WARNING LETTER TRENDS IN 1HFY2016, INCLUDING DATA INTEGRITY

and

INTERVALS BETWEEN INSPECTION and DRUG GMP WARNING LETTERS

We provide an update on drug GMP warning letters issued halfway through the FDA fiscal year and how they compare to previous years. We categorize the warning letters as those issued to compounding pharmacies / outsourcing facilities, those issued to pharma and API sites in the US and those issued to sites outside the US. A review of this timeframe for a limited set of warning letters issued in 2015 suggested that the time interval was increasing. Here we provide a full data set, both domestic and OUS, to support the conclusion regarding the increase in this time interval over the past 3 ½ fiscal FDA years.

NUMBER OF DRUG GMP WARNING LETTERS per FY

Let's start with drug GMP warning letters, how many were issued to the various types of sites, and the location of these sites. The values provided for 1H FY2016 are NOT annualized but represent only six months of data. Table 1 shows that compounding pharmacies and outsourcing facilities continue to receive an exceptional focus from FDA which began in FY2014 when legislation clarified FDA's authority over this market segment. The first half of this year again shows that more than half of the warning letters were issued to these sites. Only three sites located in the US outside of this market segment received warning letters continuing the trend of the past few years. This year may see an increase in their overall number if the trend continues, but it will likely remain in single digits. Sites outside the US continue to receive substantial attention and this year so far six of the sites are located in India and one site is located in China.

For the non-compounding pharmacy sites, the most obvious change in the first half of FY2016 shows a diminished focus on API manufacturing sites. We will follow and update this report at the end of FY2016.

Data in the table below are also shown in Figures 1 and 2 for those who like graphic representations.

In conclusion:

- The total number of drug **GMP warning letters is on track to be similar to the past few years** and the total number may actually exceed that of FY2015.
- 1H FY2016 continues the intense focus on compounding pharmacies and outsourcing facilities who received more than half of the warning letters.
- The number of API sites that received warning letters in 1H FY2016 suggest a lower number for FY2016, though absolute numbers remain small at this time.
- **All seven (7) warning letters issued to sites outside the US identify gaps in data integrity**. One of the four warning letters issued to sites in the US identifies gaps in data integrity.
- Overall this continues to raise the question of whether the exceptional focus on compounding pharmacies and outsourcing facilities diverts limited inspection and enforcement resources from pharmaceutical firms both inside and outside the US. Warning letters in both categories have diminished markedly since FY2013. This is

particularly troubling because most warning letters issued outside the US include serious data integrity shortcomings.

Table 1. FY Warning Letters Issued by Location and Product Type

	FY2013	FY2014	FY 2015	1H FY2016 NOT annualized
TOTAL	**41***	**49****	**42**	**27**
Compounding pharmacies	**3** (7%)	**27** (55%)	**24** (57%)	**16** (59%)
US (non-compounders)	**13** (32%)	**4** (8%)	**3** (7%)	**4** (15%)
OUS	**25** (61%)	**18** (37%)	**16** (38%)	**7** (25%)
API sites ***	**5** (13%)	**8** (36%)	**9** (47%)	**2** (18%)
Drug Product *** (non-compounders)	**29** (76%)	**12** (54%)	**9** (47%)	**5** (45%)
API and drug product ***	**3** **(8%)**	**2** (9%)	**1** (5%)	**3** (27%)

*Includes one re-packager not counted as either API or drug product
**Includes one warning letter regarding combination products, considered drug product
*** Percentages are calculated as (value / total number of non-compounding WLs) x 100, and rounded to a whole number

Figure 1. Drug GMP Warning Letters by Location/Type

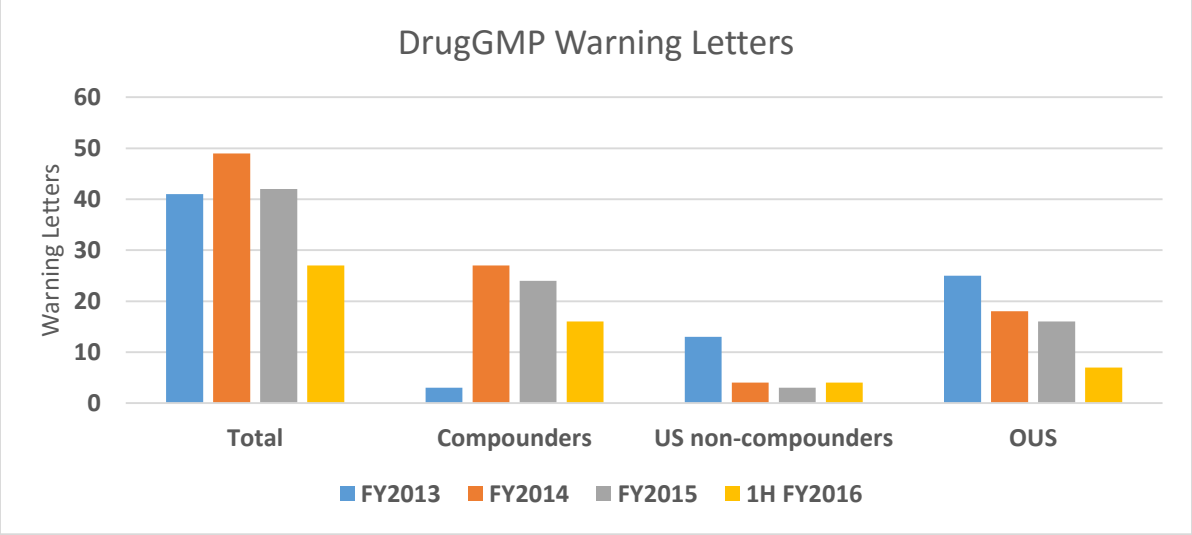
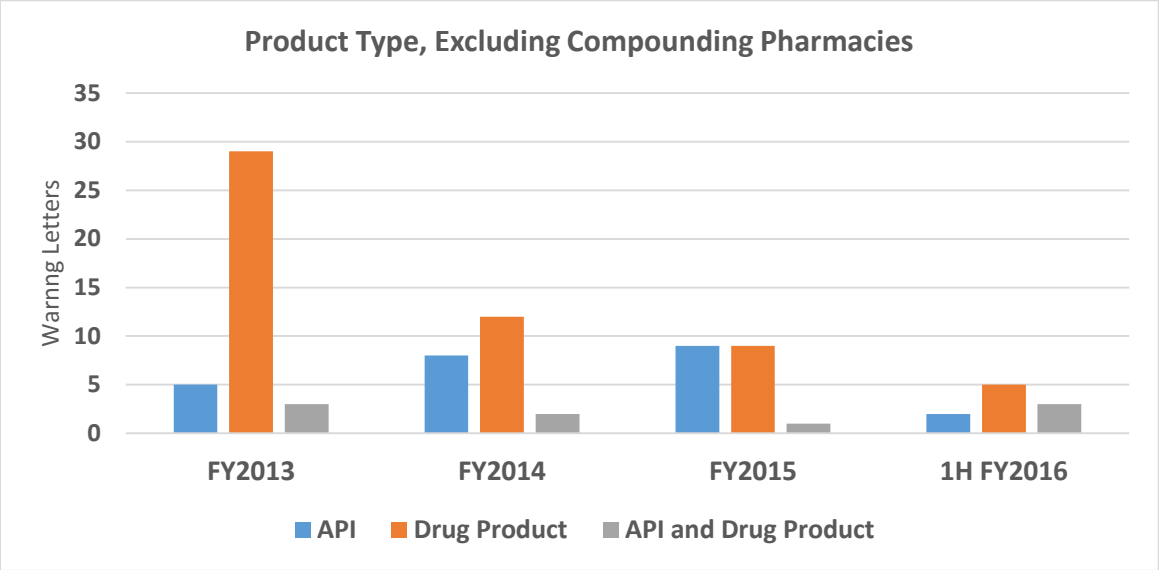


Figure 2. Drug GMP Warning Letters by Pharma Company Manufacturing Type



DRUG GMP INSPECTION TO WARNING LETTER ISSUANCE INTERVALS

Last year seemed to show an increase in the interval between inspection and warning letter issuance. Here we provide several years-worth of data to demonstrate this is generally true, with a couple of exceptions. We start with FY2013 and include 1HFY2016. Data are provided for the total number of warning letters, those issued to compounding pharmacies / outsourcing facilities, pharma firms in the US and outside the US. When two or more inspections were mentioned in a warning letter, I took the date nearest to the warning letter issued under the assumption (perhaps incorrect) that the final inspection provided the incentive that made the warning letter issuance appropriate. When tabulating the individual intervals, they are rounded to the nearest half month.

Table 2 shows that data identifying the interval between inspections and warning letter issuance for the FYs in question. Figure 3 provides a graphic representation of the data. Also see data in Table 1 for the number of warning letters in each of the FY categories.

In conclusion:

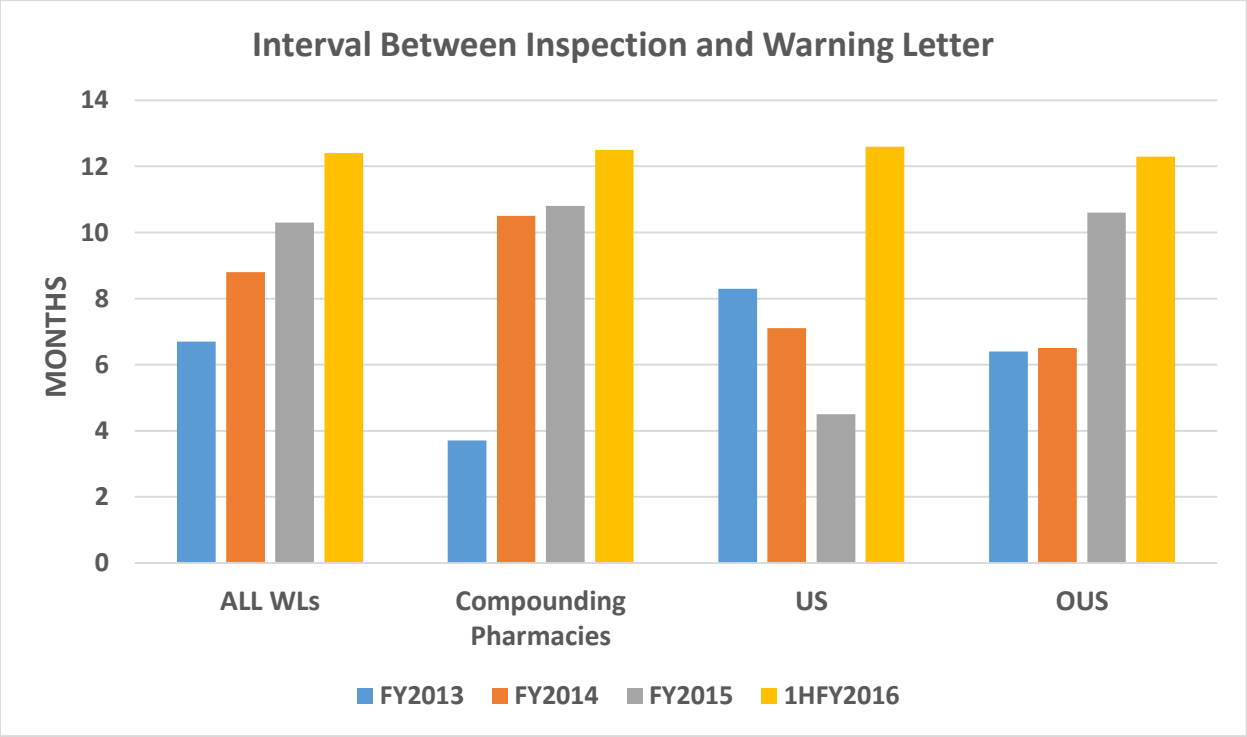
- The average interval between inspection and issuance of ALL warning letter, and those issued outside the US (OUS) almost doubled between FY2013 and 1HFY2016.
- **The average time for issuance of <u>all</u> drug manufacturer categories, including compounding pharmacies / outsourcing facilities, of warning letters in 1HFY2016 exceeded 12 months**.
- The near doubling of time between inspection and warning letters issued to sites outside the US between FY2014 and 1HFY2016 is dramatic. It's not clear why this should be the case. Often the warning letters acknowledge that the firms hired third party consultants to assist in remediation of inspection observations.

- The exception to the increase in the time interval between inspection and warning letter are the sites in the US, likely due to their limited number. FY2014, FY2015 and 1H FY2016 saw 4, 3, and 4 warning letters respectively issued to these sites. FY2013 saw 13 warning letters.
- The very short duration between inspection and issuance of warning letters for compounding pharmacy in FY2013 was likely due to their small number, 3 in this case.

Table 2. Interval Between Inspection and Warning Letter in Months

	FY2013	FY 2014	FY2015	1H FY 2016
TOTAL WLs	6.7	8.8	10.3	12.4
Compounding Pharmacies	3.7	10.5	10.8	12.5
US sites (non-compounders)	8.3	7.1	4.5	12.6
OUS	6.4	6.5	10.6	12.3

Figure 3: Interval Between Inspection and Warning Letter in Months



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