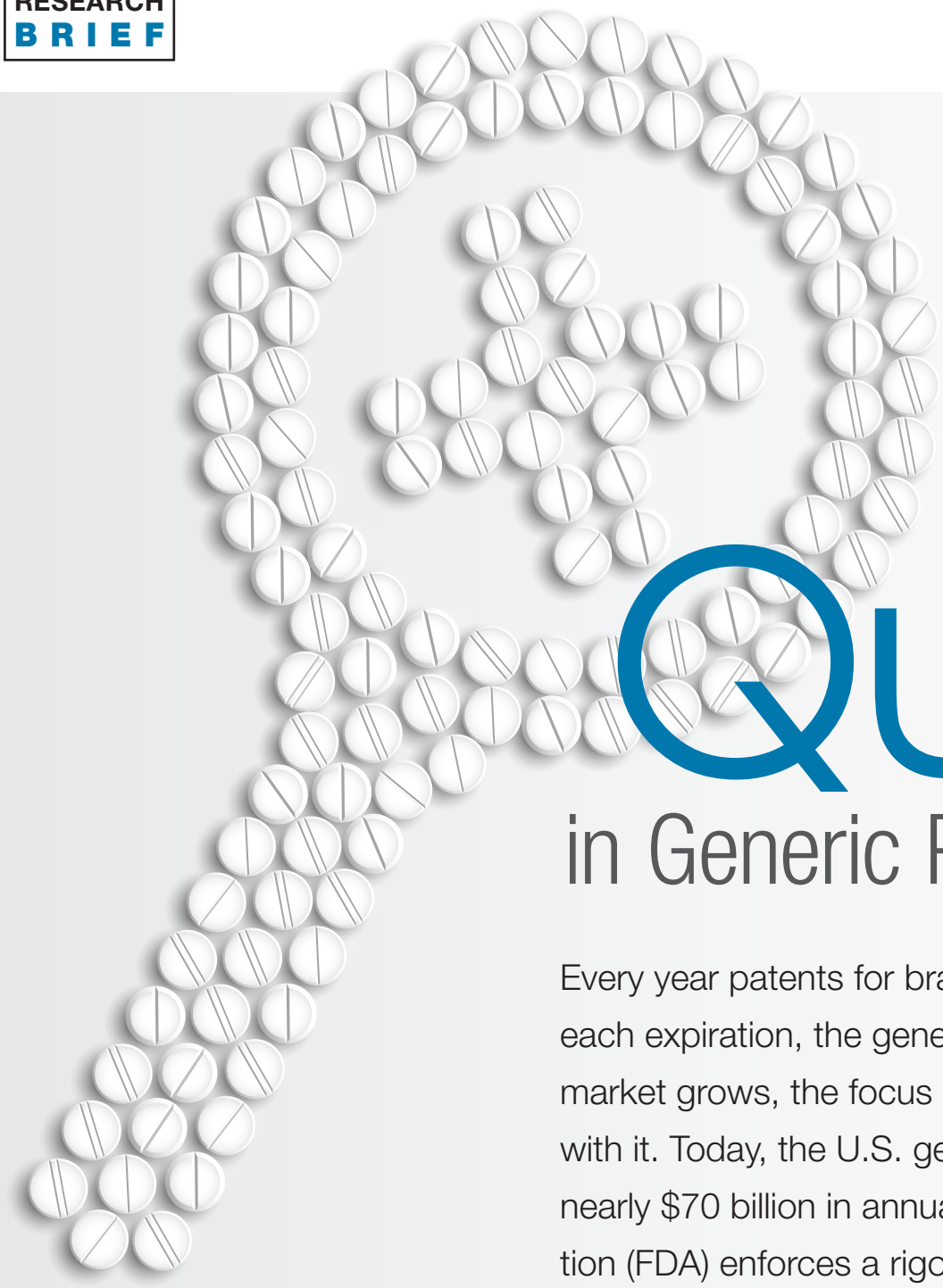
Life Sciences
RESEARCH
BRIEF

CLARKSTON CONSULTING



Quality in Generic Pharmaceuticals

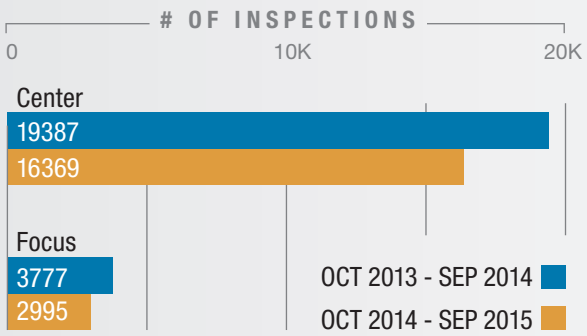
Every year patents for branded drugs continue to expire and with each expiration, the generics market expands ever larger. As the market grows, the focus on the quality and safety of generics grows with it. Today, the U.S. generic market is the largest in the world with nearly $70 billion in annual revenue.[1] The Food and Drug Administration (FDA) enforces a rigorous process for validating generics and ensuring their effectiveness. From the time of development through production, generics are held to the same high standard for Safety, Quality, Identity, Potency, and Purity (SQUIPP) as branded products.

In this fourth iteration of *Quality in Generic Pharmaceuticals*, Clarkston Consulting continues to examine the trends and shifts in the oversight and quality of the generic market through the analysis of inspection data from the FDA.

Today, the United States generic market is the largest in the world with nearly $70 billion in annual revenue.

This study examines FDA inspections by center, focus area, and result. The purpose of this study is to analyze and assess inspection data year over year with consideration to relevant industry trends over the past five years. The data analyzed for this report comes from the FDA's inspection database, specifically utilizing data from October 2013 to September 2014 compared to inspection data from October 2014 to September 2015.

Total Inspections by Center & Focus Area

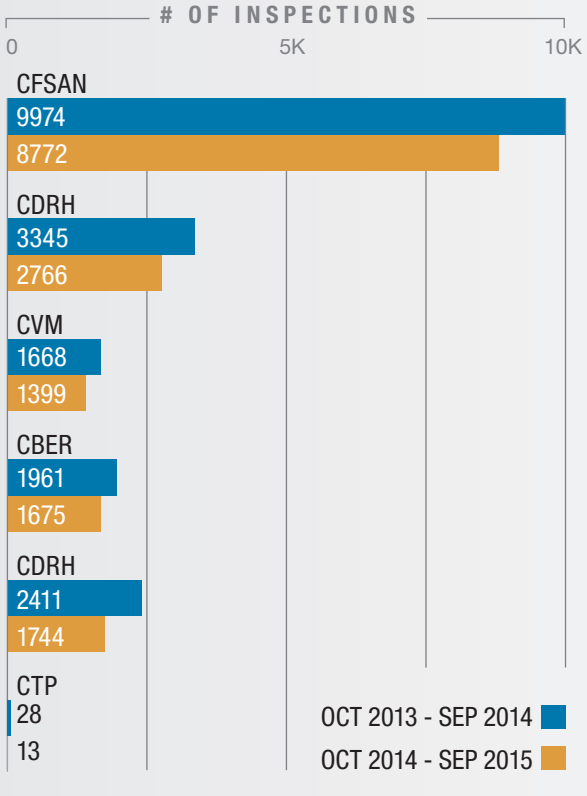


Overview

During the two-year period, there was a decrease in inspections across the entire FDA. Furthermore, there was a decrease in the focus of inspections most relevant to drug safety (e.g., branding & labeling, drug quality, vaccines, and postmarket surveillance).

Though we cannot offer specifics as to why fewer inspections have occurred, our research suggests several hypotheses. First, the FDA has been preparing for significant internal restructuring since 2012, with a substantial focus over the last two years on organizational realignment and process improvements. Along with these changes, the FDA has experienced a significant shortage of FDA inspectors. The combination of these factors is likely to have contributed to the decrease in the number of inspections. Second, with a refined risk-based approach and increased focus on data integrity issues, the FDA continued to increase the number of foreign plant inspections. Third, there were a number of mergers and acquisitions between 2012 and 2013. As it is typical for the FDA to perform an audit of the relevant facilities within six months to a year following an acquisition, a spike in inspections can be expected in that time period. Conversely, a lower number of M&A deals in subsequent years would lead to a decrease in post-merger inspections. Finally, whereas there was a decrease of 23 percent in overall inspection activity, there was a major decrease of 84 percent in inspections resulting in Official Action Required (OAR), which has already been low given the volume of drugs being produced. The comparisons and results from the analyses are detailed below.

Number of Inspections by Center



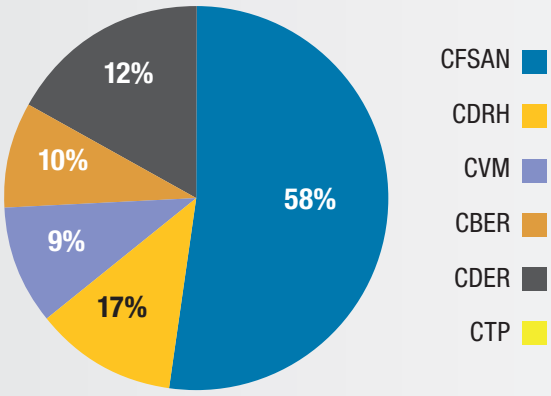
Breakdown of Inspections by Center

Consistent with previous editions of *Quality in Generic Pharmaceuticals*, the same six centers are covered in this assessment:

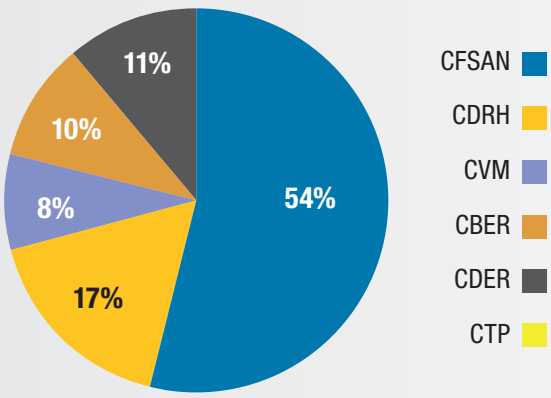
- Center for Food Safety & Applied Nutrition (CFSAN),
- Center for Devices & Radiological Health (CDRH),
- Center for Veterinary Medicine (CVM),
- Center for Biologics Evaluation & Research (CBER),
- Center for Drug Evaluation & Research (CDER), and
- Center for Tobacco Products (CTP).

Overall, there was a 28 percent decrease in the number of inspections conducted over the two-year time period with each center conducting fewer inspections. Specifically, the CDER – responsible for regulating

Number of Inspections by Center
OCT 2013 - SEP 2014



Number of Inspections by Center
OCT 2014 - SEP 2015



over-the-counter and prescription drugs, including biological therapeutics and generic drugs – had a 28 percent decrease in the number of inspections from year to year, from 2,411 inspections to 1,744. Overall, the number of inspections for the CDER, in relation to all other inspections conducted for other centers, dropped from 12 percent to 11 percent.

During this time period, the CDER was preparing for the January 2015 launch of the Office of Pharmaceutical Quality (OPQ).[2] The OPQ was created within the CDER to create a more streamlined process for improving product quality.[3] It was viewed as an upgrade from the FDA's "21st Century Initiative". The correlated assumption is that with this upgrade, there was a shift in priorities with the main focus being on the OPQ.

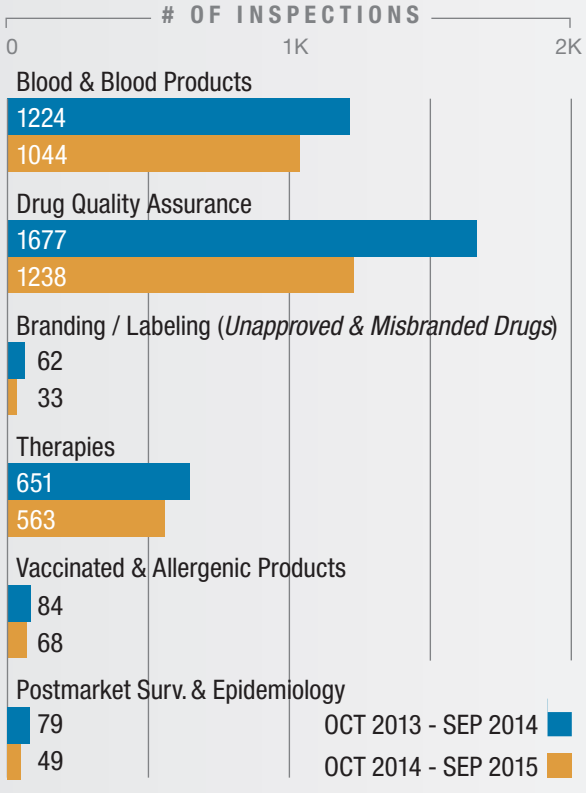
Breakdown of Inspections by Focus Area

As with the centers, there was a decrease in the number of inspections by focus area, which include:

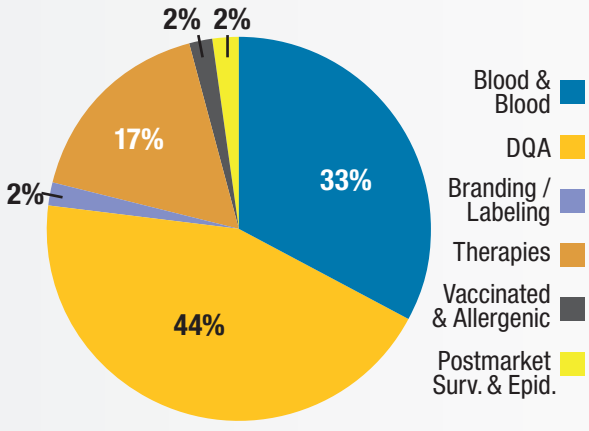
- Blood and Blood Products,
- Drug Quality Assessment (DQA),
- Drug Branding / Labeling,
- Human Cellular, Tissue, and Gene Therapies,
- Vaccinated and Allergenic Products, and
- Postmarket Surveillance and Epidemiology.

There was a 47 percent decrease in the number of inspections in Drug Branding/Labeling and a 38 percent decrease in Postmarket Surveillance and Epidemiology. These two areas saw the largest percent decrease in inspections. Drug Branding/Labeling went from 62 inspections to 33 inspections – of those 33 inspections, only three required official action.

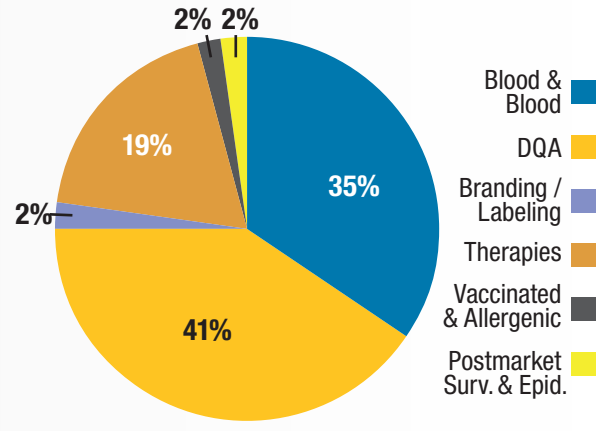
Number of Inspections by Focus Area

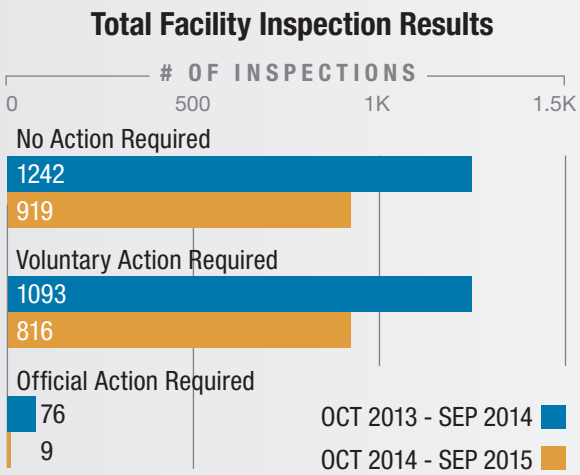


Number of Inspections by Focus Area
OCT 2013 - SEP 2014



Number of Inspections by Focus Area
OCT 2014 - SEP 2015





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Breakdown of Inspections by Results

When looking at the CDER results of the inspections between the two years, there is an overall trend that suggests an improvement in quality across manufacturers. This is shown in the numbers of incidents that resulted from the inspections. Specifically, only 9 of 1,744 inspections resulted in a need to respond to enforced recommendations, which is the biggest progress seen to date.

Spotlight on Inspection Results Classifications

Of the nine OAR inspections, there were no generic manufacturers cited by the FDA. The focus of the nine OAR inspections were:

- One in regards to Postmarketing Adverse Drug Experience and Current Good Manufacturing Practice (CGMP),
- Two for Bioresearch Monitoring of new drug studies,
- Three for Drug Quality Assurance focused on aseptic monitoring, *and*
- Three for Unapproved and Misbranded Drugs where manufacturers marketed unapproved prescription drugs for the treatment of medical conditions including where the drugs were approved by the FDA.

There were two common themes across all of the OARs. In most cases, the inspector focused on process and equipment. Most companies have detailed procedures and equipment management processes, nevertheless, inspectors invariably find areas where procedures are not being followed or equipment is not being managed properly.

Keeping in mind the results and general themes around the data, there are four elements to assist companies in managing inspections and demonstrating compliance.

Electronic Quality Management Systems

In order to maintain high quality standards, the industry is leveraging the Electronic Quality Management Systems (eQMS). With setup of the proper organization structures and processes, an eQMS can provide even the largest and most complex operations with a comprehensive, holistic view of real-time quality operations, as well as the all-critical “single version of the truth.” The establishment of common, global quality standards to be applied across the organization, regardless of the country or type of manufacturing facility, is a foundational principle of an eQMS implementation.

In even more advanced scenarios, component calibration and maintenance is done and verified without human intervention – a capability that will become more common as manufacturing volume needs increase and managing errors and costs becomes more critical.

An eQMS provides a consistent set of definitions to measure quality performance from one location to another. The eQMS aggregates vital statistics and information in a consistent manner based on key performance indicators that are both common across all divisions and unique to each location. This information is then presented at all levels of the organization in a dashboard format.

For anyone who has worked on either corporate or divisional quality, this knowledge can be an extremely powerful tool for analyzing patterns and trends as part of quality reviews, which in turn allows manufacturers to pursue systemic improvements directed at trouble areas and deploy support in advance of major downstream issues.

Equipment Calibration & Management

Observations related to the calibration, management, cleaning, and maintenance of equipment are some of the most common types of observations requiring official action by the FDA. To address and minimize these observations, generics manufacturers have worked to standardize not only the physical machinery and manufacturing environments but also the processes and systems used to manage maintenance and calibration data.

Most equipment-related observations can be avoided by implementing control systems that enforce discipline and consistency. State of the art equipment calibration and management systems provide interfaces between the system and the particular component being managed. The component cannot be brought online until a series of checks have been performed. This can include proper cleaning, calibration, and/or maintenance of the component or component parts. Security authorization capability also ensures that only authorized personnel with the proper background and training are allowed to perform such maintenance.

In even more advanced scenarios, component calibration and maintenance is done and verified without human intervention – a capability that will become more common as manufacturing volume needs increase and managing errors and costs becomes more critical.

Advances in Quality Control

Generics manufacturers have been quick to adopt technologies that are found readily in other industries, such as Process Analytical Technology and Statistical Process Controls. These technologies allow for the reduction of cost and error when evaluating quality throughout the manufacturing process. However,

Appraisal-focused QC is the more traditional approach, where testing is built-in along the way.

Prevention-focused QC allows personnel to analyze and address the root causes of issues, in an attempt to eliminate them all together in a systemic, rather than one-off basis.

the most advanced thinking in the area of Quality Control (QC) is seen in companies that split traditional QC functions: appraisal and prevention.

Appraisal-focused QC is the more traditional approach, where testing is built-in along the way.

Prevention-focused QC allows personnel to analyze and address the root causes of issues, in an attempt to eliminate them all together in a systemic, rather than one-off basis. Prevention-focused QC also looks for ways to reduce costs and eliminate activities that do not add value. These activities are often measured by the reduction in incidents, as well as the reduction in QC conversion cost (i.e., the cost of testing allocated per product volume or product revenue basis). Here are some characteristics of appraisal versus prevention-focused quality control:

APPRAISAL-Focused Quality Control	PREVENTION-Focused Quality Control
Typical of higher margin products	Typical of lower margin products
Focus is “after the fact”	Focus is “before the fact”
Focus is on recovery and minimizing the impact of the error	Focus is on avoidance and minimizing the occurrence of the error
Stop something wrong from “getting out the door”	Stop something wrong from “getting in the door”
Higher “switching costs” that discourage process innovation	Lower “switching costs” that encourage process innovation
Quality costs increase with product volume	Quality costs decrease with product volume
Quality is labor intensive	Quality is equipment intensive
Indicative of products with profit potential defined by time	Indicative of products with profit potential defined by brand

Unit Dose Serialization & Traceability

Unit Dose Serialization and Traceability Serialization have been major areas of focus for pharmaceutical companies over the past several years due to both pending and enacted legislation in the U.S. and abroad. Serialization is defined as the ability to put a unique identifier on the saleable dose of a pharmaceutical product. Traceability is the ability to then trace that product through distribution and ultimately to dispensing at locations such as pharmacies, hospitals, and clinics.

Ultimately, track and trace will allow generics companies to plan and measure their ability to impact the global human health condition.

Most pharmaceutical companies have conducted some version of a pilot activity with a plan to implement serialization, traceability, or both based on the markets where they manufacture and ultimately sell. However, generics firms spearheaded this effort. Leading generics companies do not see track and trace as just a compliance item, but rather a way to further differentiate their products, engage with patients, and ultimately plan and measure their ability to impact the global human health condition. Before and after pictures can be created and pharmaceutical companies can work together with distributors and caregivers to ensure the right medications get to the right patient populations at the right times. If the saleable unit dose can be traced through the supply chain to the end consumer, companies can use this information to analyze disease states for given geographies/patient populations. Visibility into the entire supply chain helps companies further improve their compliance, especially in case of recalls, while being able to showcase opportunities to reduce costs. Beyond all of the regulatory discussion, this is the real power and promise of track and trace. Generics companies with global distribution of a wide variety of products are unique in that they are the only companies with product portfolios and supply chain capabilities positioned to deliver on this promise.

In Conclusion

This research brief has analyzed and assessed the quality in generics utilizing FDA inspection data broken down by center, focus area, and result from October 2013 to September 2014 and October 2014 to September 2015. As in previous years, the data shows a continuing upward trend in foreign inspections, a decrease in inspections of U.S. domestic manufacturing companies, and continual internal changes to the FDA. In general, there seems to be a permanent shift of fewer inspections taking place and less official action needed.

As the patent expiry of even more branded products looms in the coming years, the generic market is expected to experience persistent growth. With this growth, the quality and efficacy of generic drugs will remain a substantial area of focus for both regulators and consumers.

References

1 IBISWorld. “Generic Pharmaceutical Manufacturing in the US: Market Research Report.” Abstract. N.p., n.d. Web. April 2016.

2 U.S. Food and Drug Administration. "Frequently Asked Questions about CDER's Quality Initiative and Office of Pharmaceutical Quality.” N.p., n.d. Web. 3 August 2015.

3 U.S. Food and Drug Administration. “Office of Pharmaceutical Quality.” N.p., n.d. Web. 4 August 2015.

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Clarkston Consulting provides management, operations, and implementation consulting services for life sciences and consumer products companies. Clarkston has achieved a 15-year average client satisfaction rate of 95% by continuously pushing for success for our clients, our consultants, and our company. For more information, please visit ***www.clarkstonconsulting.com****.*