Health Research Institute
Spotlight

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Major shift ahead in how FDA regulates drug quality

Parts of the pharmaceutical industry continue to struggle with drug quality. A major shift in the way the FDA oversees drug quality could pose new challenges for companies with inadequate control over their manufacturing facilities and supply chains.

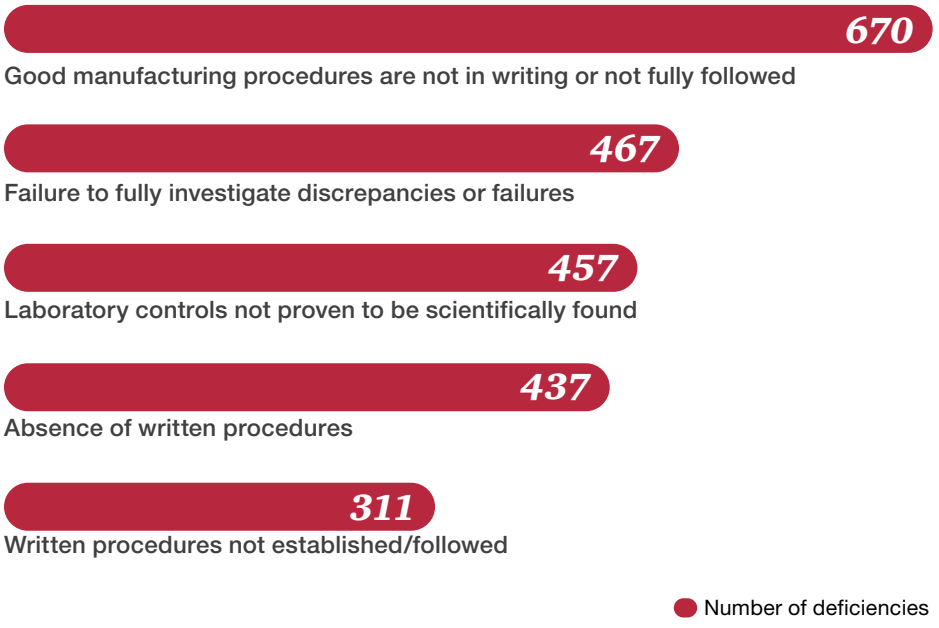
Drug manufacturers are under increasing pressure to comply with drug quality regulations. Despite a sustained effort to improve the state of pharmaceutical quality in the US, regulators continue to see repeated and common problems at drug manufacturers big and small. In response, the FDA is taking action, reorganizing its quality staff into a new department, making its quality inspections more targeted and specific, and issuing a new guidance document asking for more quality data from companies.

In recent years, FDA has cited hundreds of companies for failing to have adequate procedures around drug quality — or failing to follow them. The top deficiency observed during FDA inspections between 2011 and 2014 was failing to follow written quality procedures, according to an analysis of FDA inspection reports by HRI **(Figure 1)**.[1] Although less common, another challenge has been the handling and trustworthiness of collected data. The FDA has warned a growing number of companies since 2010 for "data integrity" violations, including allegedly altering, falsifying or inadequately maintaining data about drug quality, according to an analysis by HRI **(Figure 2)**. From 2010 to 2012, the FDA warned just five companies for such violations. Between 2013 and 2015, the number was 24.[2]

The stakes are high. If a drug is substandard in quality, it can fail to deliver its stated benefit or even injure or kill the patient. For companies, quality deficiencies can mean lawsuits, inefficient manufacturing facilities, costly remediation efforts, products prohibited from sale and expensive recalls. From 2013 to 2015, more than 4,000 drugs were recalled, many for reasons related to drug quality.[3] Quality problems also can lead to shortages — a concern of regulators, companies and patients alike.[4]

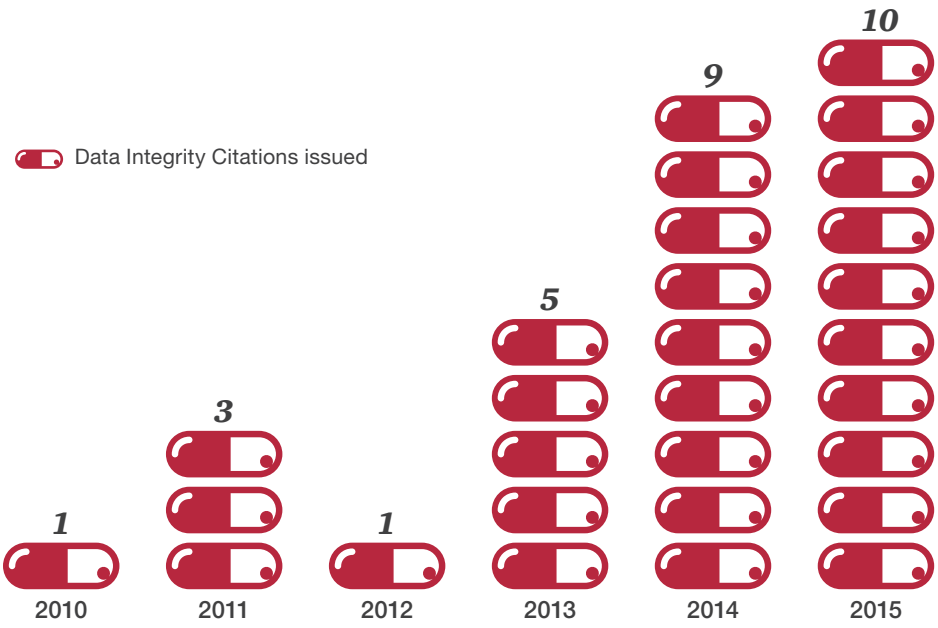
The FDA's new approach to drug quality is meant to protect consumers from substandard drugs and improve the pharmaceutical industry by increasing manufacturing efficiency. The changes offer opportunity and risk for the industry. Companies that are committed to quality and prepared to invest in improving their operations may see rewards, while companies with lesser commitments or investments may experience more and harsher regulatory scrutiny than before.

Figure 1: Top 5 observed deficiencies during FDA inspections
FY2011-2014



Source: PwC Health Research Institute analysis, FDA

Figure 2: An increasing focus on data integrity
FDA warning letters to drug companies citing data integrity violations, 2010-15



Source: PwC Health Research Institute analysis, FDA

A new regulatory approach to drug quality

Last year, the FDA established the Office of Pharmaceutical Quality. The new office combines all of FDA's quality oversight into a single department.[5] Quality oversight at FDA previously was segregated by product type — generic drugs versus new drugs — and by a product's stage of development — pre-approval versus post-approval. The new structure will allow the agency to deploy resources more strategically, which could mean greater and more consistent oversight for some sectors.

Inspections are changing, too. FDA's new Integrated Quality Assessment methodology creates a team of specialized reviewers who will work together to review and monitor drug products throughout their lifecycles.[6] Previously, inspectors had been isolated, leading to multiple assessments by reviewers using different templates. The goal is to make inspections more consistent by having relevant experts involved when they are needed most. The specialist teams will include experts on manufacturing, risk assessment, inspections, microbiology, product design and surveillance.[7]

FDA also is adopting a new risk-based inspection approach. For years, FDA tried to inspect facilities every two years. Soon, the agency will consider compliance history when deciding which facilities to inspect and how often.[8] The new approach is expected to allow the agency to focus more on facilities at higher risk of suffering from serious quality issues. The risk-based inspections approach may benefit companies investing in quality.

Measuring drug quality

FDA is drafting a list of metrics it will use to quantitatively measure the industry's state of quality. The new metrics would assess multiple factors on a quarterly basis, including lot acceptance rate, product quality complaint rate, invalidated out-of-specification rate and product quality review on-time rate.[9]

Choosing the right metrics could prove challenging. Pharmaceutical products differ in complexity and how they are made; manufacturers also differ in their tolerance for risk. For example, a risk-averse company that rejects a product upon the slightest hint of a product quality deviation would, on paper, appear to have worse lot acceptance metrics than a company with looser standards.[10] Improper use of metrics could lead to false conclusions.

For those reasons, it may be impossible for FDA to apply a single set of quality metrics to the entire industry and use it to assess a facility as either high or low quality. Instead, FDA may rely heavily on contextual data on a case-by-case basis, or on subsector-specific metrics of quality to make comparisons easier.

Implications: Risks

- ***For companies struggling with quality, the risks multiply.*** A new metrics-driven approach is likely to increase the frequency of inspections for companies most at risk of lapses in quality. FDA has said it intends to focus more on product quality than on facility compliance. Problems found with the manufacture of a drug at one site may result in follow-on inspections at other sites where the drug is made. As metrics are regularly communicated to regulators, companies may feel like an inspection is never done—just on pause.
- ***Quality can be an expensive investment.*** Not all companies stand to benefit equally from FDA's new approach. Low-margin businesses may find it difficult to afford the investment in quality that FDA's new approach demands. Metrics will take time, personnel and information technology resources to generate.[11] These investments will either be borne by companies or passed on to the consumer, resulting in higher drug prices for some products.
- ***Quality is difficult to measure.*** The pharmaceutical industry generally supports the use of metrics, yet the devil is in the details.[12] Regulators and manufacturers will struggle over identifying metrics that are meaningful and accurate. A small number of companies may falsify metrics or seek to game the metrics system. Companies will need to be able to understand the complexities of their manufacturing operations at a holistic level to put data into context. As regulators adopt a more quantitative approach, companies will need to know what separates a quality facility from a failing one.
- ***Inspections are going global.*** FDA is ramping up inspections of foreign manufacturing sites.[13] As global regulators increasingly share data, a local problem at a critical manufacturing facility can quickly lead to sanctions by multiple regulators, freezing up a product's global sales.
- ***Uncertainty lies ahead. FDA's metrics-based approach to drug quality may well face major challenges prior to implementation.*** Some in the industry contend that FDA's authority to demand data and documents during inspections does not give it sufficient authority to demand the creation of specific metrics. Others claim FDA must issue its proposal through regulation instead of guidance. These hurdles may require FDA to reissue its guidance as a regulation, delaying full implementation of its new approach.

Implications: Benefits

- ***Metrics lead to improvements.*** The broader use of standardized metrics by the industry will support benchmarking across sectors, potentially leading to efficiencies and improvements. The use of trusted third-parties to collect, analyze and compare data will allow companies to leverage this information.
- ***The benefits of investing in quality are extensive.*** Companies with high levels of quality may benefit from fewer inspections, quicker drug approvals, fewer recalls, fewer plant shutdowns or slowdowns, and greater product availability. Higher levels of product quality and availability may improve margins, help ward off competition, and allow companies to negotiate pricing premiums for high-quality products.
- ***Breakthrough products require breakthrough quality.*** Industry and regulators' efforts to accelerate product approval is dependent upon a company having its manufacturing operations up and running to an acceptable degree.[14] A high-functioning quality operation may facilitate faster approvals, especially for breakthrough drugs, which rely on a rapid assessment of product quality.[15]
- ***Regulatory efficiency may benefit industry.*** A smarter allocation of resources will allow FDA to focus more on high-risk products. FDA has said it might allow companies with exemplary quality metrics to fast-track some manufacturing changes after a drug is approved, which could accelerate market access and reduce backlogs.[16] Inspections will become more uniform, though potentially more difficult as specialized inspectors, already familiar with the product and armed in advance with data, can hone in on problems more easily.

Endnotes

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About this Research

This report is based on information obtained between November 2015 and January 2016 through interviews with health quality experts, analyses of FDA compliance and quality databases, and a review of federal regulations, guidance and statutes related to drug quality. HRI also analyzed Warning Letters issued by FDA between January 1, 2010 and December 31, 2015, as well as facility inspection observations issued between January 1, 2011 and December 31, 2014.

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PwC's Health Research Institute (HRI) provides new intelligence, perspectives and analysis on trends affecting all health-related industries. The Health Research Institute helps executive decision makers navigate change through primary research and collaborative exchange. Our views are shaped by a network of professionals with executive and day-to-day experience in the health industry. HRI research is independent and not sponsored by businesses, government or other institutions. The HRI regulatory team tracks legislative and regulatory issues across the health industries and delivers the most timely, relevant and thought-provoking business insights in a concise, easily-accessible format.

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