RISK FACTORS USED IN SCHEDULING FDA DRUG GMP INSPECTIONS

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Detailed charts and summary of FY2017 FDA Enforcement Statistic.

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The global supply chain for drug products sold in the US has become increasingly more complicated in the past decades. What was once a mostly domestic industry has become global including the sourcing of raw materials, APIs including their starting materials and intermediates, drug product manufacture, packaging, labeling, and distribution Moreover, each of these specific areas source materials from around the globe also.

Consider also re-packagers of raw materials, APIs, intermediates and bulk drug product this becomes a spaghetti map of confusion to trace the history of each component back to its original manufacturer for a single drug product.

The globalization of the supply chain has expanded the scope of sites FDA must routinely inspect from those in the US to facilities worldwide.

For example, in FY2017 FDA identified just over 5,000 human pharmaceutical manufacturing sites worldwide, about 60% are located outside the US. Similar globalization exists in the food industry and device industry. It becomes a daunting task for FDA to inspect all regulated sites with a specific frequency.

Partly in response to the heparin incident of 2008, FDA made many changes and refinements to ensure that all manufacturers of products distributed in the US meet GMP regulations. The July 2012 "Food and Drug Administration Safety, and Innovation Act" (FDASIA) amendment to the FD&C Act codifies many of these authorities and includes:

Section 702 of FDASIA explicitly states that drug manufacturing sites located outside the US must register with FDA. Occasionally FDA issues warning letters for a firm's failure to register.

Section 705 of FDASIA amendments to the FD&C Act formally changed the inspection frequency for drug manufacturers from biennial (which FDA never met for all sites under their oversight) to a risk-based schedule for drug inspections of all sites registered with FDA.

Although FDA assigns inspections on a risk-based frequency, they must be inspected every four years according to item 'D' under 'Risk Factors' in FDASIA legislation. FDA implemented a risk-based approach to inspections beginning in FY2005 as a component of the "Pharmaceutical Quality for the 21st Century – A Risk-Based Approach" published in 2002. The Final Report from 2004 is HERE. FDASIA formalizes this approach in legislation.

Section 708 of FDASIA gives FDA the authority to receive and protect information from foreign agencies, and also to exchange information with those agencies. Health authorities had been sharing information informally, but this formalized the authority.

Section 712 amended the FD&C Act to recognize foreign inspection outcomes.

Based on the authority in Section 708 and 712 above, FDA entered into a Mutual Recognition Agreement with the EU authorities who are faced with similar global supply chains and resource limitations. Reliance on each others inspections permits each health authority to leverage limited inspectional resources and openly share information about manufacturing sites. This agreement includes fifteen European health authorities with the recent addition of Portugal to the list of qualified member states.

FDA continues to refine the GMP inspection process. FDA made changes to the field organization and ORA in 2017 whereby a structure based on product type replaces the previous geographic structure.

The new organization also expects inspectors to develop in-depth knowledge in specific area(s) rather than being expected to be a jack-of-all-trades in the areas that FDA regulates. Developing inspector expertise in given areas is an aspirational goal and a work in progress, albeit a necessary one, for FDA to be able to adequately assess many of the new technologies in human medicines and devices.

In another welcome refinement, FDA now updates the Inspection Classification Database monthly. The website, however, explicitly states that it "...does not represent a comprehensive listing of all conducted inspections."

It also does not include inspections conducted by the States, PAI inspection and inspections that await an enforcement action decision.

A recent statement by Commissioner Gottlieb states that FDA updates the database to "support inclusion of facility status based on classification of inspection reports from recognized foreign regulatory authorities." I could not find any foreign inspection outcomes posted in the tabulation ending August 29, 2018, posted on the FDA website and is worth monitoring in the future.

As well as more frequent updates of the inspection database, FDA is committed to communicating inspection classification information to the inspected facility within 90 days of the close of a surveillance inspection as part of GDUFA II legislation. FDA is applying this across the board to all drug manufacturers and not limiting it to generic drug facilities.

Note this does not necessarily include communication of outcomes of pre-approval inspections or for-cause inspections within this same timeframe. "Integration of FDA Facility Evaluation and Inspection program for Human Drugs: A Concept of Operations" provides a full description of this effort. FDA appreciates the impact that an OAI decision may have for a generic firm seeking approval of a product that is currently in shortage and is working to effectively communicate the information so that firms may quickly make necessary remediations.

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FDA's most recent efforts at transparency in the drug GMP inspection planning process is found in MAPP 5014.1, "Understanding CDER's Risk-Based Site Selection Model" used to prioritize sites for routine surveillance GMP inspections. The MAPP is effective September 26, 2018. This MAPP addresses inspections of sites that manufacture commercial drug product, in process material, and active pharmaceutical ingredient used in the manufacture of human drugs.

FDA excludes the following type of sites from the scope of this MAPP:

- Compounding sites registered under 503B of the FD&C Act
- Medical gas sites
- Excipients
- Investigational drug manufacturing sites

The latter two types of sites can be inspected if necessary, generally for-cause. FDA states that the model is under continuous improvement with "statistical analyses ...used to assess the correlation between certain outcomes and current prospective risk factors." More on this later in the article.

The risk factors identified on page 3 of the MAPP are those taken from FDASIA section 705, as identified above, supplemented with additional risk factors.

These additional risk factors include:

- Site type (manufacturer, packager, control lab)
- Time since the last inspection
- FDA compliance history
- Inspection history from qualified foreign regulatory authority which currently includes a collection of countries within the EMA group
- Patient exposure
- Hazard signals including but not limited to FARs, BPDR, MedWatch Reports, recalls
- Inherent product risk including dosage form, route of administration, sterile vs. non-sterile dosage forms, API load, biologic product, therapeutic class, narrow therapeutic index drugs, and emergency use drugs

The MAPP states that the site selection model is used to generate a score for each site. Some of the scores are based on empirical evidence others are based on subject matter expert's judgment. It is difficult to find fault with any of the risk factors identified and considered during development of the score development process. It does, however, raise some important questions.

What factors are used to establish "FDA compliance history"? I see this factor as a composite of Hazard Signals as defined above and previous inspection outcomes. In the interest of transparency, it would be helpful to understand what is considered in this risk factor and whether it is based on empirical data or expert judgment.

More important, and challenging, is the weighting applied to each of the identified risk factors as a site score is assigned. I worked for a firm that developed an algorithm to determine time intervals between corporate GMP audits based on a selection of risk factors similar to those in the FDA MAPP. The challenge with such programs comes in assigning the number of risk categories so that weighting of each leads to a meaningful result. Using too many risk factors, each with an assigned weighting, can obscure important information and fails to distinguish among sites with important differences as an experienced auditor would judge them. FDA states that they perform an annual review of the model. I would like to see the data generated for this review. Some of these data are undoubtedly proprietary and not able to be publicly released, but other information should be releasable. One relevant analysis might be the number, or percentage, of sites that were the subject of import alerts, warning letters or recalls and whether those sites had higher risk scores than others who were not the subject of such enforcement actions in that year. For FY2018 it would be interesting to know whether the manufacturer(s) of the valsartan API that was contaminated by a carcinogenic impurity had a risk score that suggested potential problems. Perhaps this is true because this API site was subject to inspections in both 2016, 2017 and 2018. This problem has already resulted in recalls by many valsartan drug product manufacturers. I encourage FDA to publish their annual review results, appropriately redacted, so that the industry could have ongoing confidence in the process.

The new MAPP is a welcome addition to FDA's ongoing efforts at transparency in the GMP inspection process. The risk factors identified are not novel and largely reflect those identified in FDASIA legislation from 2012 including reliance on qualified foreign inspections. While this MAPP does not appear to include novel approaches or requirements, it is an important communication from the agency so that sites may better understand the inspection planning process. The process itself is remarkably similar to processes that pharmaceutical firms use to determine inspection frequency for their suppliers, CMOs and company-owned manufacturing sites so should come as no surprise to the regulated industry.