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ANALYSIS OF FDA FY2019 DRUG GMP WARNING LETTERS

RESOURCE TYPE

IN THIS SUMMARY WE IDENTIFY

– A detailed summary of the drug GMP warning letters issued in FY2019, as well as a comparison of trends since FY2013

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Fiscal Year (FY) 2019 was a fascinating year for drug GMP warning letters in the diversity of topics addressed, depth of focus, and trends in enforcement actions. This article presents a comprehensive summary of the drug GMP warning letters issued in FY2019, including an evaluation of trends since FY2013. The data presented for FY2019, ending September 31, 2019, is based on drug GMP warning letters posted by the FDA no later than January 20, 2020.

The term "compounding pharmacy" as used here includes outsourcing facilities and, for the purpose of this analysis, is considered a separate category from other drug manufacturers based on their legal foundation. These sites are located in the United States, but they are not considered with data from U.S. drug manufacturing sites in most analyses in this article.

Outsourcing facilities were established by the FDA under an amendment to the Food Drug & Cosmetic Act in November of 2013. The data from these sites is included in **Figures 1, 2, 11, and 12**. All other tables and figures omit this market segment data. All data reflect fiscal years with the exception of **Figure 10** that shows the trend over time of issuance of warning letters to OTC firms in calendar years (CY).

The narrative and figures address four broad areas, including trends between FY2013 and FY2019 in:

- Type of manufacture (API, dosage form, API and dosage form, compounding pharmacy/ outsourcing facility) and country associated with the site that is the subject of the warning letters.
- Time interval between the inspection and issuance of a warning letter including data presented by compounding pharmacy sites, US sites, and OUS sites.
- Particular targets of warning letters, including over-the-counter (OTC) and homeopathic drug products, drug product manufacturers, API manufacturers and Human Cell Therapy Product (HCT/P) manufacturers.
- Notable topics, including but not limited to data integrity associated warning letters, nitrosamine contamination of Angiotensin II Receptor Blockers (ARBs), API re-packagers, and the first warning letter citing failure to comply with requirements in the Drug Supply Chain Security Act amendments to the FD&C Act.

Five high-level conclusions can be drawn from the FY2019 warning letter data; additional conclusions are provided at the end of this report.

- Warning letters issued to firms in the US far exceed the number issued to firms OUS for the first time in the 8 years for which I present data. (**Figures 1 and 2**)
- Warning letters to compounding pharmacies continue to decrease following a trend that began in FY2017 after a high was reached in FY2016. (**Figures 1 and 2**)
- Warning letters that include a data integrity component continue to decrease, a trend that began in FY2017 after they reached a high in FY2016. (**Figures 6 and 7**)
- The intervals between inspection and warning letters continue to decrease with the exception of warning letters issued to compounding pharmacies where the interval increased in FY2019. (**Figures 11 and 12**)
- A notably diverse group of market segments and topics are included in the FY2019 warning letter collection including

but not limited to failure to comply with the DSCSA, failure of re-packagers to include complete information on CoAs, GMP deficiencies that led to nitrosamine contamination of Angiotensin II Receptor Blocker (ARB) APIs and drug products, warning letters issued in the OTC market segment, and finally, warning letters issued to human cell therapy producers. (**Figures 8, 9 and 10**)

Overall Warning Letter Data

Figure 1 and **Figure 2** show that drug GMP warning letters more than doubled from FY2015 to FY2016 and continued to increase through FY2019. The increase continues, but has been more gradual in the past three fiscal years. **Figure 1** also shows that while the FDA continues a focus on compounding pharmacies, the number of warning letters issued to these entities has decreased significantly for the past three years. The number of warning letters issued to these firms in FY2019 is approximately 34 percent of the number issued at the high point in FY2016. I doubt that this is because they have become more GMP compliant. Two factors may have contributed to this decrease: 1) many firms have decided to cease the compounding of sterile injectable drugs after inspection by FDA and 2) FDA has taken a new and intense focus on OTC firms in the past two years. Further, regarding outsourcing facility compliance with GMPs, the FDA published draft guidance describing how outsourcing facilities might comply with GMP regulations in December 2018 and published a 51-page second draft on January 22, 2020.

Note that data from compounding pharmacies/outsourcing facilities is not included except in **Figures 1, 2, 11, and 12**. All other tables and figures omit this market segment data.

Figure 3 shows that FY2019 warning letters issued to API sites is approximately half the number issued in FY2018 which was down slightly from the peak in FY2016 and FY2017. The number of warning letters issued to drug product sites, however, increased substantially again this year to a total of 96 and represents 86 percent of all drug

Figure 1 Warning Letters Issued from FY2013 through FY2019

	FY2013 *	FY2014 **	FY2015	FY2016	FY2017	FY2018 ***	FY2019 ****
TOTAL	**41**	**49**	**42**	**102**	**114**	**127**	**130**
Compounding Pharmacies	3	27	24	56	45	32	19
US (Non-Compounders)	13	4	3	11	20	22	68
OUS	25	18	16	35	49	73	43
API Sites	5	8	9	19	19	17	8
Drug Product (Non-Compounders)	29	12	9	23	47	73	96
API and Drug Product	3	2	1	4	3	2	1

* In FY2013 one re-packager is not counted as either API or drug product.
** In FY2014 one warning letter regarding combination products was considered to be in the drug product category.
*** In FY2018 two warning letters to contract laboratories were not counted as either API or drug product.
**** In FY2019 one warning letter was issued to a drug distributor, two to a API re-packager, one to a drug product re-packager, and two to CLOs that are not counted in any of the API or drug product categories.

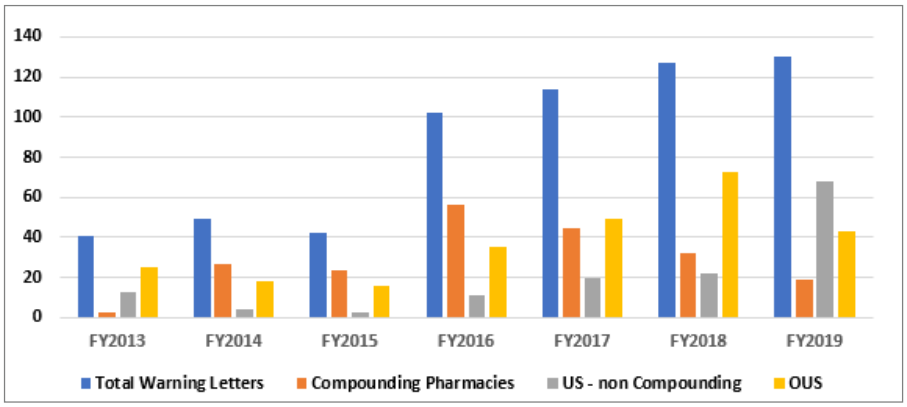


Figure 2 Warning Letters Issued from FY2013 through FY2019

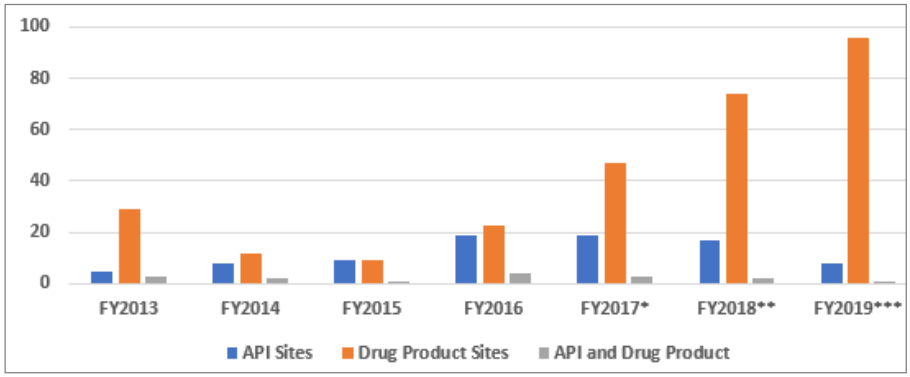


Figure 3 Drug GMP Warning Letters by Type of Manufacturing Site

GMP warning letters issued to sites excluding compounding pharmacies. We will address later some reasons for the increase in the number of warning letters issued to this group.

Figure 4 presents the location of the firms outside the US that were the subject of warning letters in FY2013 through FY2019. The number of warning letters issued regarding sites in India increased slightly from FY2017 and FY2018. Firms in China, however, saw a dramatic decrease in warning letters from the previous year and the number is now more consistent with values from FY2016 and FY2017. Last year, sites that were the subject of warning letters were

Figure 4 Countries OUS Where Firms Receiving Warning Letters Were Located

	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019
COUNTRY/GEOGRAPHY							
India	7	7	8	10	14	14	16
Europe	7	3	3	5	8	9	2
China	2	5	2	15	17	24	15
Canada	4	1	1		3	5	1
Taiwan	1			2		2	1
Australia	1	1				3	
New Zealand			1				
Jamaica	1						
Japan	2			1	3	3	
Mexico		1				3	
Thailand			1				
Brazil				2	1		
Singapore					1		2
South Korea					2	9	4
Dominican Republic						1	
Turkey							1
Costa Rica							1

located in 10 countries outside the US, and this year that number fell to 9.

Figure 5 shows the distribution of all drug warning letters issued in FY2019 based on geographic region or countries where the firms are located. FY2019 is notable because this is the first year that warning letters issued to firms in the US exceed those issued regarding sites outside the US since I began monitoring this in FY2013. These data show that significantly more than half of the warning letters in FY2019 were issued to firms in the US. China and India together continue to be locations for a significant number of warning letters issued OUS. This shift in location of recipients of warning letters begs the question of whether the number of inspections outside the US decreased, and those inside the US correspondingly increased in FY2019. Dr. Woodcock presented data in her testimony before Congress on December 10, 2019 showing this is not true. The FDA conducted 698 inspections in the US, and 966 outside the US in FY2019. Dr. Woodcocks testimony states that "FDA's Inspections of foreign drug manufacturing facilities increased sharply after 2006 and have exceeded inspections of domestic drug facilities since 2015." Thus, even with fewer inspections conducted in the US the number of warning letters is markedly higher.

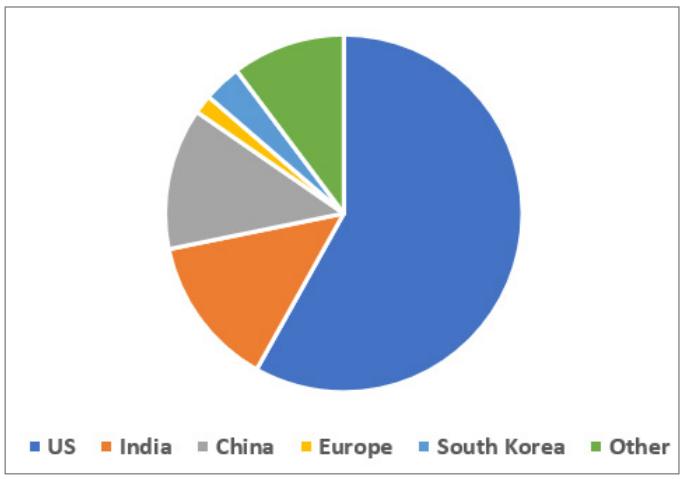


Figure 5 FY2019 Warning Letters by Geographic Location of Firms

Data Integrity

Rather than writing a separate article on Data Integrity in warning letters, this year I'm consolidating that information here. **Figure 6** shows that the percentage of all warning letters with a data integrity component continues to decrease after

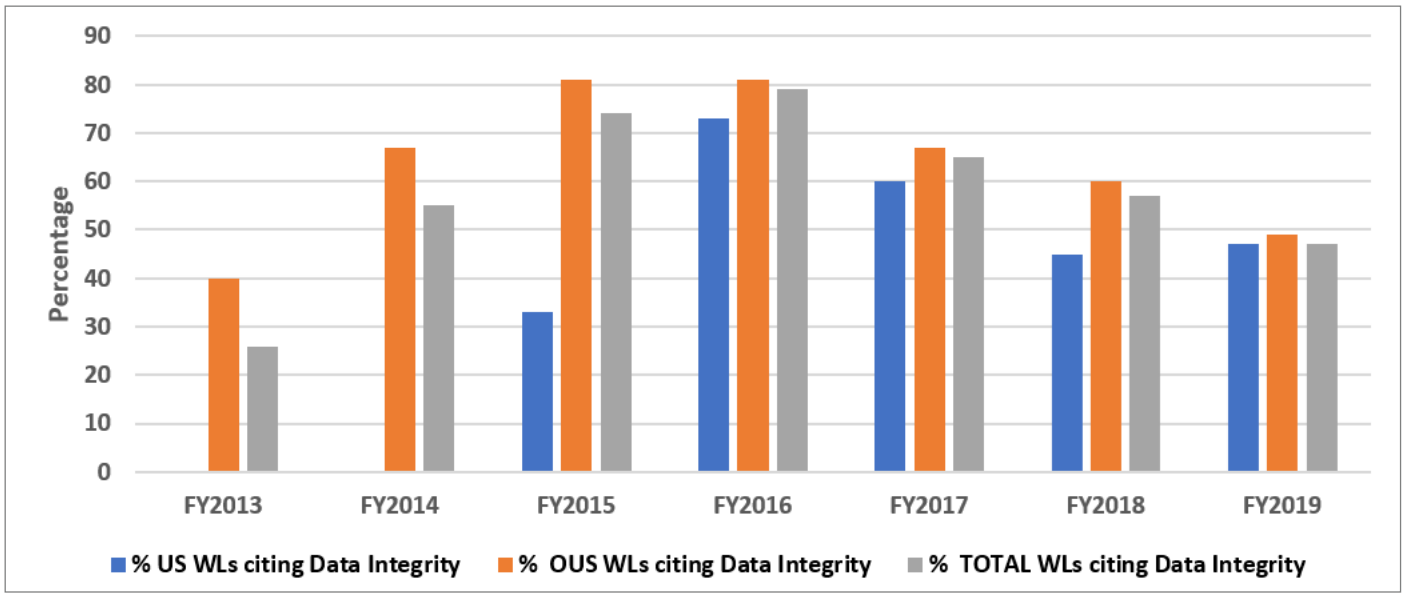


Figure 6 Warning Letters with a Data Integrity Component

reaching a high of almost 80% in FY2016. Warning letters to sites outside the US with a data integrity component also continue to decrease. Sites in the US, however, are up slightly over last year, perhaps due to the increased number of warning letters issued to firms here. It is also interesting to note that 38 percent (20 total) of warning letters to OTC/homeopathic manufacturers included a data integrity component. In FY2019, the percentage of warning letters issued to sites in the US, OUS, and overall is remarkably similar at just under 50 percent.

Figure 7 shows the geographic distribution of warning letters with warning letter deficiencies. The US takes first place this year with 32, India was second with 9, and China was third with 6. The remaining 5 warning letters are divided among other countries.

Although the absolute number of warning letters with a data integrity component issued to India and China this year seems reasonably low, it is useful to evaluate these as a percentage of the total number of warning letters issued to firms in the country. The data below result from calculation of data in **Figure 4** and **Figure 7**.

- 56 percent of the warning letters issued to firms in India included a data integrity component.
- 40 percent of the warning letters issued to firms in China included a data integrity component.
- 47 percent of the warning letters issued to firms in the US included a data integrity component.

The deficiencies cited in this area have not changed much since this topic was first identified more than 15 years ago. Firms continue to fail to exercise adequate controls over computer systems, fail to review all analytical raw data, fail to review audit trails, have demonstrable disagreement between electronic data and paper data that address the same event including batch records and human machine interfaces (HMI), discard both electronic and paper based GMP data, and abort electronic analytical test runs without adequate reasons.

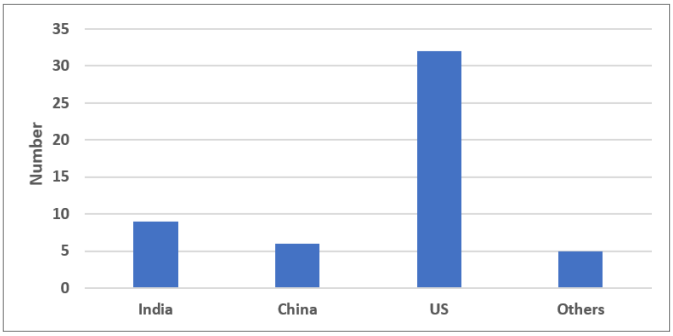


Figure 7 Number of Warning Letters Citing Data Integrity by Geography

Drug Product Manufacturers

Let's take a deeper dive into drug product manufacturers that were the recipients of warning letters in FY2019. Drug product manufacturers are a diverse group including firms that manufacture OTC/homeopathic drugs, manufacturers of human cell and tissue products, and prescription dosage form manufacturers of biotech or chemically synthesized sterile products and non-sterile products.

OTC/Homeopathic Drug Products

Figure 8 shows that OTC/homoeopathic drug

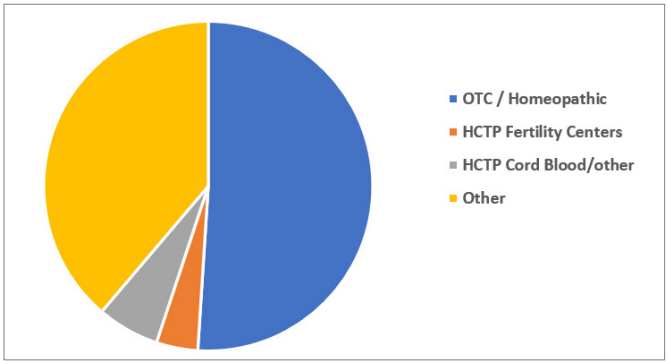


Figure 8 Drug Product Warning Letters by Product Type

product manufacturers received more than half of the drug product warning letters in FY2019. This continues a trend that started a few years ago. **Figure 9** shows that over half of these firms that received warning letters in FY2019 were in the US, with China and India a distant second and third. Twenty of the warning letters issued to OTC/homeopathic firms also included a data integrity component.

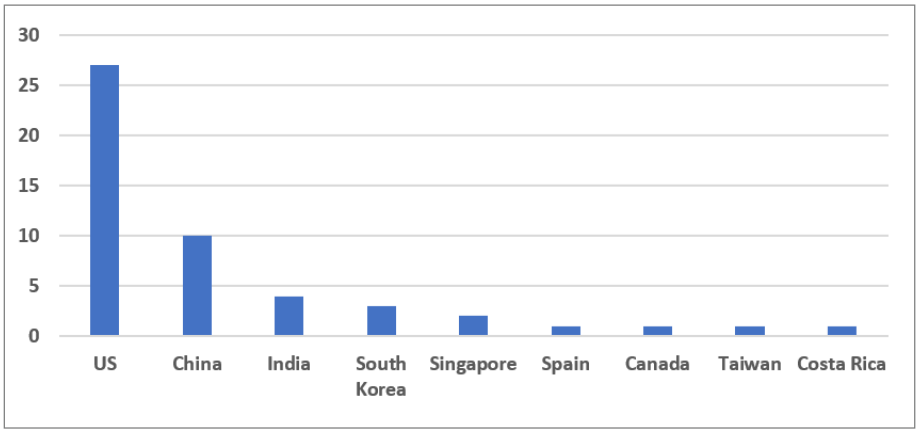


Figure 9 OTC Warning Letters by Country

Figure 10 shows trends for issuance of warning letters to these firms over calendar years. Between CY2010 and CY2013, the number of warning letters issued to these firms ranged between 1 and 6. The dramatic increase began in CY2017 and continues through this year. Many of the violations noted in these warning letters identify fundamental failures to understand and comply with GMPs including, but certainly not limited to:

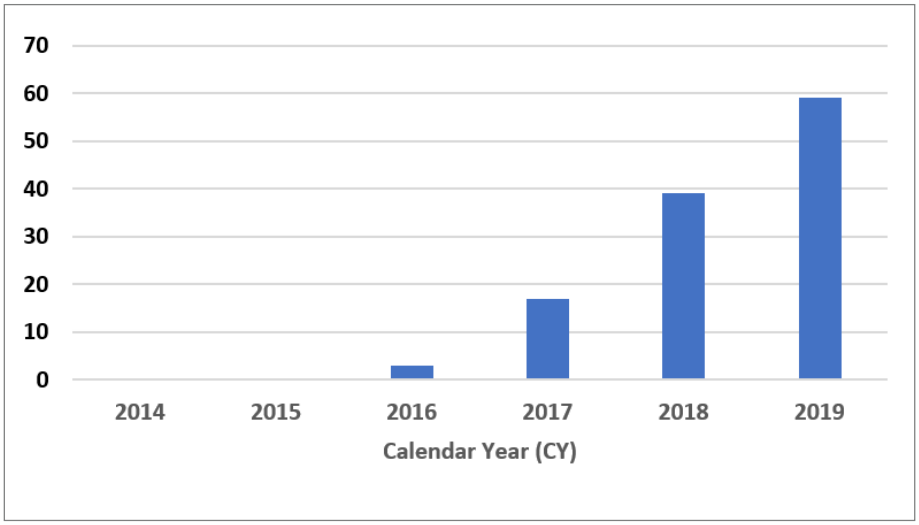


Figure 10 Warning Letters Issued to OTC Firms, CY2014-CY2019

- Failure to test incoming raw materials and components, including APIs, for identity. Rather, materials and components are accepted on the basis of the supplier's CoA although the supplier has not been qualified, and the results on the CoA have not been validated and periodically confirmed.
- Drug product is released for distribution without adequate testing including identity and strength of the active ingredient and adequate microbiological evaluation.
- Manufacturing processes are not validated, and the firm does not have a process for ongoing monitoring to ensure the process remains in a state of controls.
- Absence of basic SOPs for GMP activities including, but not limited to the responsibilities of the Quality Unit, change control, OOS investigations, deviation management and complaint management, just to name a few.
- Batch records did not have adequate detail of all the critical manufacturing operations.
- Inadequacy in water (likely purified water USP) generation

and distribution systems, maintenance, sampling, and control.

- And frequently, all of these shortcomings are combined into a statement that the Quality Unit does not have the appropriate power and authority they should have to ensure that drugs have the quality, purity, potency, and safety that they are purported to have.

The type of deficiencies at these firms clearly skews any metrics that may be done on inspection observations and warning letter deficiencies. This is an important class of manufacturers if only because of the number of individuals their products touch. We likely all have medicine cabinets with at least a few of these products that we use frequently. We probably have not seen the end of the FDA's laser-like focus on this product category and I look for more in FY2020.

Human Cell Therapy Drug Products

We previously covered the FY2018 and 2019 inspection observations for the human tissue and cell therapy products. This is a diverse product category and include sites such as fertility clinics, stem cell clinics, and gene and cell therapy manufacturers. This group received 10 warning letters in FY2019. Four of them were sent to fertility clinics and six were issued to firms selling either cord blood products (Stemell, Cord for Life and Genetech), an amniotic membrane patch allograft (Stratus Biosystems), adipose tissue harvested and modified for autologous use (StemGenex Biological Laboratories), and advanced stem cell allografts (Human Biologics of Texas/Globus Medical). Genetech who received their warning letter on November 19, 2018, distributed their products to Liveyon LLC. Liveyon Labs Inc in Yorba Linda, CA received a warning letter early in FY2020, on December 5, 2019. Liveyon Labs initiated a Class II recall of 91 lots of HPVC Cord Blood products on September 28, 2018 and terminated the recall on November 5, 2019. The FDA gives the reason for the recalls as "Human tissue allografts, where in-process controls were not followed allowing tissue to be processed in a manner that could cause contamination or cross-contamination during processing, as well as the introduction, transmission or spread of communicable disease through the use of the tissue, were distributed."

I expect letters to human cell and tissue firms to increase in FY2020 and beyond as both gene and cell therapy firms expand in number and enforcement discretion is slated to end for the hundreds of rogue stem cell clinics.

Stem cell therapies have been problematic with many firms operating outside the FDA's framework for regenerative medicines. On June 4, 2019 the courts held that US Stem Cell Inc (FL) and their Chief Scientific Officer "...adulterated and misbranded a stem cell drug product made from a patient's adipose tissue." The firm received a warning letter in 2017 for marketing a stem cell product without FDA approval and for significant non-compliance with GMPs. This is clearly a problematic area for FDA, and we will watch carefully as FDA's enforcement discretion identified in a final 2017 guidance draws to a close late in 2020. I expect letters to human cell and tissue firms to increase in FY2020 and beyond as both gene and cell therapy firms expand in number and enforcement discretion is slated to end for the hundreds of rogue stem cell clinics. On the gene therapy side, the Pink Sheet (26 January 2020) recently identified six product candidates currently under review at FDA with five designated as breakthrough therapies. A recent

court case in California, however, calls into question FDA's approach to regulation of autologous cell therapy. More to come here, for sure.

Prescription Drug Products other than HCTPs, Parenteral and Non-Sterile Dosage Forms

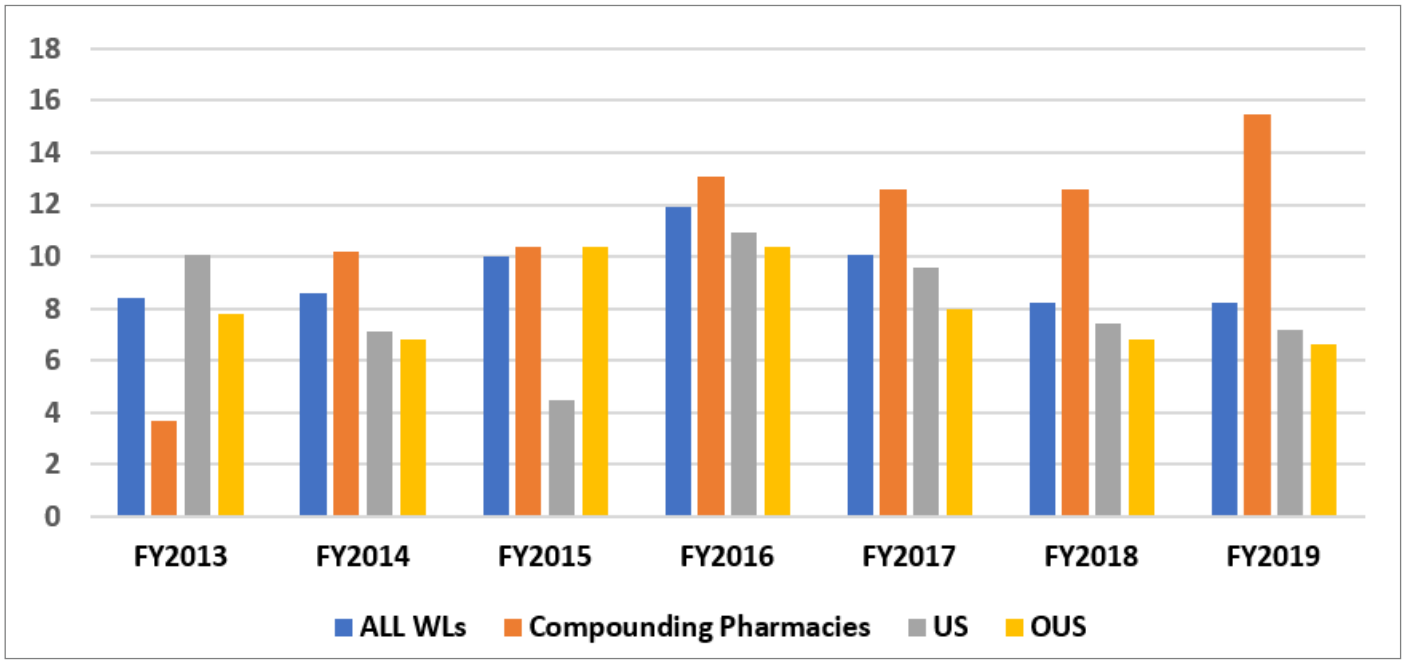
The remaining warning letters issued to drug product manufacturers include parenteral products and non-sterile drug products including solid oral dosage forms and creams/ointments. FDA continues their focus on parenteral products, particularly those made using aseptic processing, as being in the category of highest risk products.

Interval between Inspections and Warning Letters

Figure 11 and **Figure 12** present the time interval between the FDA inspection and issuance of warning letters. These data are rounded to the nearest half month. It has been a stated goal of FDA to substantially decrease this interval to a target of 6 months. The interval for issuance of warning letters for compounding pharmacies

Figure 11 Months Between Inspection and Warning Letter

	All Warning Letters	Compounding Pharmacies / Outsourcing Sites	US	OUS
FY2013	8.4	3.7	10.1	7.8
FY2014	8.6	10.2	7.1	6.8
FY2015	10	10.4	4.5	10.4
FY2016	11.9	13.1	10.9	10.4
FY2017	10.1	12.6	9.6	8
FY2018	8.2	12.6	7.4	6.8



continues to be problematic and increased this year to 15.5 months. The interval for warning letters issued to sites in the US has continued to decrease from a high of 10.9 months in FY2016 to 7.2 months in FY2019. For firms outside the US, the interval also decreased from a high of 10.4 months in FY2015 to 6.6 months in FY2019. Taking all warning letters together, the time interval has decreased from a high of 11.9 months in FY2016 to 8.2 months in FY2019, the same interval as in FY2018.

Among the warning letters issued to sites OUS, 26 import alerts were issued in the category of: failure to follow drug GMPs, distribution of unapproved new drugs, and refusal of inspection. Thus, sixty percent of the firms who received a warning letter were placed under one of these import alerts.

Other Notable Topics in Warning Letters in FY2019

FDA generally identifies the information firms must provide in response to warning letters. This year it struck me the frequency with which FDA requests an "independent assessment" of the topics in question. FDA has clearly decided that many firms are not capable of performing an effective assessment and identifying appropriate, effective remediation activities.

In 76 warning letters, FDA either suggests the firm hire qualified consultants or acknowledges they have done so, sometimes both. Seventy-nine percent of warning letters issued OUS and 62 percent of the warning letters issued for firms located in the US included this recommendation.

The identification of the various nitrosamine contaminants in Angiotensin II Receptor Blocker (ARB) API and drug products resulted in a collection of warning letters issued to the following firms, for example: Zhejiang Huahai Pharmaceutical Co. Ltd, Aurobindo Pharma Limited, Hetero Labs Limited, Lantech Pharmaceuticals Limited, Mylan Laboratories Limited and Torrent Pharmaceuticals Limited. These sites manufac-

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ture either a "sartan" API and/or drug product. All sites to which these warning letters were issued are in China or India. Although the warning letter issued to Mylan Laboratories Limited was sent to the CEO in the US, the site in question is in India. Among this collection, the one issued to Lantech Pharmaceuticals Limited identified the problematic issue of recovered solvents and the lack of control of these solutions which is now considered to be one source of nitrosamine contaminants. In addition to warning letters, dozens of products have been the subject of Class II recalls. The FDA has published methods for identification and quantitation of specific nitrosamine contaminants, along with interim acceptable daily limits. The EMA also addressed this topic and published Information on nitrosamines for marketing authorization holders on September 19, 2019. On October 9, 2019 the EMA published a "Questions and answers on "Information on nitrosamines for marketing authorization holders." WHO also published information on nitrosamine impurities.

In FY2019, FDA issued the first warning letter that cites failure to comply with requirements of

the November, 2013 Drug Supply Chain Security Act (DSCSA) amendments to the FD&C Act. This warning letter was issued to McKesson Corporation in San Francisco, CA, on February 7, 2019, based on observations from a form 483 issued

FDA places a high priority on ensuring a secure and accurate supply chain based in part on documentation accompanying purchased products, particularly certificates of analysis.

at the close of the inspection on July 3, 2018. First of a kind enforcement actions are always of interest in terms of what they tell us about the FDA's potential future enforcement in this area. Also, the text in the enforcement action provides insight into what the FDA found to be the specific objectionable activity or process so others who operate in this area may evaluate their procedures and processes.

The warning letter, dated February 7, 2019, identifies an inspection of the corporate headquarters in San Francisco, CA. The warning letter identifies three deficiencies where McKesson Corp failed to comply with the requirements of section 582(c)(4), identification of suspect product and notification. The warning letter describes three examples supporting their conclusions and three examples of inadequate corrective actions. Effective January 1, 2015, trading partners are required to quarantine and investigate suspect product to determine whether it is illegitimate and to notify FDA and trading partners if the illegitimate product is found. FDA published guidance on the topic, Identification of Suspect Product and Notification, in December 2016. This was clearly a situation where the firm had plenty of time to come into compliance.

Another interesting group of warning letters addresses the topic of information that re-packagers include on the certificate of analysis (CoA) provided to customers. FDA places a high priority on ensuring a secure and accurate supply chain based in part on documentation accompanying purchased products, particularly certificates of analysis. Four warning letters were issued in FY2019 where re-packagers did not identify the original manufacturer of the API, but rather transferred the information to their own letterhead and did not include any information regarding the original manufacturer. Three of the firms are located in the US, the fourth is located in India. The three firms that received the four warning letters including this deficiency include: Vipor Chemical Private Ltd., Spectrum Laboratories (here and here), and B&B Pharmaceuticals Inc.

Spectrum Laboratories received two warning letters based on their practices at two sites. They attempted to convince FDA that their practices were satisfactory, though that seems to have been woefully unsuccessful. The June 4, 2019 warning letter to Spectrum notes that because six of the repackaged APIs list only Spectrum's name on the label, this falsely represents that Spectrum is the manufacturer. Thus, FDA deems these APIs to be misbranded because the labels are false and misleading. FDA also notes that both of the sites had similar deficiencies and thus "...failures at multiple sites demonstrate that management oversight and control over the manufacture of drugs are inadequate." Although the second Spectrum site received a warning letter for this same shortcoming, FDA did not note the issue of misbranding.

Conclusions

FY2019 was a fascinating year for drug GMP warning letters both in the diversity of topics addressed, depth of focus, and trends in enforcement actions. The most significant news is that

the number of warning letters issued to sites in the US increased significantly. For the first year since I started monitoring this in FY2013, warning letters issued to firms in the US constituted a majority of the drug GMP warning letters, far outpacing India and China combined.

Warning letters issued in FY2019 were issued to a diverse group of firms both inside and outside the US. The number issued to OTC firms and HCT/P firms both increased. We saw a decrease, however, in the number of warning letters issued to compounding pharmacies/outsourcing facilities that began in FY2017. Similarly, we saw a decrease in the number of warning letters that identify data integrity shortcomings, again for the third year.

FDA issued a cluster of warning letters to firms associated with Angiotensin II Receptor Blocker (ARB) APIs and drug products, including mention of the use of recovered solvents in at least two of them. Another group that received warning letters were re-packagers who neglected to identify the original manufacturer of the product on CoAs. Along with these two groups, this year saw a focus on the API and drug product manufacturers for Angiotensin II Receptor Blockers (ARB). Enforcement for this group of products also included recalls of hundreds of lots of product. This year we also saw many warning letters where FDA requested "independent assessments" from firms who received warning letters and recommended that many firms hire qualified GMP consultant(s) to assist them in coming into GMP compliance.

Now, for FY2020 predictions. I see a continuing focus on OTC manufacturers; there are many of them and they seem to fail to understand the fundamentals of GMPs. The enforcement discretion with stem cell clinics is supposed to cease at the end of the year, but a court case in California could have significant impact for FDA's jurisdiction in the area of autologous stem cell clinics. At least six gene therapy products are currently under review at FDA so we will see those PAIs along with the start of routine inspections of the gene therapy firms that now have approved products. Sterile drug products, particularly those produced using aseptic processing, will remain a priority. FY2020 could well be as interesting as FY2019!

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Barbara Unger formed Unger Consulting, Inc. in December 2014 to provide GMP auditing and regulatory intelligence services to the pharmaceutical industry, including general GMP auditing, gene and cell therapy, and auditing for data management and data integrity. Her auditing experience includes leadership of the Amgen corporate GMP audit group for APIs and quality systems. She also developed, implemented, and maintained the GMP regulatory intelligence program for eight years at Amgen. This included surveillance, analysis, and communication of GMP related legislation, regulations, guidance, and industry compliance enforcement trends. Barbara was the first chairperson of the Rx-360 Monitoring and Reporting work group (2009 to 2014) that summarized and published relevant GMP and supply chain related laws, regulations, and guidance. She also served as the chairperson of the Midwest Discussion Group GMP-Intelligence sub-group from 2010 to 2014. Barbara was the co-lead of the Rx-360 Data Integrity Working Group from 2017 through 2019.
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