FDA and MHRA MOST RECENT INSPECTION OBSERVATIONS

INTRODUCTION:

Part of a comprehensive GMP Intelligence program is the monitoring of enforcement actions, including FDA forms-483, warning letters, recalls, import alerts, consent decree agreements and EU reports of GMDP noncompliance. This article presents the most recent GMP inspection data from CDER and MHRA. The CDER data are from inspections conducted in FY2016 and the MHRA data come from inspections conducted in 2015.

The CDER drug inspection observations supplement the information we previously published regarding CDER Drug GMP warning letters from the same time. The analysis herein includes data from the FY2016 form-483 observations and compares results with those from the three previous fiscal years. Raw data come from the FDA website, though are presented in a different manner. For example, I have combined the frequencies of all observations that cite 21 CFR211.192, into a single number. In the FDA data, there are multiple line items for 211.192, each with a different frequency. For example, in the FDA listing the most frequently cited item is 211.22(d), '*procedures not in writing, fully followed*.' When the full collection of times that 211.192 and 211.42(c) are cited, however, they become number one and number two respectively with 211.22(d) becoming the third most frequent citation. FDA uses the term 'frequency' which seems to be the number of times a given citation was identified in the forms 483 collection supporting these data.

Only forms-483 that were issued through the Turbo EIR system are considered in these data which provides a distinct limitation. No forms-483 issued to API manufacturers or issued outside of the Turbo EIR system are included. This becomes important to consider with FDA's increased focus on API manufacturers, particularly outside the US.

We also look at the GMP inspection data from MHRA. The recently published a 78-slide deck presents GMP Inspection Deficiency Data Trends for 2015. The MHRA provides graphic representation of the observations linked to the Chapters or Annexes that were cited. In this respect, it differs from the FDA published data that does not provide graphics.

EXECUTIVE SUMMARY:

- The number of forms-483 included in this analysis remains reasonably constant over the past four fiscal years even though it does not represent all drug inspections conducted by FDA, particularly inspection of sites that manufacture APIs.
- Deficiencies in investigations remains at the top on this list over the past four years. We as an industry cannot seem to get this quite right.
- In general, the regulations cited and their relative order has remained reasonably constant over the past four fiscal years. Even though a few items have changed place, none of the numbers are striking.
- MHRA issued 51 '*critical*' deficiencies, in a total of 304 inspections of which 79 (26%) were overseas inspections and 224 (74%) were in the UK.
- The EU GMP Guide Chapters and Annexes that had critical observations include: Chapters 1,4,6, and 8; Annex 1 and 11. Scaling of the graphs made it impossible to accurately determine the specific number of each.
- The MHRA cited a total of 3176 deficiencies in the 303 inspections. Criticals constituted 2% of the deficiencies, Majors were 29%, and Others were 69%.

FDA FORM-483 INSPECTION OBSERVATIONS:

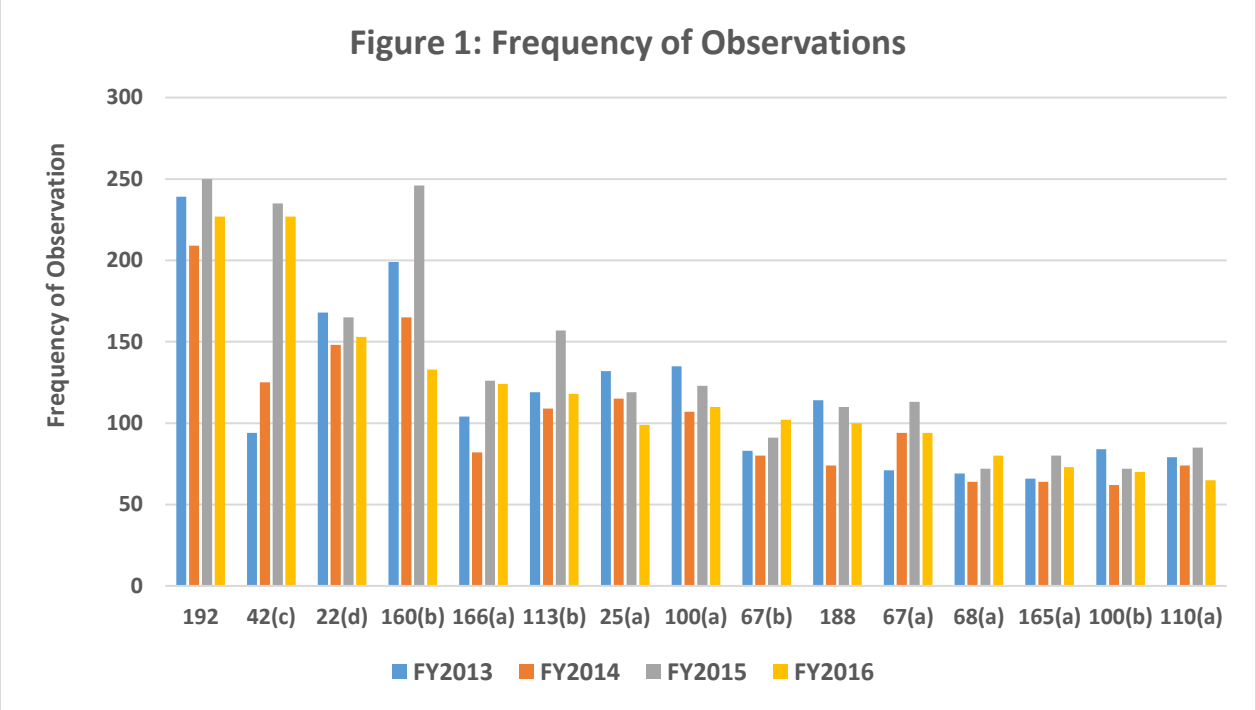
The following data are based on inspections generated using the FDA Turbo-EIR system. The number of forms-483 remained quite similar over the four years in question, with FY2014 having the fewest. Forms-483 issued to API manufacturers or issued outside of the Turbo EIR system are not included.

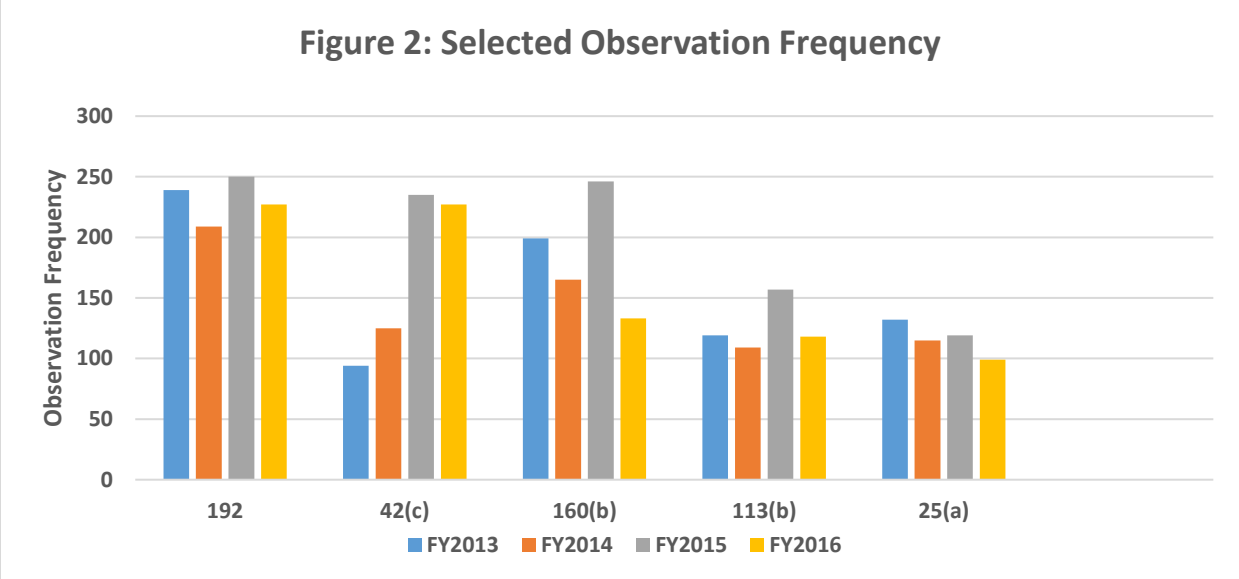
Table 1 shows only the most frequent group of inspection observations, the FDA tabulation shows all. Table 1 is organized in the order of those observations with the highest to lowest frequency for this year.

TABLE 1: Inspection Observations Issued Through Turbo-EIR System per Fiscal Year. These are shown in the order of highest to lowest for FY2016.

CITATION	SHORT DESCRIPTION	2013	2014	2015	2016
Total Forms 483 issued thru Turbo EIR system for 'Drugs'		690	645	678	691
211.192	Production record review, investigations of discrepancies	239	209	250	227
211.42(c)	Requirement for adequate facilities to prevent contamination or mix-ups	94	125	235	227
211.22(d)	Quality unit responsibilities should be in writing and should be followed	168	148	165	153
211.160(b)	Development of scientifically sound specifications	199	165	246	133
211.166(a)	Expiration dating should be supported by appropriate studies	104	82	126	124
211.113(b)	Validation of aseptic processes including sterilization	119	109	157	118
211.100(a)	Written procedures shall describe production and process controls	135	107	123	110
211.67(b)	Procedures shall describe cleaning and maintenance of equipment	83	80	91	102
211.188	Batch production records	114	74	110	100
211.25(a)	Staff shall have training, education and experience to perform their jobs	132	115	119	99
211.67(a)	Equipment shall be cleaned and maintained	71	94	113	94
211.68(a)	Automatic equipment including computers shall be routinely calibrated and inspected	69	64	72	80
211.165(a)	Specifications shall be established for drug product	66	64	80	73
211.100(b)	Activities shall be documented at the time of performance	84	62	72	70
211.110(a)	Processes shall be validated	79	74	85	65

Figure 1 below shows the data from Table 1 graphed over four fiscal years, 2013 – 2016. While there is some variation from year to year, the frequency with which specific regulations are identified remains generally constant. Figure 2 shows additional detail of several of the areas where the frequency of the observation did show some variation between FY2015 and FY2016.

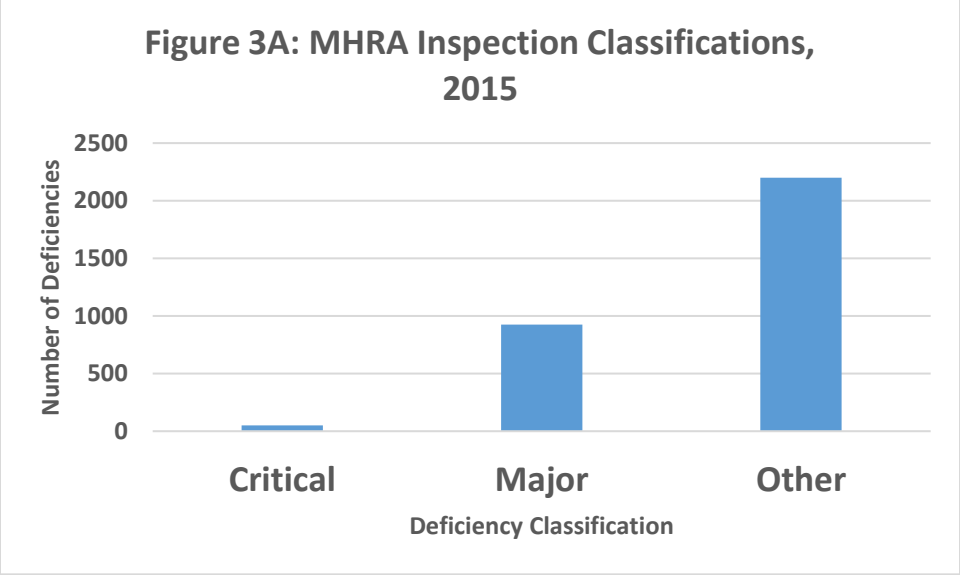


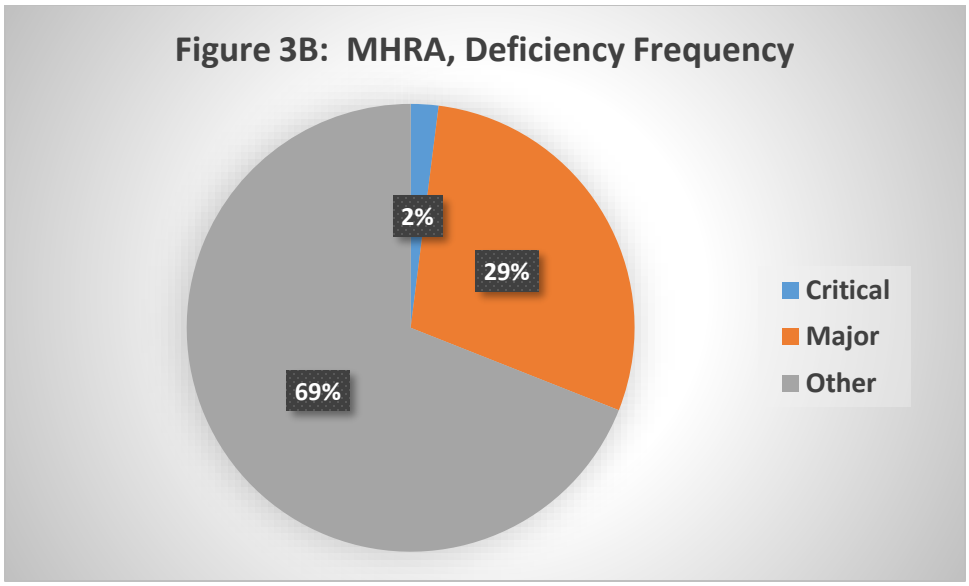


In conclusion, there is little change in the overall frequency of inspection observations, as characterized by the regulation cited, between FY2013 and 2016. This may have been different if all inspected sites, including API sites had been included in the metrics. The three most frequent observations in FY2016 cite 211.192 (investigations), 211.42(c) (validation of aseptic processes including sterilization) and 211.160(b) (scientifically sound specifications. In several instances, though, the order of the observations did change in FY2016, and these are highlighted in gray in Table 1. While 211.192 continued in first place for all four fiscal years, 211.42(c), *Requirement for adequate facilities to prevent contamination or mix-ups* moved from third place to second place, even though the actual number of those observations decreased. Citations against 211.160(b) *Development of scientifically sound specifications* went from second place to fourth place this year. Observations citing 211.113(b) *Validation of aseptic processes including sterilization* dropped from fifth place to sixth place in 2016 and the actual number decreased significantly to FY2013 levels. Finally, observations identifying 211.25(a) '*Staff shall have training, education and experience to perform their jobs'* dropped from eighth place to tenth place this year.

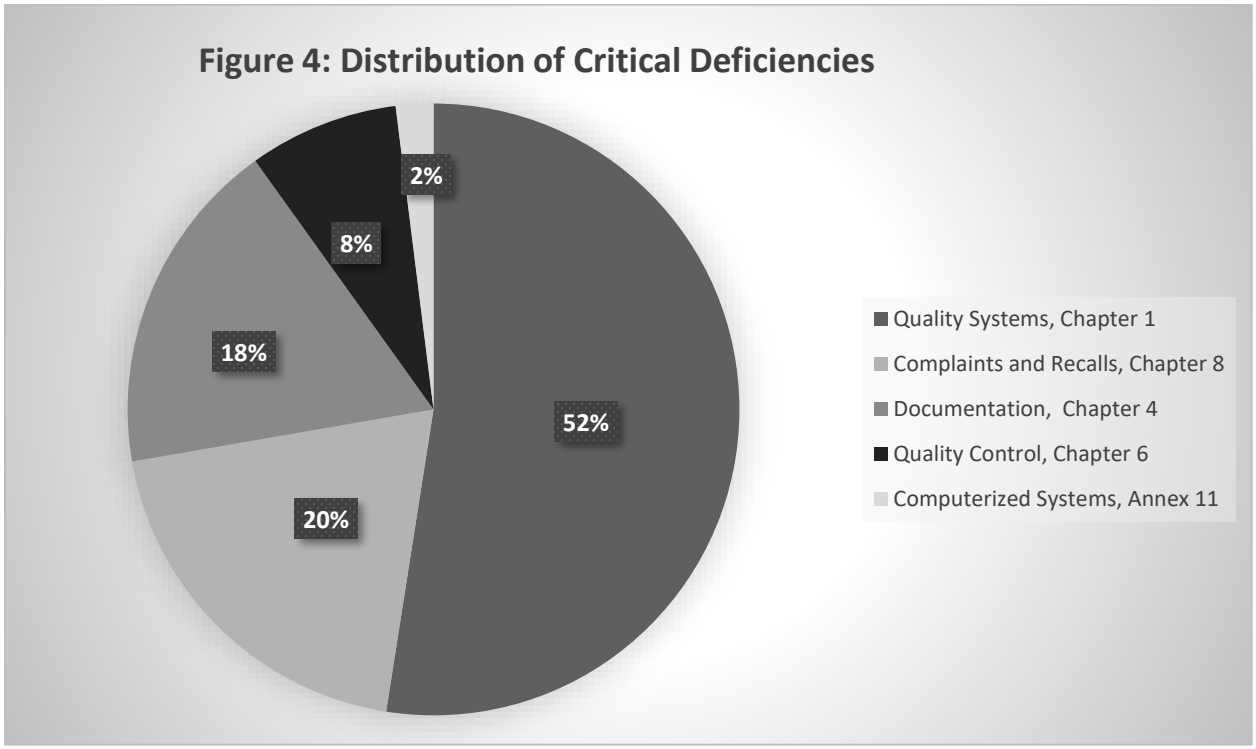
MHRA Inspection Deficiencies

I won't reproduce the graphics from the MHRA slide deck; do read those because they contain a wealth of information at a very granular level. The areas with critical deficiencies include, in order of most frequent (% of critical deficiencies): Quality Systems (53%), Complaints and Recalls (20%), Documentation (18%), Quality Control (8%), and Computerized Systems (2%). Figure 3A shows the distribution of deficiencies among the three classifications by actual number. Figure 3B shows this distribution of deficiencies among the three classifications by percentage. Figure 4 shows the distribution in percentages, of critical deficiencies using the MHRA identified categories and the associated Chapter / Annex.





The MHRA inspections identified 51 total 'critical' observations for 2% of the total number of inspection identified deficiencies. About a third of the deficiencies are in the 'major' category and almost 70% are in the 'other' category. We cannot compare this with the US FDA inspection observations because the FDA does not classify their observations. In the future, perhaps health authorities will adopt a common classification categories for inspection observations.



The Quality System was the subject of the majority of MHRA identified critical GMP deficiencies in 2015 followed by an almost equal percentage for Complaints and Recalls and Documentation. Quality Control followed and a single critical deficiency was identified in Computerized Systems.

The fifty-one (51) critical observations cluster in four (4) of nine (9) EU GMP Chapters, and two (2) of nineteen (19) GMP Guide Annexes. These include:

- Chapter 1: Pharmaceutical Quality System
- Chapter 4: Documentation
- Chapter 6: Quality Control
- Chapter 8: Complaints and Product Recalls
- Annex 1: Manufacture of Sterile Medicinal Products
- Annex 11: Computerized Systems

CONCLUSIONS:
It is difficult to directly compare these areas with those identified by FDA. FDA does not categorize the criticality of inspection observations as the MHRA and other health authorities do. We can, however, say that with observations addressing 'investigations' at the top of the list, 'quality unit responsibilities' third on the list and 'staff training' at number 10, it's clear that the Quality System is a high priority for both FDA and MHRA. Computer systems is identified separately by MHRA in Annex 11 but in forms-483 this type of observation is generally identified as 211.68(b) that addresses controls over computer systems. Part 11, *Electronic Records; Electronic Signatures*, is rarely, if ever, identified in either forms-483 or warning letters.

For those who use inspection observations as a means of monitoring and improving their own quality systems, both publications provide ample resources against which firms can measure their own potential vulnerabilities.

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