drug product.
**Includes one warning letter regarding combination products, considered drug product.
*** Includes one warning letter to a contract laboratory, not counted as either API or drug product.
**** Includes three warning letters to contract laboratories, not counted as either API or drug product.

GMP compliant, but likely because many have decided to cease the compounding of sterile injectable drugs.

FY2018 warning letters issued to API sites decreased slightly compared to FY2017. The number of warning letters issued to drug product sites, increased over 50 percent from 47 in FY2017 to 73 in 2018. This is likely associated with the increase in warning letters issued to OTC manufacturers from 17 in CY2017 to 39 in CY2018.

FDA has continued a focus on homeopathic drug manufacturers and manufacturers of human cell and tissue products with three and four warning letters respectively in 2018. FDA continues to exercise enforcement discretion here and will intervene with enforcement actions when public health

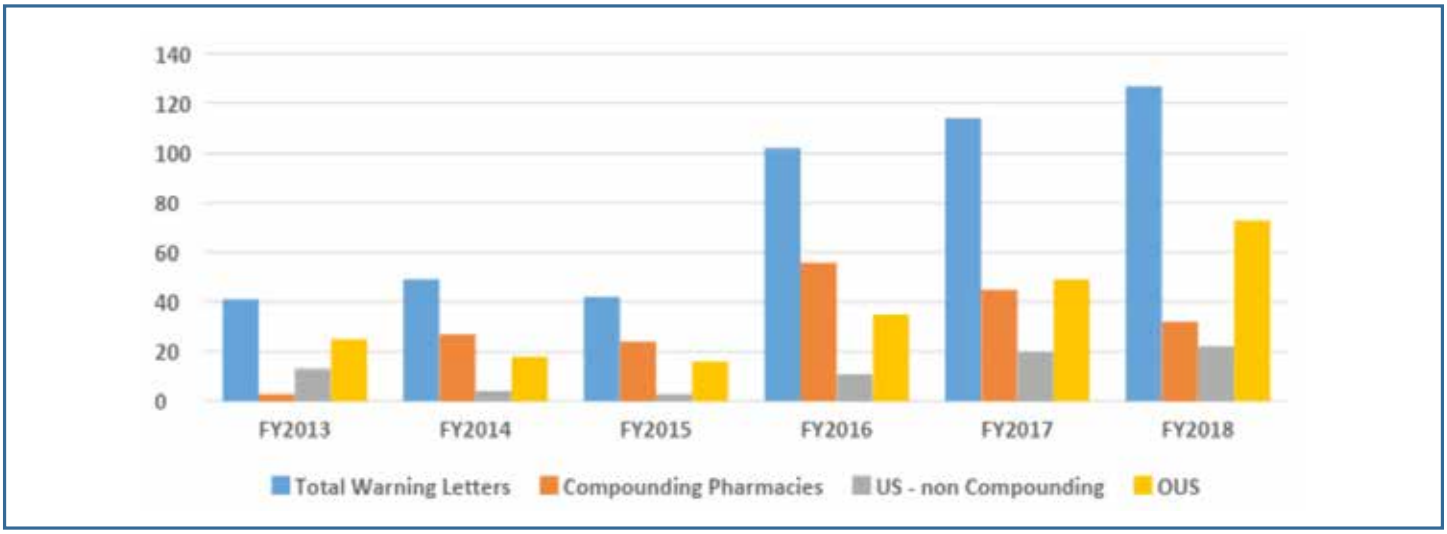

FIGURE 1 DRUG GMP WARNING LETTERS FROM 2013 TO 2018

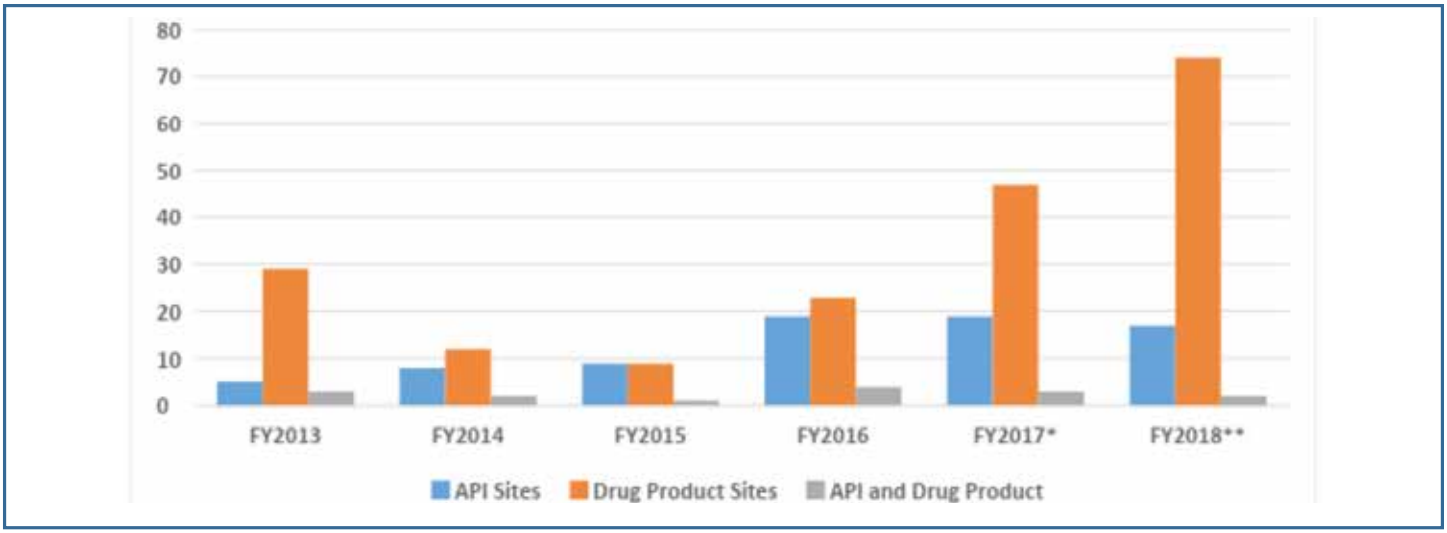

FIGURE 2 WARNING LETTER, TYPE OF MANUFACTURING SITE

TABLE 2: DRUG GMP WARNING LETTERS ISSUED REGARDING SITES OUTSIDE THE U.S.

Country / Geography	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	TOTAL
China	2	5	2	15	17	24	65
India	7	7	8	10	14	14	60
Europe	7	3	3	5	8	9	35
Canada	4	1	1		3	5	14
South Korea					2	9	11
Japan	2			1	3	3	9
Taiwan	1			2		3	6
Australia	1	1				3	5
Mexico		1				3	4
Brazil				2	1		3
New Zealand			1				1
Jamaica	1						1
Thailand			1				1
Singapore					1		1
Dominican Republic						1	1

is at risk. I expect letters to human cell and tissue firms to increase in FY2019 and beyond.

And finally, while not addressed in a table or figure, the FDA continued to cite deficiencies in process validation. Specifically, the FDA cited the failure to implement an ongoing process monitoring program to ensure that the manufacturing process remains in a state of control. This is applicable to all types of drug manufacture, oral and topical dosage forms, as well as sterile injectables (see **Figures 1** and **2**).

Table 2 shows the geographic distribution of warning letters issued outside the U.S. China received the largest number of warning letters issued to a single country in FY2018 and over the six-year period. India received the next highest number of warning letters, followed at a distance by Europe. Over the past four years the number of warning letters to sites in China has steadily increased, while warning letters issued to sites in India have increased then held steady. European countries include the UK, and are counted together. European area

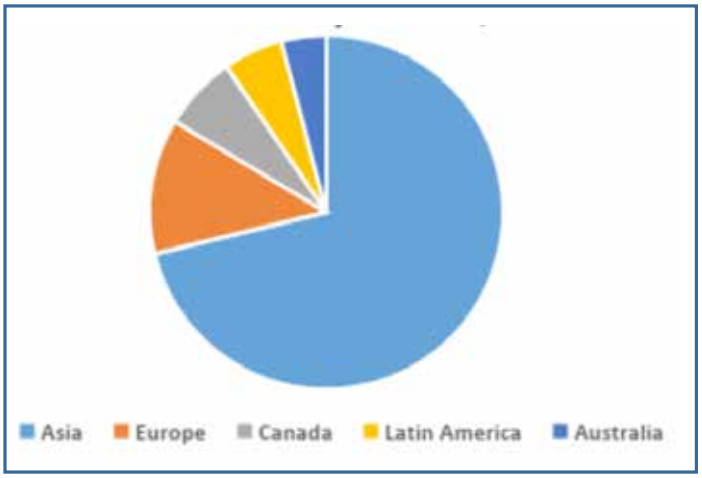

FIGURE 3 OUS WARNING LETTERS BY REGIONG, FY2018

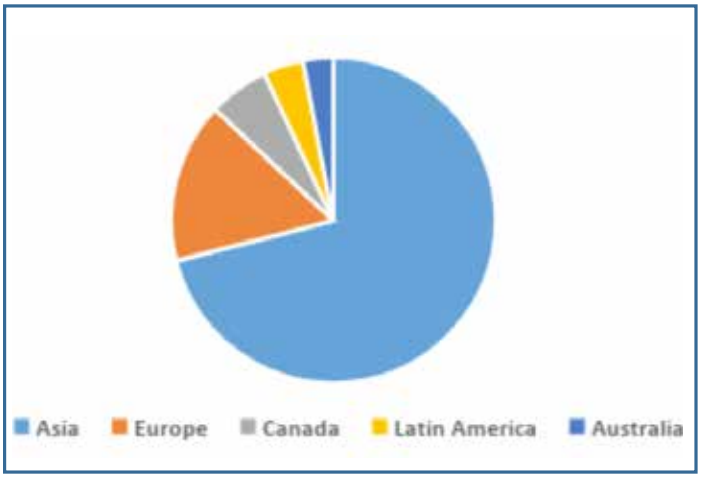

FIGURE 4 OUS WARNING LETTERS BY GEOGRAPHY FY2013 - 2018

countries with sites that have received warning letters over the six fiscal years include: Ireland, Spain, Czech Republic, Italy, Portugal, Denmark, Austria, Netherlands, Germany, Hungary, the U.K., and Switzerland.

sites in 'Asia' (Japan, China, India, Taiwan and Hong Kong) account for approximately 71 percent of drug GMP warning letters issued outside the U.S. the same as the percentage over the six year period FY2013 – FY2018.

Figures 3 and **4** show that sites in 'Asia' (Japan, China, India, Taiwan and Hong Kong) account for approximately 71 percent of drug GMP warning letters issued outside the U.S., the same as the percentage over the six year period FY2013 – FY2018.

In FY2018 and the six year period FY2013-FY2018 sites in Europe received 12% and 16% of warning letters respectively. With the Mutual Recognition Agreement between the U.S. and the EU, it will be interesting to see if the number of warning letters to European sites begins to decrease in FY2019. This agreement includes twenty health authorities in the EU effective November 28, 2018 with the remaining EU authorities expected to be added by July 2019.

OTC MANUFACTURERS

CY2018 included a dramatic focus on OTC manufacturers worldwide reminiscent

of the focus on compounding pharmacies and outsourcing facilities that began in 2014.

Table 3 and **Figure 5** show the warning letter enforcement data on this group of manufacturers for the last eleven

TABLE 3: WARNING LETTERS ISSUED TO OTC MANUFACTURERS BY COUNTRY, BY CY

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
USA		3	6		1	1			1	7	10
Mexico				1	3					1	2
China									1	4	10
South Korea										2	5
Europe						1			1	0	4
Canada					1	1				1	1
Singapore										1	
Philippines										1	
Jamaica						1					
Japan						1					
Taiwan										0	2
Dominican Republic										0	1
Australia										0	1
India										0	3

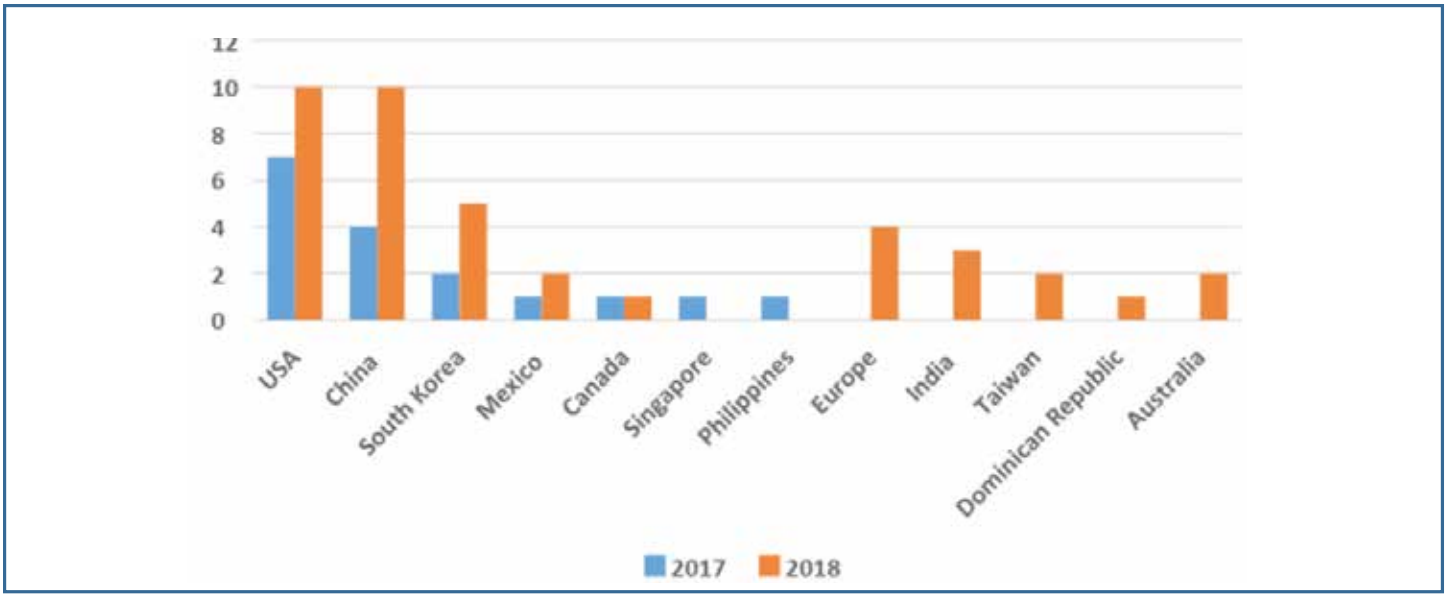

FIGURE 5 OTC WARNING LETTERS IN CY2017 AND 2018

years. The dramatic changes began in CY2017 and increased again in CY2018. The numbers for CY2018 will likely increase beyond those reported here as additional warning letters issued in 2018 are posted in early 2019.

FY2018 warning letters continued to focus on contracted activities, an area of focus that in my opinion will continue into the foreseeable future. At least twenty warning letters mention contracted activities compared to at least eleven last year.

Sites in China and the US each received 10 warning letters, sites in South Korea received five and sites in Europe received four. Six additional countries had sites that received either one, two or three warning letters. Both China and South Korea saw more than two-fold increases between CY2017 and 2018. The number of countries increased from seven in CY2017 to ten in CY2018.

FY2018 warning letters continued to focus on contracted activities, an area of focus that in my opinion will continue into the foreseeable future. At least twenty warning letters mention contracted activities compared to at least eleven last year.

Thus, 21 percent of warning letters issued to firms that were not compounding pharmacies were directly associated with contract manufacturing or testing. Five sites were located each in South Korea, China and the US; Europe had three sites and Australia had two.

IMPORT ALERTS ASSOCIATED WITH WARNING LETTERS

Seventy-three warning letters were issued regarding sites outside the U.S., and 47 of these had associated import alerts for failure to comply with drug GMPs or refusal of an inspection.

So not only did 64 per cent of firms that received warning letters have the expense associated with remediation of the warning letter itself, they are prevented from selling product from these sites in the U.S., excluding FDA-identified medically necessary products.

In many cases this likely provides an economic hardship. Firms in China received 24 warning letters and twenty-one of these also were placed on import alert. China, India, and Korea taken together,

TABLE 4: DATA INTEGRITY DEFICIENCIES IN WARNING LETTERS, EXCLUDING COMPOUNDING PHARMACIES

	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018
Total WLs	38	22	19	46	69	95
U.S. WL Sites with data integrity	0 of 13 (0%)	0 of 4 (0%)	1 of 3 (33%)	8 of 11 (73%)	12 of 20 (60%)	10 of 22 (45%)
OUS Sites with data integrity	10 of 25 (40%)	12 of 18 (67%)	13 of 16 (81%)	29 of 35 (81%)	33 of 49 (67%)	44 of 73 (60%)
TOTAL NUMBER of WARNING LETTERS CITING DATA INTEGRITY	10 (26%)	12 (55%)	14 (74%)	37 of 46 (79%)	45 of 69 (65%)	54 of 95 (57%)

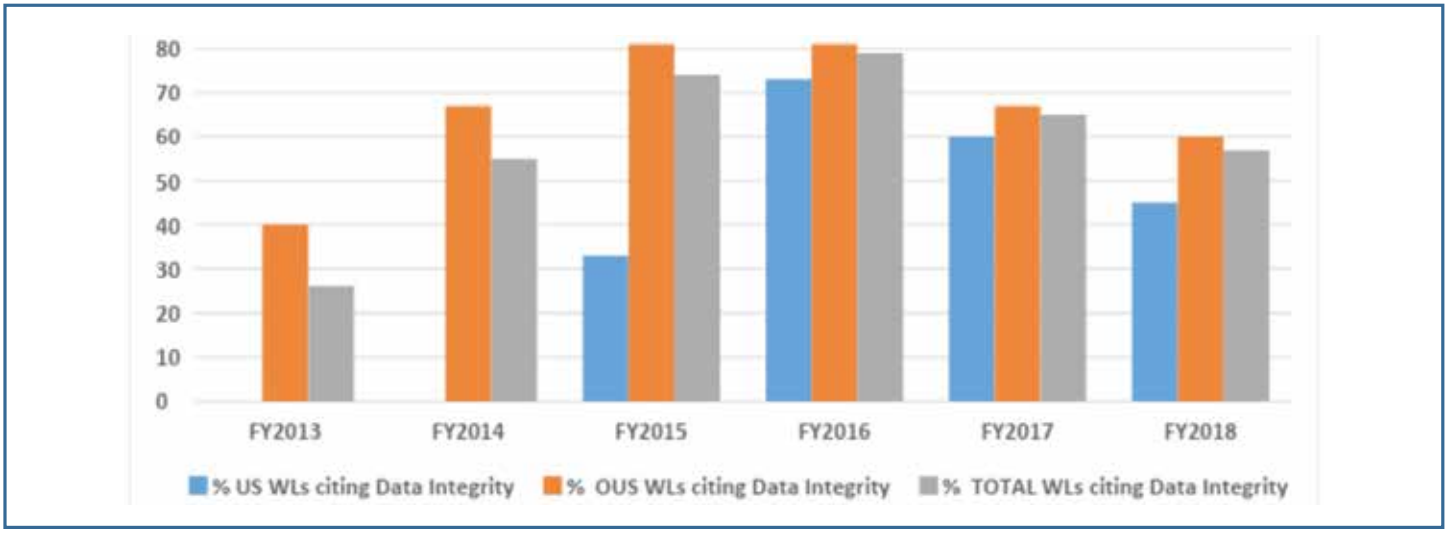

FIGURE 6 WARNING LETTERS ASSOCIATED WITH DATA INTEGRITY

account for 68 percent of the import alerts associated with warning letters. Each country likely had additional sites that were the subject of import alerts but these were not associated with warning letters.

DATA INTEGRITY DEFICIENCIES IN WARNING LETTERS

Table 4 shows the number of warning letters issued both inside and outside the U.S. that included references to data management and data integrity. This group and analysis excludes those warning letters issued to compounding pharmacies.

Data integrity deficiencies in warning letters continue to identify the predicate rule(s) to which firms did not adhere.

Figure 6 provides a graphic representation of the data. The percentages for both

US and OUS warning letters have consistently decreased between FY2016 and FY2018; perhaps we've turned the corner here but we still have a long way to go to eliminate this problem.

INTERVALS BETWEEN INSPECTION AND WARNING LETTER

Table 5 and **Figure 7** show the interval between inspection and issuance of a warning letter for the six most recent fiscal years. The data for all three major categories shows a decrease in the time between inspections and warning letter issuance. The most significant change happened for the sites outside the U.S., which saw a decrease from 10.4 months in FY2016 to 8.0 months in FY2017. The time between inspection and warning letter issuance is longest for compounding pharmacies at 12.6

TABLE 5 MONTHS BETWEEN INSPECTION AND WARNING LETTER

	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018
All Warning Letters	8.4	8.6	10	11.9	10.1	8.2
Compounding Pharmacies	3.7	10.2	10.4	13.1	12.6	12.6
U.S. Sites	10.1	7.1	4.5	10.9	9.6	7.4
OUS Sites	7.8	6.8	10.4	10.4	8.0	6.8

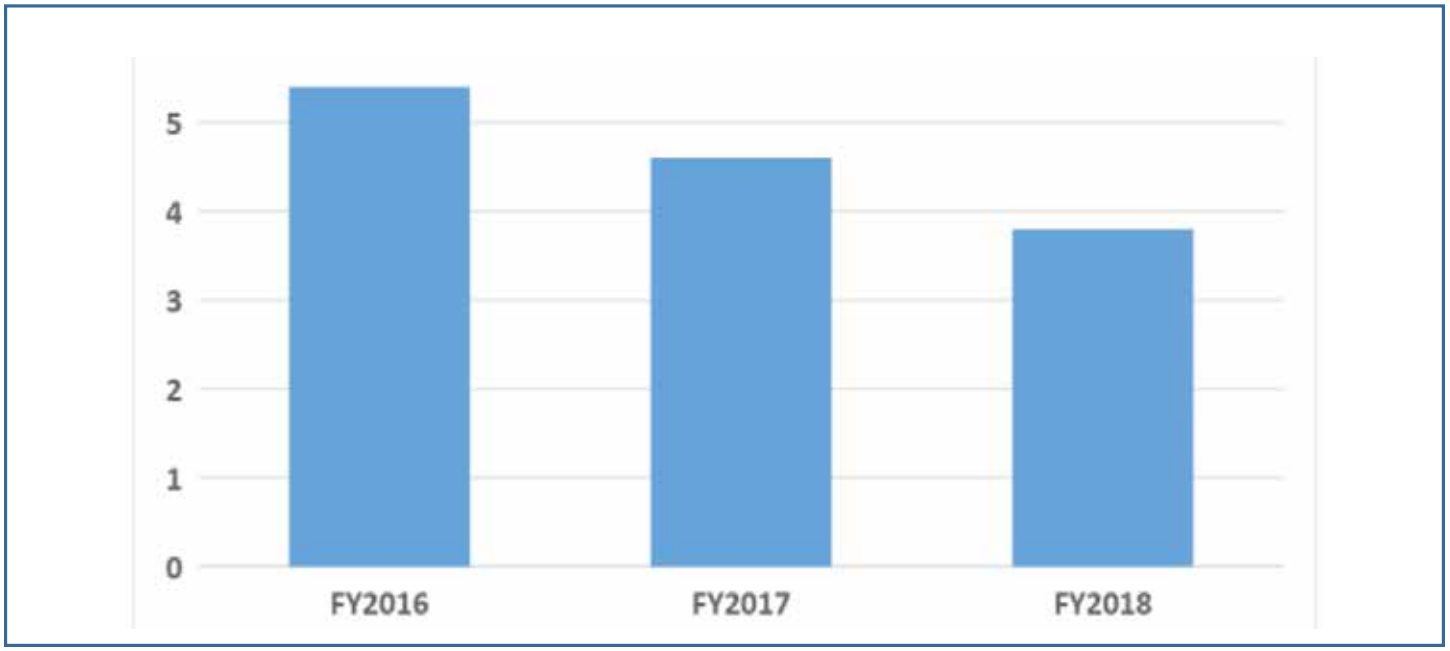

FIGURE 7 MONTHS BETWEEN INSPECTION AND WARNING LETTER ISSUANCE

TABLE 6 INTERVAL TO ENFORCEMENT ACTIONS AFTER INSPECTION

	FY2016	FY2017	FY2018
Inspection to Warning Letter, Overall	11.9	10.1	8.2
Inspection to Import Alert	5.4	4.6	3.8

months, though this is about 0.5 month shorter than in FY2016. The high point for this interval was reached in 2016

Table 6 and Figure 6 show that the interval between the inspection and imposition of an import alert decreased in FY2018 compared with FY2017. These data include only those associated with warning letters and may not be representative of import alert timing for firms who do not receive a warning letter. Though only three years are represented here, the time interval has consistently decreased. The import alerts addressed here include failure to follow GMPs (Import Alert 66-40) and refusal of inspection by a foreign establishment (Import Alert 99-32).

CONCLUSIONS

FY2018 saw another year of increase in the number of drug GMP warning letters issued by the FDA, though not as dramatic a difference as in some previous years.

Compounding pharmacies and outsourcing facilities continue to receive enforcement attention though we seem to have officially turned the corner here with decreasing number and percentages of warning letters issued to this group in two consecutive years. We will continue to monitor this metric and see whether FY2019 shows a similar decline.

Contract manufacturers and their sponsors were a focus again this year, and I would expect that to continue and expand in FY2018. Some sponsors will only take their responsibilities for selection and oversight of contract manufacturers seriously if they suffer an economic impact, such as a contract manufacturer that is subject to a serious enforcement action that results in a delay to product approval or a cessation of manufacture to undertake necessary facility and equipment remediation.

The breakaway category for warning letters in FY2018 was manufacturers

of OTC drug products. This group, on the whole, appears to have failures in fundamental aspects of GMP, including the need for an effective quality unit, testing of incoming materials and components rather than simple reliance on the supplier's certificate of analysis, testing of product prior to release to the market and failure to have real time data to support expiry labeling..

China continues to lead in the country receiving warning letters, as it did in FY2017.

China continues to lead in the country receiving warning letters, as it did in FY2017. This year saw the addition of the Republic of (South) Korea to the countries whose companies received an increasing number of warning letters. I would expect this to continue into FY2019 also.

Now where are we heading in 2019? Overall, look for the following trends in warning letter enforcement actions:

- A diminishing focus on compounding pharmacies and outsourcing facilities though warning letters and recalls will continue in significant number.
- Continued focus on data integrity and data governance.
- Continued focus on OTC manufacturers because of the number of individuals using these products and the seemingly poor understanding and compliance with GMPs as shown in this year's warning letter collection.
- Contract manufacturers and laboratories and those that contract for their services will see continued attention by the FDA.
- There likely will be ongoing and increased attention in process validation, particularly ongoing process monitoring, as required in both the FDA and EMA validation guidance.
- Stem cell product manufacturers, and manufacturers of human tissues and cellular products will see increasing enforcement actions based on their overall potential impact on public health and the FDA's stated focus to improve risk-based enforcement in those areas. FDA is exercising enforcement discretion until 2020 at which time they expect these firms to be operating under Investigational New Drug (IND) applications for therapies that are not approved under a BLA or NDA.