Analysis Of
CDER OFFICE OF PHARMACEUTICAL QUALITY REPORT ON THE STATE OF PHARMACEUTICAL QUALITY

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Govzilla
1905 Marketview Drive
Suite 205
Yorkville, IL 60560
support@fdazilla.com
Telephone: +1 (844) 332-3320

THIS REPORT COVERS:

Overview of the CDER Office of Pharmaceutical Quality Report on the State of Pharmaceutical Quality published by the FDA: FY2009-2018 for inspection outcomes, 2016-2018 for product quality defects, 2017-2018 for Site Catalogue and 2018 for the Product Catalogue.

AUTHOR: BARBARA UNGER
UNGER CONSULTING, INC.

FDA recently published the 12-page CDER Office of Pharmaceutical Quality Report on the State of Pharmaceutical Quality. It includes a wealth of data collected over different time periods: FY2009-2018 for inspection outcomes, 2016-2018 for product quality defects, 2017-2018 for Site Catalogue and 2018 for the Product Catalogue. Interestingly, inspection data gathered by European agency inspections are included because they are recognized under the existing MRA.

FDA now assigns a numerical score to inspection outcomes. This began in FY2017, so they haven't been doing this for long enough for meaningful trends to be available. While they do give some overall values, it begs lots of questions for which the information would be welcome.

The report is data rich and certainly worth a careful read for a broad perspective on OPQ activities in FY2018. The 2017 Annual Report is available for comparison, but it is much more qualitative and lacks the scope and depth of detail found in the 2018 report.

The two most interesting features from FY2018, in my opinion, are the following, and we'll look at them in more detail in the following sections:

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Demographics and performance of sites that manufacture products without an application may be a surprise who has followed enforcement actions over the past few years. This manufacturing group includes OTC monograph products, homeopathic products, and I'm going to assume outsourcing facilities and perhaps compounding pharmacies. This may explain the FDA's focus in the past couple of years on sites in the first two categories and the focus on outsourcing facilities for the past several years.

Inspection Outcome Scores

This was far and away from the most important information in the report for me. FDA has discussed that a scoring system was being developed, but this is the first time I've seen any reported results. If only there were additional categories!

FDA describes the site inspection score as being based *"...on a scale of 1 to 10, as a measure of a site's compliance to Current Good Manufacturing Practice (CGMP) regulations based on the classification of FDA Drug Quality Inspections conducted over the last 10 years."*

This suggests that the scores are likely aggregate scores over the time period rather than scores for individual inspections and years. This unfortunately can obscure meaningful granularity within a given site inspection history.

FDA states that the *"...inspection score is only used for comparison purposes to look for trends and target resources."*

FDA also states that *"Compliance with CGMPs provides assurance the drug product consistently meets the intended specifications."*

This last statement raises a whole raft of questions. The mention of meeting drug product specifications raises the question about how drug substance and API manufacturers are scored, and it seems to imply that if the drug product meets "the intended specifications" that becomes the primary criteria in GMP assessment. I don't think that's what FDA meant, but a clarification would be welcome.

TABLE 1: Inspection Score Results*

PHARMACEUTICAL SITE CATEGORY	SCORE
Europe, ANDA Sites	8.2
EU Sites	7.9
All sites, Application Supported	7.8
Overall Industry Score, FY2017	7.7
US Sites	7.7
All Sites, Immunology Products	7.7
All Sites, two or more routine inspections	7.6
All Sites, Overall Industry Score	7.5
Rest of World (outside of US, EU, China and India)	7.2
All Sites, Sterile Products	7.2
All Sites, Non-Sterile Products	7.1
China	7.0
India	7.0
India, ANDA Sites	7.0
Sterile Products, No Application	6.7
All Sites, No Application	6.6
All Sites, Initial Inspection Only	6.0
Sites Involved in Drug Recalls	5.9

* All are from FY2018 except the overall score noted as FY2017

These scores have only been collected for FY2017 and 2018, so trends are virtually impossible to discern.

Table 1 provides the collection of all scores provided within the FY2018 Annual Report in descending order, highest to lowest.

The striking feature is the narrow range of average scores reported for the various categories, from 5.9 to 8.2.

Where does statistical significance begin? Are scores that differ by 0.2 points statistically different? Providing an average score obscures much of the valuable granularity that would be useful to the regulated industry.

These scores raise more questions than they answer! It would be interesting to have additional data, in all cases, the low, high, and median along with the total number of sites in each category for which a score is provided.

The following 'categories' are just a few that come to mind:

- What constitutes a minimally acceptable score for GMP compliance, and do these differ among product types (e.g., sterile, non-sterile, application, non-application)?
- Inspection of biotechnology firms separated into the following categories:
  - cell therapy and gene therapy, products regulated under 21 CFR 1271
  - recombinant DNA therapeutic proteins including those which will be regulated as biologics in 2020
  - Other
- Inspections conducted by the EU authorities under the existing MRA, separated by sites in the EU vs. sites in the Rest of World broken out by sterile vs. non-sterile sites.

- Inspections conducted of API/drug substance/intermediate sites separated by geography.
- Scores for firms that lead to the issuance of a Complete Response Letter.
- Scores for the most recent inspection for firms subject to new consent decree agreements or seizures for the given FY.
- Scores for firms where repeat observations from previous inspections were identified.
- Scores for inspections which immediately preceded a warning letter for all categories and broken out by:
  - Geography
  - API/ drug substance/intermediate manufacture
  - Application vs. non-application sites
  - Compounding pharmacies and outsourcing facilities combined
  - Sterile product sites
  - Non-sterile product sites

What We Can Learn

Now that I've voiced my wish list let's take a look at a few bits of the wisdom we can learn from the data provided.

Most interesting is that the scores include data based on EMA inspections conducted under the MRA. With the European ANDA sites receiving the highest score of 8.2, does this suggest that there is a bias toward domestic manufacturers for these inspections?

Overall inspection scores from sites in Europe and the US are higher, 7.9 and 7.7 respectively, than those for China and India, both at 7.0.

Sites supported by applications (NDA, ANDA, and BLA) have a higher average score, 7.8, than those not supported by an application which have an average score of 6.6.

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The non-application sites would include OTC products, homeopathic products, and those made by compounding pharmacies and outsourcing facilities. It's interesting that their average scores differ only by 1.1 points out of ten while the issuance of warning letters to compounding pharmacies and outsourcing firms approaches ten fold the number of warning letters issued to others.

The past two years has seen a stunning focus in warning letters issued to OTC firms so that factors in here too. While the fact that these type of sites score differently comes as no surprise to anyone who has watched trends over the past few years, the differences in their average score of only 1.2 beg for an explanation.

All sites making sterile products score only 0.1 point higher on average than sites making non-sterile products.

First inspections overall score the lowest with an average of 6.0. In my opinion, this is likely skewed by the intense focus FDA has shown in the past two years toward enforcement against

OTC manufacturers and compounding firms/ outsourcing facilities in the past five years. It seems unlikely that this is based on PAI results for ANDA, NDA, and BLA products.

FDA also notes that the FY2018 inspect score for all sites that manufacture the Angiotensin II Receptor Blockers (the 'sartans') scored 7.4, not significantly different from the overall score for all sites in FY2018.

FDA also mentions that this average "....does not include recent FY2019 inspections at some of these sites prompted by positive findings of nitrosamine impurities." This is troubling. If FDA inspections cannot be predictive of these types of problems, it suggests that either investigators and/or inspections may not be adequate to protect the US public.

Alternatively, and more troubling, is the possibility that politics came into the picture for scoring inspection of these sites generally in India and China. It's always easier to find deficiencies when given a roadmap rather than having to make the discoveries without directions.

Demographics

This is a far-ranging section that looks at inspections conducted, the type of applications, or no application product and at application quality. FDA states that at the end of FY2018, their site catalog included 4,676 drug manufacturing sites. Application-based sites constituted almost 60% of the sites, and non-application sites constituted just over 40%. Other notable information presented in this section includes:

India, China, South Korea, and German make up 31% of the drug manufacturing sites that supply the US market. "All Others" make up 30% and the US contributes 39%. Remember this is simply the number of sites and does not address the percent of prescriptions that include API/drug product manufactured in that country.

'No application' sites grew just over 20% in number in the site catalog in FY2018, ANDA sites increased by approximately 8%, and biotech sites increased just over 5%. The percentage represents changes in the site catalog, not % of the sites overall.

The United States had 47% of the drug quality inspection sites, India had 13%, China had 9%, and other countries made up the remainder. This seems surprisingly focused in the US.

FDA reports more than 1,000 sponsors for original and supplemental applications, with ten firms accounting for 20% of all submissions. The top two firms in this group of ten also received more Complete Response Letters than approvals. The data do not say whether these are ANDA or NDA submissions, but I would assume those are ANDA submissions.

Firms that are not subject to routine surveillance inspection accounted for 41% of recalls over the past five years. FDA notes that just over 1,000 recalls are attributed to an API re-packager with cross contamination issues and a secondary re-packager who had label mix-ups. It should not be a surprise that problems at firms like this are associated with a large number of product recalls.

Conclusion

The report addresses other areas which I've not covered here; it's worth a careful read based on the depth of the data provided. We encourage the FDA to continue to publish reports with this depth of data and to consider the questions we've raised that may provide additional value to the regulated drug industry.