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Quality Metrics May Reduce FDA Inspections For Pharma Cos.

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Quality metrics are utilized throughout the pharmaceutical industry to monitor quality control systems and processes and to drive continuous improvement efforts in drug development and manufacturing. The U.S. Food and Drug Administration, through a recently-published draft guidance and its corresponding Federal Register notice, is making good on its decade-old promise to create a system in which pharmaceutical manufacturers consistently and reliably produce "high-quality drug products without extensive regulatory oversight."[1] This guidance offers transparency to industry by painting a clear picture of what the agency is thinking with regard to the use of certain quality metrics for risk-based oversight. Entities that work to internalize this guidance and produce timely, thoughtful reports to the agency that demonstrate highly controlled manufacturing and a robust quality measurement system should see positive results: less frequent agency inspections and greater ability to self-regulate.

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The guidance, entitled Request for Quality Metrics, and the forthcoming corresponding public meeting are intended to explain how the agency plans to use quality metrics data to further develop its risk-based inspection scheduling, to identify situations in which there may be a risk for drug supply disruption, to improve efficiency and effectiveness of establishment inspections and to improve the FDA's evaluation of drug manufacturing and control operations.[2] The agency will request data of owners and operators of establishments that are required to register under section 510 of the act and that are engaged in the manufacture, preparation, propagation, compounding or processing of finished dosage forms (FDF) of covered drug products or active pharmaceutical ingredients (API) used in the manufacture of covered drug products. The FDA states that it plans to make its requests at the time that the guidance is finalized. It will provide notice in the Federal Register of its requests.

The FDA noted that the quality control unit in each reporting establishment will generally be best positioned to compile reports for submission to the FDA. It would ask for data to be aggregated and reported in a readily accessible format. Establishments would submit quality metrics data reports for a one-year period that begins after the agency issues its requests, with reports being submitted within 60 days of the end date of the reporting period. Data to be reported include:

- The number of lots attempted of the product;
- The number of specification-related rejected lots of the product, rejected during or after manufacturing;
- The number of attempted lots pending disposition for more than 30 days;
- The number of Out-of-Specification (OOS) results for the product, including stability testing;
- The number of lot release and stability tests conducted for the product;
- The number of OOS results for lot release and stability tests for the product that are invalidated due to lab error;
- The number of product quality complaints received for the product;
- The number of lots attempted that are released for distribution or for the next stage of manufacturing the product;
- If the associated Annual Product Reviews (APRs) or Product Quality Reviews (PQRs) were completed within 30 days of annual due date for the product; and
- The number of APRs or PQRs required for the product.

The FDA intends to calculate the following quality metrics for each product and establishment, where applicable:

- Lot Acceptance Rate;
- Product Quality Complaint Rate;
- Invalidated Out-of-Specification Rate; and
- APR or PQR on Time Rate.

The agency also notes various optional metrics under consideration and requests public comment on whether establishments should have the opportunity to submit additional, optional metrics as evidence of manufacturing robustness and a commitment to quality. The guidance also requests public comment on whether the agency should make its requests annually or at a different frequency, as well as possible alternative approaches with regard to data collection timeframes in order to reduce the burden on data collection and alternative approaches that would allow inclusion of a limited text field for data points or metrics.

Importantly for industry, the agency has made clear that the initial use of the metrics will be to consider a decreased surveillance inspection frequency for certain establishments. The FDA expects the quality metrics program to play an important role in addressing risk-based inspection scheduling. For example, establishments that have highly controlled manufacturing processes will have the potential to be

inspected less often (and would therefore be considered a lower priority for inspection) than similar establishments that demonstrated uncontrolled processes (and would therefore be considered a higher priority for inspection).

The agency also intends to consider whether the quality metrics may provide a basis for it to use improved risk-based principles to determine the appropriate reporting category for post-approval manufacturing changes. Additionally, the agency intends to use the data as one factor in identifying establishments that may pose significant risks to consumers, such as risks from unsafe products and drug shortages. The agency believes that evaluation of the data will enable it to work with these establishments toward early resolution of quality problems and to reduce the likelihood that the establishment's operations will be disrupted and impact the drug supply.

Notably, the agency made clear that it does not intend to publicly disclose quality metric data submissions. The failure to report requested quality data may elevate an establishment's predicted risk in the FDA's prioritization of inspections and may lead to an earlier inspection. Additionally, products associated with such an establishment may be deemed adulterated under section 501 of the act, which could subject the establishment to enforcement action.

The public meeting will be held on Aug. 24, 2015, from 8:30 a.m. to 5 p.m. at the FDA White Oak Campus, 10903 New Hampshire Ave., Bld. 31 Conference Center, the Great Room (Room 1503 Section B/C), Silver Spring, MD 20993. The agency will accept electronic or written comments until Sept. 28, 2015.

This is a real opportunity through public comment for companies to have their voices heard on these issues, generally, and to weigh in on the metrics, reporting frequency and data collection approaches that work best for the systems already in place, more specifically. This guidance represents a profound inflection point in agency working and thinking and will be a necessary primer for pharmaceutical companies and, by extension, device companies as we look to the not-so-distant future. It is very likely that, after the public meeting and period for public comment, the FDA will implement this program.

The concept of risk is the sum of process steps and hand-offs. Some processes and hand-offs carry greater opportunity for misadventure than others. Quality is the result, along the way, of material deviations noticed, analyzed and addressed before time and options run out. Just as successful quality should be prospectively built in by companies, the agency is now endeavoring to devote more resources to a priori considerations, rather than to less efficient a posteriori audits. The FDA has clearly concluded that effective protection of the public health must become increasingly preemptive. Success with the FDA is about both anticipation and aligned execution. Strong quality control units and robust quality measurement systems aligned with the agency's quality metrics will prove to be essential. Armed with the knowledge of the agency's proposed quality metrics, companies can take action today by thinking more proactively about the protection of public health, implementing system checks to catch and address issues more quickly and ensuring that their future reports evidence highly controlled manufacturing processes. By doing so, companies should be able reap a significant reward — placement on the lower priority inspection lists.

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[1] See FDA Pharmaceutical Quality Oversight (describing the FDA's 2004 vision to modernize the regulation of pharmaceutical manufacturing and enhance product quality, as articulated by Janet Woodcock, Director of FDA CDER).

[2] In publishing this report, the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research cite, as the agency's authority to make requests for information relating to quality metrics, section 704 of Food, Drug and Cosmetic Act, under which the agency has the authority to require owners and operators of certain establishments to provide upon request records and information. Additionally, section 706 of the Food and Drug Administration Safety and Innovation Act amended the act to provide the agency with increased authority to increase safety and quality throughout the drug supply chain.