REDICA Systems

Analysis of FDA Drug GMP Warning Letters for FYs 2020 and 2021

EXPERT ARTICLE

WRITTEN BY

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It has been an interesting two years, to say the least! We have seen unprecedented upheaval in FDA activities from drug approvals to routine inspections and enforcement. It became apparent sometime in mid-2020 that the pandemic was going to be with us for a while and health authorities scrambled to address what this meant for submission review, product approvals, routine inspections, and enforcement.

Both industry and FDA were addressing onsite versus remote work conditions. Both sides were learning on the fly, focused on safety of employees, safety of patients, continuing to push forward the development of investigational products, and maintaining an uninterrupted supply of commercial products.

The data presented here address fiscal years 2020 and 2021, ending Sept. 30, 2021, and trends since FY2013. Drug GMP Warning Letters considered in these metrics were posted by the FDA no later than December 1, 2021. Many Warning Letters were issued for unapproved drug product/adulteration of hand sanitizers but only those which included FDA requests for information were included in this analysis.

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. Outsourcing facilities were established by the FDA under an amendment to the Food Drug & Cosmetic Act in November of 2013. 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.

Traditional compounding pharmacies do fill a necessary medical need, but outsourcing facilities appear more of a burden for FDA enforcement. We will see that this segment of the industry continues to be an enforcement thorn in FDA's side ever since its inception. In my opinion, the FDA enforcement efforts in this area far outweigh the value that these firms provide to public health.

The narrative, tables, and figures address the following for the two most recent fiscal years along with trends from FY2013:

– Type of manufacturer (API, dosage form, compounding pharmacy/outsourcing facility), country where the facility is located, and intervals between inspections and Warning Letter

- Particular target activities that were the subject of Warning Letters in the past two years
- Interval between inspections and Warning Letter

Warning Letter analyses from previous years may be found here and here.

EXECUTIVE SUMMARY

The following are noteworthy summaries of focus and trends that are followed by a more detailed discussion of each.

- After a steady increase in the number of drug GMP Warning Letters issued beginning in FY 2015, the number of **these enforcement actions decreased** by approximately 20% in FY2020. The number of FY2021 Warning Letters fell again by 60% over FY2020 (**Figure 1** and **Figure 2**).
- Although **compounding pharmacies and outsourcing facilities** continue to receive enforcement attention from FDA, the absolute numbers of the total have continued to decrease (**Figure 1** and **Figure 2**).
- In FY2019, the US number of pharma Warning Letters substantially exceeded those issued to sites outside the United States for the first time since FY2013. This excludes Warning Letters issued to compounding pharmacies and outsourcing facilities. This reversed in FY2020 and in FY2021 the same number were issued to sites in and outside the US. (**Figure 3**). Looking at the percentage of Warning Letters issued to each area, FY2019 saw a precipitous decrease in those issued to OUS firms and FY 2020 and 2021 the values were almost identical for each area (**Figure 4**).
- **Data integrity continues to be a focus** of deficiencies cited in Warning Letters. After decreasing in the percentage of the total from FY2016 through FY2019, the percentages increased in FY2020 and increased again in FY2021. The percentage of Warning Letters citing data integrity do, however, remain lower than at the peak in FY2016 (**Figure 7**).
- In FY2021 the **countries outside the US** which were home to sites receiving Warning Letters included China (4), Mexico (3), India (2), and one each for firms in Honduras, Japan, Turkey, Malaysia and Colombia. It is noteworthy that no firms located in the European Union received a Warning Letter.
- The intervals **between inspections and Warning Letters edged up** in FY 2021 after decreasing for the past few years. Note that these percentages do not include all drug GMP Warning Letters because adequate data are not available for those resulting from regulatory review assessments (Figure 6)
- Almost **80% of Warning Letters** issued to drug product firms, excluding compounding pharmacies and outsourcing facilities, were issued to **firms that manufactured over the counter products**. This includes Warning Letters issued to sites both inside and outside the US.

– Approximately 40% of all drug GMP Warning Letters from FY2021, excluding compounding pharmacies and outsourcing facilities, were issued to firms based on **requested document review and did not include an onsite inspection**.
– For the first time that I am aware, FDA implemented an **import alert for a single product type from a country regardless of the manufacturer.** Hand Sanitizers from Mexico were the subject of this alert largely based on the substitution of methanol for ethanol or for ethanol content that did not meet label claim. A collection of Warning Letters was issued to manufacturers of adulterated hand sanitizers, but have attempted to include only those where documents were requested for review. Manufacturers conducted numerous recalls for adulterated hand sanitizers in the past two fiscal years.
– Warning Letters included citations for the **use of raw materials and APIs from suppliers that were either the subject of an import alert** or Warning Letter restrictions. Manufacturers and sponsors should monitor these actions as they apply to their supply chain.

DRUG WARNING LETTER DETAILS

OVERALL

The COVID-19 pandemic astounded everyone, regulators and industry alike, with the scope and depth of changes that occurred almost immediately. Firms needed to figure out how to accomplish work remotely whenever possible while ensuring enough staff on site to safely manufacture, test, package and distribute medical products. The health agencies, including FDA, realized a few months into the pandemic that onsite inspections were going to be limited for a longer time than originally anticipated. FDA limited onsite inspections to only those that were mission critical.

This approach had a major impact on product approvals where an onsite inspection was necessary and for those sites who were attempting to have Warning Letter restrictions lifted. Recently, FDA has mostly resumed domestic inspections, while those outside the US continue to be limited to those which are mission critical.

In FY2021 FDA issued approximately twelve GMP Warning Letters on the basis of document review only, without an onsite inspection. This also includes a couple of cases where firms refused to provide the requested documents. For these documents, FDA sent a request for records and other information under their authority in section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 374(a)(4).

Sites associated with these requests were located in the US, China, Mexico, Malaysia, Honduras, India, Colombia, and Turkey. While the date(s) of the document request(s) were identified in the Warning Letter, no date was provided to identify review completion.

Figure 1 and **Figure 2** shows the distribution of drug GMP Warning Letters attributed to U.S. non-outsourcing facilities, outsourcing facilities and compounding pharmacies, firms located outside the United States, and total drug GMP Warning Letters. While there were fewer Warning Letters issued in FY2020 than in FY2019, the dramatic evidence of the pandemic effect occurred in FY2021.

We are now seeing the diminished number of drug GMP Warning Letters that we saw in 2013 through 2015. The number of drug GMP Warning Letters decreased significantly in all categories, by 50% or more.

	FY2013	FY2014	FY2015	FY2016	FY2017	FY2018	FY2019	FY2020	2021
TOTAL	41	49	42	102	114	127	130	106	42
Compounding Pharmacies	3	27	24	56	45	32	19	23	12
US (non-compounders)	13	4	3	11	20	22	68	40	16
OUS	25	18	16	35	49	73	43	43	14

Figure 1 | Drug GMP Warning Letters, FY 2013 through FY 2021

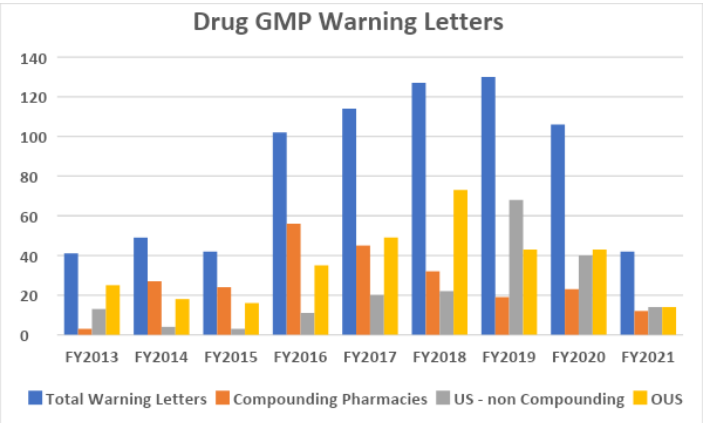

Figure 2 | Total Drug GMP Warning Letters

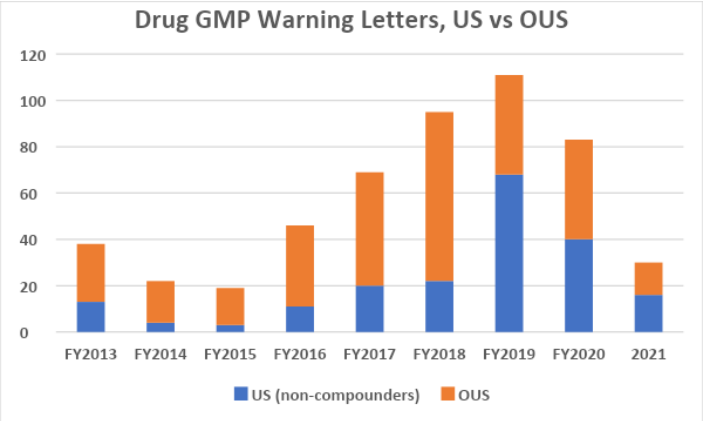

Figure 3 | Drug GMP Warning Letters issued to sites inside and outside of the U.S.

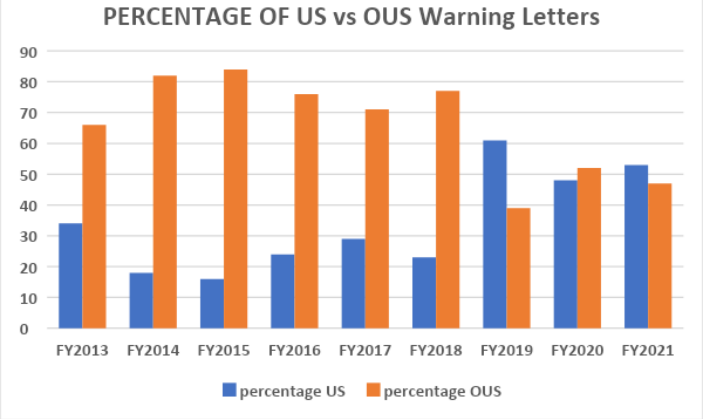

Figure 4 | Percentage of u.s. versus non U.S. Warning letters

Figure 3 shows the distribution of drug GMP Warning Letters excluding outsourcing facilities since FY2013. The number of Warning Letters issued to sites in the US was higher than those issued to facilities outside the US only in FY2019 and 2021. The last two years have seen this be effectively the same for the two geographic areas.

Figure 4 shows similar comparison to **Figure 3**, except that values are percentages rather than absolute numbers.

The drop in Warning Letters issued are shown, quarter over quarter, for FY 2020 and FY 2021 in **Figure 5**. This figure also identifies when the Warning Letters based on remote regulatory assessments first appeared. Data show that the most dramatic decrease became evident in Q1 FY2021 where the number decreased to 11 from 26 in the immediately preceding quarter. And the number of Warning Letters continued to decrease in the following two quarters to 8 Warning Letters and finally 6 Warning Letters in Q3 FY2021.

Q4 FY2021 saw a bounce back to 17 issued Warning Letters, six of which resulted from remote assessments. This is a lagging metric for the pandemic effect because there has generally been an 8 and 14 month overall lag between the inspection and Warning Letter issuance in FY 2018 through FY 2020 depending on the facility type and location.

Approximately 40% of all drug GMP Warning Letters from FY2021, excluding compounding pharmacies and outsourcing facilities, were issued to firms based on **remote document review and did not include an onsite inspection.** This includes firms both inside and outside the US. All but one of the firms who received Warning Letters based on document review only were OTC manufacturers, the other was an API manufacturer.

Approximately 40% of all drug GMP Warning Letters from FY2021, excluding compounding pharmacies and outsourcing facilities, were issued to firms based on remote document review and did not include an onsite inspection.

While firms have received Warning Letters in the past for failure to provide documents during inspections or refusing to permit an inspection, this is the first time that Warning Letters were issued based on document reviews only. And to have there be this many of them in FY2021 is striking and indicates that we may see more enforcement based on remote reviews.

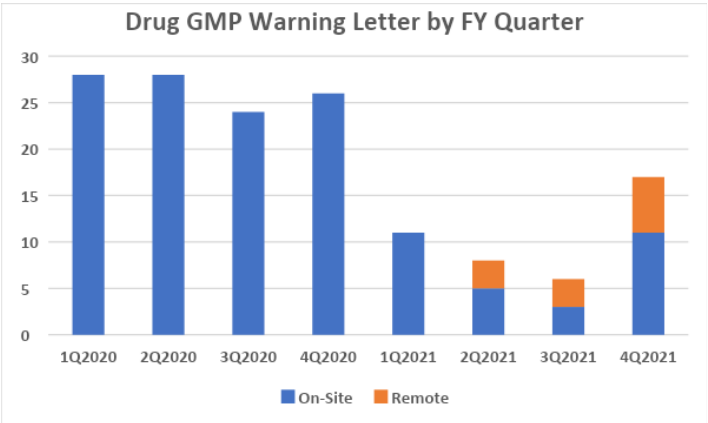

Figure 5 | Drug GMP Warning Letters issued by quarter for FYs 2020 and 2021

INTERVAL BETWEEN INSPECTION END AND WARNING LETTER

Figure 6 presents the interval between inspection end and Warning Letter issuance since FY2013. The overall increase in FY2021 was largely driven by the increase in the interval for compounding pharmacies/outsourcing facilities. And here, the increase in the interval resulted for outsourcing facilities came from a handful of Warning Letters that took more than 25 months to issue. Values in all categories, however, did increase in FY2021 unlike FY2020 where they were continuing to decrease. It will be useful to watch how this might (hopefully!) improve in the next couple of years.

YEAR	ALL WLs	Outsourcing / Compounding Pharmacies	Issued US	Issued 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
FY2019	8.2	15.5	7.2	6.6
FY2020	8	14.1	6.8	6
FY2021	10.8	16.7	8.4	7.7

Figure 6 | Months between inspection end and GMP Drug Warning Letter issuance, FY 2013 through FY 2021

DATA INTEGRITY

Failures in data governance and data integrity continue to be identified in drug Warning Letters. After three years of decrease, 2017–2019, the two most recent fiscal years saw the percentages increase significantly. The percentages, however, have not reached the previous high of almost 80% in FY2016. This continues to be a problem that industry has not been able to resolve. The deficiencies are largely the same as they were ten or more years ago including, but not limited to:

- Failure to investigate and report OOS results
- Invalidation of OOS results without justification
- Data that are not retained or reviewed
- Data that can be overwritten, aborted sample sets
- Shredding of records
- Audit trails not enabled or reviewed just to identify a few

FDA has not changed their interpretation of the regulations, nor have there been any changes in guidance or expectations. Industry just has not effectively implemented the requirements. **Figure 7** shows the data since FY2013.

OTHER AREAS OF FOCUS

The areas of focus seem particularly driven by the type of firms that FDA inspects and in FY2020 and FY2021 we saw, yet again, a focus on firms that manufacture OTC drug products. Manufacturers of this product category demonstrate consistent shortcomings in fundamental aspects of **supplier controls**. Often:

- Vendors are not audited or qualified
- The materials are not tested upon receipt but rather are accepted on certificate of analysis results
- For this group, products are often released for distribution without completed analytical testing, and/or without real time stability data and programs to support expiry dating
- Analytical methods are often not validated
- Frequently, these products are not supported by process validation and an ongoing program to monitor process performance
- Purchased glycerin was not tested for the absence of DEG, which can cause serious health problems or death
- The Quality Unit in these firms does not appear to be given adequate authority to execute their responsibilities.

Failure to implement adequate **supply chain controls** is also associated with the nitrosamine contamination of the 'sartans' and other prescription drug products in FY2020 which resulted in a flurry of recalls of medically important products. In this case, the pharma firms and API firms did not adequately address

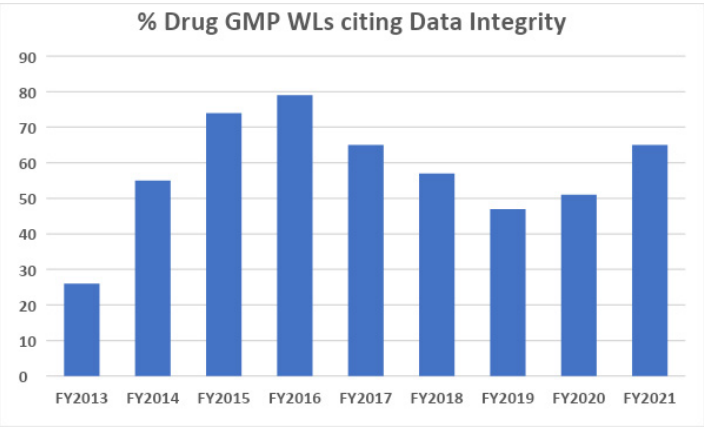

Figure 7 | Warning letters that cite data integrity

the use of **recovered solvents**, nor did they adequately clean equipment to prevent carryover of contamination. Impurity profiles for recovered solvents were not adequately established.

Rounding out the shortcoming in supply chain controls were firms who purchased APIs from **sites that were under import alert** or Warning Letters enforcement.

Inadequately **designed, validated and monitored water systems** was also a frequently identified deficiency in the past two years. Systems were cited for having dead legs, threaded piping, and biofilms. Inadequate monitoring of microbial attributes of water systems was a frequent failure and contamination of water systems with Burkholderia cepacia led to multiple health alerts and drug product recalls. The water system failures generally applied to purified water, rather than water for injection (WFI), generation and distribution systems.

And finally the issue of foreign particulates in parenteral products remains with us. This problem has been around for decades and is now the subject of a draft guidance issued December 16, 2021, Inspection of Injectable Products for Visible Particulates.

CONCLUSION

Fiscal years 2020 and 2021 were exceptional in many ways and the pandemic served to identify limitations in the FDA enforcement processes and procedures. Depending on the trajectory of COVID mutations in the coming year, we may see an exacerbation of these problems, or we may begin the return to "normal."

Even if we proceed along the later line, we should expect FDA and other health authorities to continue to rely on remote document review, to supplement on site inspections. FY2022 will be a year of transition regardless of the direction that industry and the agency moves toward.

EU inspectors were also impacted by the COVID pandemic, but they seemed to adjust more quickly and effectively to implement recognized remote inspection. FDA seemed to underestimate the impact and longevity of the pandemic and was left scrambling and currently without acknowledged remote inspection processes.

Following are the things I'm watching for in FY2022 (which began October 1, 2021):

– **Continued focus on OTC manufacturers** inside and outside the United States because of the magnitude of the public that these products impact, and the GMP failures that FDA has identified at these firms over the past few years.

– As we return to more onsite inspections, I would expect an increase in Warning Letters to pharmaceutical (not OTC) firms as corners were likely cut when limited staff were on site and the pressures to produce with limited staff likely became more intense. This will likely not increase to the levels seen FY2019. Yet. We need a few years of "normal" before I see that happening.

– Enforcement focus will continue to focus on **extraneous particulates** in sterile parenteral products, **cross contamination and inadequate or missing risk assessments**. The concern about cross contamination will extend in a newly focused way to gene and cell therapy manufacturers as identified in the form 483 issued at the close the April 2021 inspection of Emergent Manufacturing Operations in Baltimore Maryland. Extraneous particulates in drug product are the subject of a recent draft guidance from FDA.

– FDA will need to address how the travel limitations have negatively impacted **PDUFA approval times** because inspections were not conducted. They will also need to address the inspections necessary to **clear Warning Letters and complete response letters,** most challenging of which are in countries outside the United States.

– I personally expect more wheel spinning, but no meaningful progress, by FDA in regard to developing maturity models for Quality Systems and Quality Metrics. These are appealing concepts, but their consistent implementation across

thousands of firms and dozens of geographies makes this more of an aspiration than a discrete achievable goal.

– If FDA returns to unannounced inspections at sites outside the US, I would look for more Warning Letters to come from these specific inspections.

And what do I *wish* for in the new fiscal year:

– FDA should resolve the issue regarding the hundreds, if not thousands, of firms that manufacture and distribute cell therapy products without either an IND or approved BLA. I encourage them to take definitive enforcement in this area so that a total lack of compliance is no longer rewarded. This will take courage and perhaps a legal opinion to clearly establish FDA authority in this area. The current approach of nibbling around the edges, appears to penalize those firms that have sought to conform to requirements. This product category does not have a level playing field.

– Enlarge the legal framework for inspections so that remote regulatory assessments are deemed to be actual inspections with issued forms 482 and 483. It would be likely that FDA needs to publish guidance identifying expectations and timeframes. As we all know, the guidance rarely happens quickly.

Although this article addresses only FDA, the MHRA recently published an inspectorate blog that includes a ICRMA paper on the type of remote "inspection" approaches taken by global health authorities. For those looking for an FDA specific update on remote regulatory assessments, a Resiliency Roadmap for FDA Inspectional Oversight was published in May 2021.

Both show that global health authorities recognize that the pandemic will continue to impact travel and inspections in 2022. I think it also shows that agencies will continue with some aspects of "remote evaluations" even after inspection practices resume on site.

We will continue to keep you up to date on important FDA practices and policies in the areas of GMP enforcement as we progress through FY2022.

ABOUT THE AUTHOR

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 and auditing and remediation in the area of 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 a comprehensive 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 also the co-lead of the Rx-360 Data Integrity Working Group from, 2017 through 2019. She currently serves as a GMP consultant to the Redica Systems team, beginning in 2015, then known as FDAzilla.

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