REDICA Systems

Analysis of 2021 U.S. FDA 483 GMP Observations

EXPERT ARTICLE

WRITTEN BY

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A comprehensive GMP intelligence program includes monitoring health authority enforcement actions including:

- US FDA forms 483
- Establishment Inspection Reports
- Warning letters
- Recalls
- Import alerts
- Consent decree agreements
- MHRA annual summaries of inspection deficiencies
- EU reports of GMDP noncompliance

In addition to enforcement actions, a comprehensive program includes monitoring new or revised laws, regulations and guidance.

This article focuses on US FDA data presenting the most recent publication of FDA GMP drug inspection data, which address drug inspections conducted in FY2021. I examine data from FY2021 and evaluate six years' worth of trends in drug GMP inspection enforcement. For additional data on years before 2016, please refer to an article published last year.

The presentation of some data herein differs from data presented on the FDA website, even though it uses the same raw data. For example, I combine all observation listings that cite 21 CFR 211.42(c) into a single value, rather than identifying them in separate line items.

The data do not represent the FDA's complete collection of inspection observations for the year. In past years, these data represented approximately one-third of all forms 483 issued, so conclusions must be tempered by the incomplete nature of the data. The data include only forms 483 issued through FDA's electronic system; it does not include forms 483 issued to API manufacturers because §211 is not applied to those manufacturers or Forms 483 that are issued outside of the electronic system.

In addition to the FY2021 update and trends from previous five years, we include a tabulation of inspection observations other than 21 CFR 211. This includes the following data for the past five years:

- 21 CFR 212 (PET drugs)
- 21 CFR 310 (New Drugs)
- 21 CFR 314 (Applications for FDA Approval to Market a New Drug)

– 21CFR 329 (Nonprescription Human Drug Products Subject to Section 760 of the Federal Food, Drug and Cosmetic Act)
– 21 CFR 361 (Prescription Drugs for Human Use Generally Recognized as Safe and Effective and Not Misbranded: Drugs Used in Research)
– Federal Food, Drug and Cosmetic Act, section 501, Adulterated Drugs and Devices
– Federal Food, Drug and Cosmetic Act, other sections

FDA DRUG FORM 483 INSPECTION OBSERVATIONS

The striking feature for FY2021 is the continued decrease in the number of forms 483, which decreased to less than 30% of those issued in FY2019. This is shown in **Table 1** and **Figure 1**.

FDA inspections came to a grinding halt midway through FY2020 with the travel and safety limitations caused by the COVID-19 pandemic. This limitation continues to impact the FY2021 values as the numbers of forms 483 continued to decrease. Domestic inspections resumed late in the FY but inspections outside the US remain limited to mission critical efforts only.

Table 2 shows only the 10 most frequent inspection observation citations for 21 CFR 211 for FY 2021. The FDA uses the term "*frequency*" to represent the number of times the agency identified a specific citation in its tabulation. **Table 2** presents those observations from the highest to lowest number for FY2021. The four most frequently cited regulations for FY2021 include:

– §211.192 *Investigations of discrepancies* moved from

Fiscal Year	Number of Forms 483
2016	691
2017	694
2018	716
2019	779
2020	349
2021	215

TABLE 1 | TOTAL NUMBER OF FORMS 483 IN THE SYSTEM

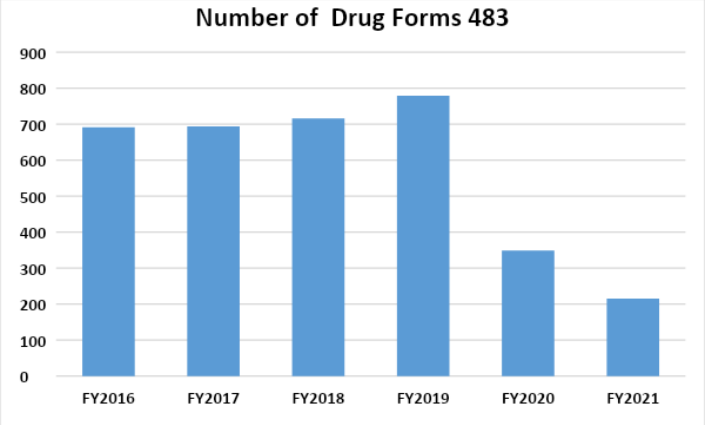

FIGURE 1 | TOTAL NUMBER OF FORMS 483 IN THE FDA SYSTEM

third place in FY2018 to second place in FY2019 and is in first place in FYs 2020 and 2021. It has historically been among the most frequently cited regulations.

– §211.22(d) *Procedures applicable to the quality control unit shall be in writing and shall be followed* moved from first place in FY2019 to second place this year. Again, this is another regulation that has been among the top group for many years.
– §211.160(b) *Lab controls should include scientifically sound specifications* was fourth place last year and third place this year.
– §211.100(a) *Production and process controls shall be supported by written procedures* is a common observation issued to OTC manufacturers who frequently have not conducted process validation for some or all products.

New in the top group for FY2021 is §211.68(b)

– §211.68(b) likely represents the FDA's continued focus on data governance and data integrity, particularly for electronic data both in manufacturing (e.g., electronic batch records) and laboratory instrumentation.

Based on the limitations of having far fewer forms 483 in both this fiscal year's collection and last years diminished numbers, it's virtually impossible to identify meaningful year over year trends. Instead, I've taken a cumulative approach over the past five years for the top 10 observations from FY2021 (see **Table 2**), shown in **Figure 2**. The three cumulative most frequently cited regulations for these five years include:

– §211.192 *Investigations of discrepancies* moved from third place in FY2018 to second place in FY2019 and is in first place in FY2020. It has historically been among the most frequently cited regulations.
– §211.22(d) *Procedures applicable to the quality unit shall be in writing and shall be followed* moved from first place in FY2019 to second place this year. Again, this is another regulation that has been among the top group for many years.
– §211.160(b) *Lab controls should include scientifically sound specifications* was fourth place last year and third place this year.

These three citations are the same this year as they were for FY2020 and have rotated among the top three positions for the past five years.

The FDA's focus on OTC manufacturers may explain some of the reasons that having and following procedures for the quality unit, §211.22(d), continues at or near the top of the list. Often, these firms often either do not have a quality unit or have one that fails to perform its responsibilities.

The FDA continues to hold the quality unit responsible for implementing an effective quality system at all pharmaceutical firms. Also, OTC firms are often deficient in the validation of the manufacturing process, as captured in §211.100(a).

The collection of drug form 483 observations includes citations other than § 211. We include those in **Figure 3**. Observations that cite the FDCA section 501 are in the number one

	SHORT DESCRIPTION	2017	2018	2019	2020	2021
Total Form 483s issued using the FDA tool for Drug Inspections		694	716	779	349	215
§211.192	Investigations of discrepancies	278	183	167	128	86
§211.22(d)	Procedures applicable to the quality unit shall be in writing and shall be followed	185	208	215	111	80
§211.160(b)	Lab controls should include scientifically sound specifications	207	209	145	84	55
§211.100(a)	Production and process controls shall be supported by written procedures	116	102	129	59	47
§211.42(c)	Facilities shall include defined areas of sufficient size	148	134	156	56	45
§211.25(a)	Personnel qualifications	113	47	113	39	43
§211.68(b)	Appropriate controls shall be exercised over computer systems	84	83	102	57	41
§211.166(a)	Stability testing	72	111	135	42	37
§211.67(b)	Equipment cleaning and maintenance	91	112	124	45	36
§211.194(a)	Laboratory records shall include complete data	122	136	107	54	33
§211.67(a)	Equipment shall be cleaned/sanitized or sterilized	54	81	99	42	33

TABLE 2 | DRUG GMP INSPECTIONS, §211 CITATION FREQUENCY BY FISCAL YEAR

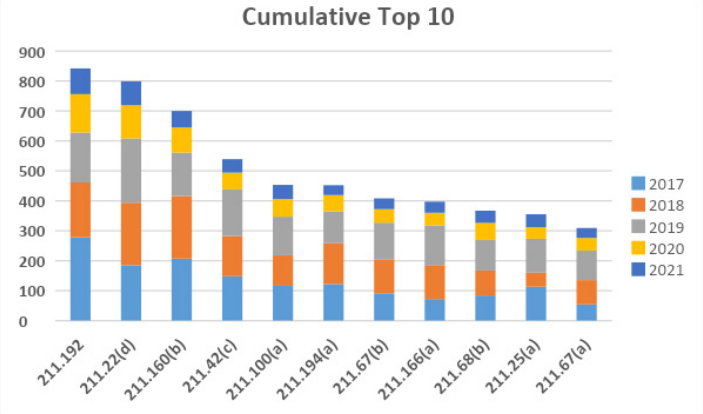

FIGURE 2 | TOP 10 CITATIONS FROM FY 2017 THROUGH FY 2021 FOR 21 CFR 211

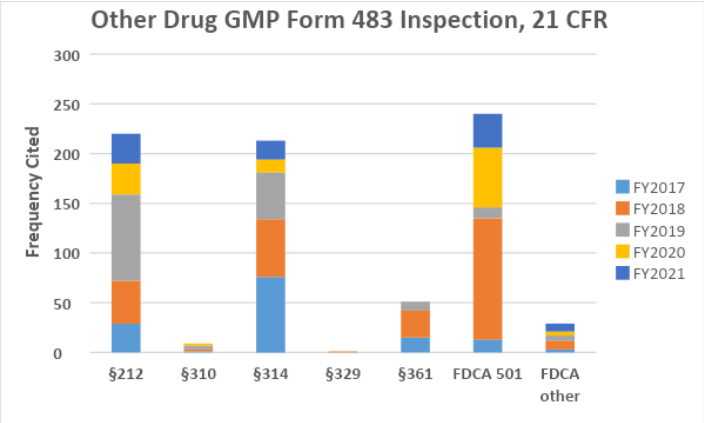

FIGURE 3 | TOTAL CITATIONS FOR 21 CFR OTHER THAN 211

position followed closely by §212 and §314. The four other citation categories, §310, §329, §361 and other FDCA sections bring up the remainder.

CONCLUSIONS

For those who use inspection observations to benchmark and improve their quality systems, the FDA's annual data provide ample resources against which firms can measure their potential vulnerabilities and gauge the probable focus areas during upcoming GMP inspections. Identifying and monitoring trends this year within the collection of 483 observations is difficult because of the substantial decrease in the number of inspections and Forms 483.

§211.192 moved up to first place this year after being in second place last year. It has consistently ranked among the most frequent citations; the industry still struggles with ensuring that investigations, including those for out of specification events, meet expectations. The lack of adequate written procedures and responsibilities for the quality unit, §211.22(d), remains a very consistent citation over the five years addressed herein. Forms 483 observations that include text such as "The quality unit is inadequate…" often result in additional enforcement action, including warning letters.

With effective vaccines available in the first half of CY2021, the number of on-site FDA inspections effectively resumed for domestic sites. While the FDA is performing remote data reviews, it does not appear to count these as inspections and is not issuing forms 482 or 483, though this is all subject to change as we move forward. It would be reasonable to expect that the FDA will develop processes for the conduct of remote inspections or incorporate elements of remote inspections even when it returns to more frequent on-site inspections. The world has changed, and while it may take a while for the FDA to develop processes and procedures for this, we should expect that it will happen.

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.

Barbara received a bachelor's degree in chemistry from the University of Illinois at Urbana-Champaign. You can contact her at barb.unger@redica.com.