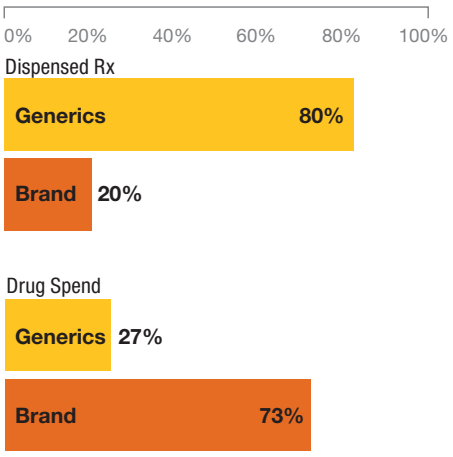
CLARKSTON CONSULTING

Quality in Generic Pharmaceuticals

It has been almost a year since Clarkston first released its study on Quality in Generic Pharmaceuticals. Within that year, the industry has seen several pivotal events. The Generic Drug User Fee Amendments of 2012 (GDUFA) was signed into law. There was much discussion of quality and bioequivalence, given some high profile cases that made headlines. Generic pharmaceuticals filled 80 percent of the prescriptions dispensed in the U.S., but consumed just 27 percent of total drug spend.[1] And industry and regulators have continued to work toward finalizing the pathway for U.S. biosimilars – a critical event that will increase patient access to an entirely new type of cost effective life enhancing medication.

It is with this backdrop that we now release the second installment of the Quality in Generic Pharmaceuticals report. What has changed is an increased focus on inspections of foreign facilities. These still make up a small fraction of the overall drug facility inspections, but have increased some 70 percent from the data used to create this analysis just one year ago. What remains the same is the very small volume to incident ratio that demonstrates the clear safety and efficacy of generic drugs. And finally, what has dynamics of both permanence and change, are the best and emerging practices that generic pharmaceutical companies are using to ensure they maintain their high standards of quality as their distribution base covers an ever larger and more global patient population.

Dispensed Rx vs. Drug Spend Percentages[1]



The data used for this analysis comes from the FDA's inspection database.[2] Our previous report used the data set covering inspection activity for the two years from October 2008 through September 2010. In refreshing this report, the FDA has added inspection results for the two year period ending September 2012. Comparisons between these time periods and conclusions drawn from the analysis are detailed below.

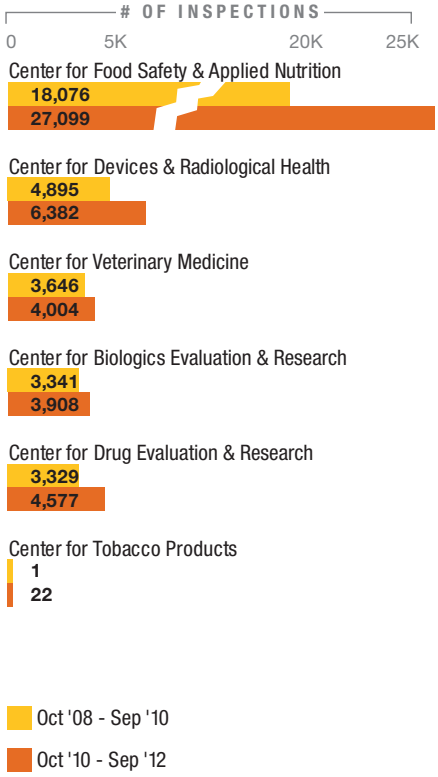
Breakdown of Inspections by Center

FDA inspection activity across all centers increased between the periods of comparison, with food showing the greatest increase and veterinary medicine showing the least. Like any other large organization, the FDA works to align financial and personnel resources to the areas of need that they have in order to fulfill their mission. At a macro level, there were clear increases in the amount of inspection activity in the areas of food, drugs, and medical devices. And whereas inspections of foreign drug/biologic manufacturing facilities have increased, it will be critical for the FDA to continue to focus resources and energy on the global supply chain, including API manufacturers, contract manufacturers, and packagers. Hopefully the increased funding from GDUFA, plus better analytics and operational efficiencies at the FDA, will help in this regard.

Drug and Biologics Inspections by Focus Area

FDA inspection activity for the primary categories of drug and biologics inspections increased approximately 27 percent between the periods. The largest percentage increases were in the areas of Drug Quality Assurance and Drug Branding/Labeling. In assessing this data we begin to see the trends related to generic pharmaceutical quality. Whereas the number of drug quality assurance inspections increased by 41 percent, the number of incidences where an inspection of a generic facility resulted in some kind of official action being required actually decreased, as outlined in the next section.

Inspections by Center



Drug & Biologics Inspections by Focus Area

Drug and Biologics Facility Inspection Results

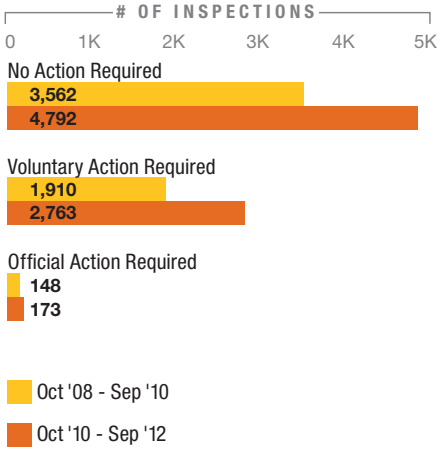
FDA inspection activity for pharmaceutical manufacturing facilities showed a 22 percent increase in "No Action" and "Voluntary Action" inspection results, with a decrease of two percent in "Official Action" inspection results. Of the 173 inspections resulting in "Official Actions Required," only 23 of these were issued to manufacturers of generic drugs. This is a two percent decrease on a percentage basis from the 25 issued between October 2008 and September 2010.

Spotlight on Inspection Results Classifications

Of the 7,728 drug related quality inspections conducted by the FDA between October 1, 2010 and September 30, 2012, only 23 resulted in requests for Official Action by a generics manufacturer (even though generics manufacturers make a disproportionately greater volume of the drugs we take than do traditional pharmaceutical companies). What are the three kinds of actions that the FDA can indicate coming out of an inspection?

- *NAI. No Action Indicated. No objectionable conditions or practices were found during the inspection (or the significance of the documented objectionable conditions found does not justify further FDA action).*
- *VAI. Voluntary Action Indicated. Objectionable conditions were found and documented but the district and/or center is not prepared to take or recommend any regulatory actions (advisory, administrative, or judicial) since the objectionable conditions do not meet the threshold for regulatory action. The district may use an Untitled Letter, Regulatory Meeting or other communication with responsible individuals to inform the establishment of findings that should be corrected. A written response by the establishment may be an option, but is not necessary. Any corrective action is left to the establishment to take voluntarily.*
- *OAI. Official Action Indicated. Objectionable conditions were found and the district and/or center is prepared to take or recommend regulatory actions (advisory, administrative, or judicial) since the objectionable conditions do meet the threshold for regulatory action. Typically, an OAI classification should be made only if an FDA-483 has been issued and the documented evidence supports the action recommended.*

Drug & Biologics Facility Inspection Results



Official Action Required Percentages

Summary Results

Within the 173 FDA inspections requiring some form of official action (including the 23 inspections of generics manufacturers), FDA observations typically fell into one of the following categories, with Investigations, Equipment, and Quality Control representing the most frequently cited.

- Complaint handling
- Computer system validation
- Equipment
- Investigations
- Laboratory records
- Material handling
- Microbiology
- Packaging / labeling
- QC organization
- QC testing
- Reporting
- Stability
- Written procedures

Generics manufacturers have worked to minimize these types of observations by taking a proactive approach typically referred to as Quality by Design, or QbD. Quality by Design applies basic principles of building in processes and controls to ensure repeatable results that meet specifications. More emphasis is placed on "preventing" quality issues in the first place, rather than "catching" them at the time of batch release. The concept of Quality by Design is not new. It stretches back over 60 years found in industries that are usually either (1) heavily regulated due to the need for precision manufacturing, or (2) that manufacture higher volume/lower margin products.

Branded pharmaceutical companies traditionally enjoyed such high margins that they used the "addition of people" rather than the "improvement of processes" to ensure quality. But generics clearly fall into both categories above, making Quality by Design a relevant and necessary set of principles from which to operate.

By using Quality by Design principles, here are some of the ways that generic pharmaceutical companies are minimizing many of the quality issues that are more prevalent within their branded counterparts:

- Electronic Quality Management Systems
- Equipment Calibration and Management
- Advances in Quality Control
- Unit Dose Serialization and Traceability

Quality by Design, or QbD, applies basic principles of building in processes and controls to ensure repeatable results that meet specifications.

Electronic Quality Management Systems

Generics have adopted the use of Electronic Quality Management Systems or 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 and most important "single version of the truth." The establishment of common, global quality standards to be applied across the organization, regardless of the type of manufacturing facility or country, is how eQMS starts.

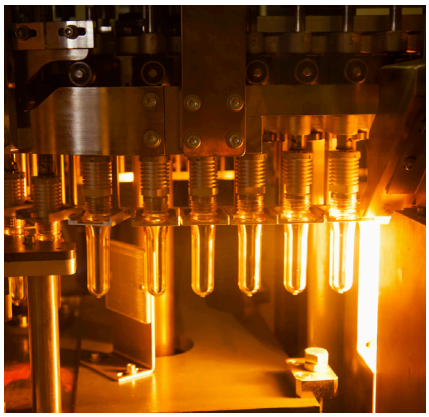
These guidelines, often called "Division Directives," are then built upon at the site/location level. The eQMS then aggregates vital statistics and information in a consistent fashion based on key performance indicators that are both common (from the Division Directives) and unique to a particular location. The eQMS provides a consistent set of definitions such that statistics mean the same thing from place to place. 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, they can see how this knowledge can be an extremely powerful tool. The eQMS allows for patterns and trends to be analyzed. Systemic improvements can be directed to trouble areas. Resources can also be deployed in advance of major downstream issues being realized.

The eQMS allows for patterns and trends to be analyzed. Systemic improvements can be directed to trouble areas. Resources can also be deployed in advance of major down-stream issues being realized.

Equipment Calibration and Management

As stated above, observations related to the calibration, management, cleaning, and maintenance of equipment are one of the most common types of observations requiring official action by the FDA. To address and minimize this, 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/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.

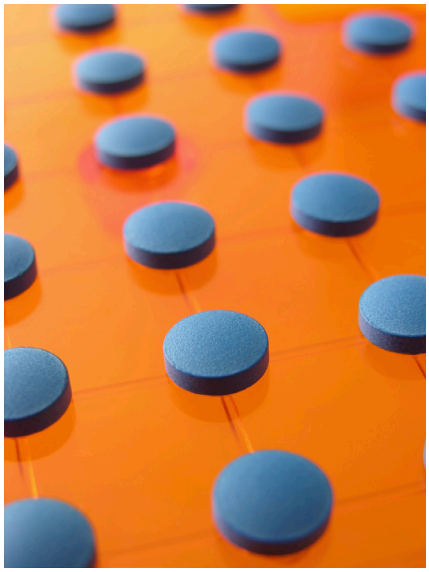
Advances in Quality Control

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 in cost and error of evaluating quality throughout the manufacturing process. However, the most advanced thinking in the area of Quality Control is seen in companies where they are splitting the traditional QC function into two distinct areas of focus: 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 the root causes of issues and deal with them, in an attempt to eliminate them all together in a systemic, rather than one-off basis.

Prevention-focused QC also looks for ways to eliminate non-value added activities and reduce costs. These activities are often measured on 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 in 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



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

Unit Dose Serialization and Traceability

Serialization and traceability have been major areas of focus for pharmaceutical companies over the past several years due to both pending and enacted legislation in the US and abroad. Serialization is defined as the ability to put a unique identifier on the saleable dose of 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.

Most pharmaceutical companies have done some kind of pilot activity with a plan to implement serialization or traceability or both based on the markets where they manufacture and ultimately sell. But leading generics companies see track and trace as not just a compliance item, but rather a way to further differentiate their products, engage with patients, and ultimately have a way to plan and measure their ability to impact the global human health condition. If the saleable unit dose can be traced through the supply chain to the end consumer, analyses of disease states in given geographies/patient populations can be done. Before and after pictures can be created, and pharmaceutical companies and caregivers can work together to ensure the right medications get to the right patient populations at the right times.

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, what often makes headlines are the one-off incidents that surprise us and capture our attention. What should also make headlines is an analysis of the facts. The facts show that generic drugs fill 80 percent of the prescriptions dispensed in the U.S., but consume just 27 percent of the total drug spend. The facts also show that generics companies have an extremely low number of official actions required based on the results of FDA quality inspections. And finally, the facts show that the best generics companies will continue to make manufacturing excellence an utmost priority, ultimately reaping the benefits of increased global reach and market share, just as patients will reap the benefits of the reduced costs of healthcare overall.

The Facts are Clear

- Generic drugs fill 80% of the prescriptions in the U.S., but consume just 27% of total drug spending
- Generics companies have an extremely low number of official actions required based on the results of FDA quality inspections
- The best generics companies will continue to prioritize manufacturing excellence

References:

1 http://www.gphaonline.org/GPhA_Reports/GPhA_2012_Annual_Report/

2 http://www.fda.gov/iceci/enforcementactions/ucm222557.htm

Observations Defined

- **Complaint Handling**. *Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product.*
- **Computer System Validation**. *Failure to maintain appropriate validation of computer or other automated processes used to perform calculations in connection with drug manufacturing or laboratory analysis.*
- **Equipment**. *Written procedures are not established and followed for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.*
- **Investigations**. *Failure to thoroughly investigate the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed.*
- **Laboratory Records**. *Laboratory records are deficient in that they do not include a complete record of all data obtained during testing.*
- **Material Handling**. *Failure to follow written procedures describing the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures.*
- **Microbiology**. *Failure to follow appropriate written procedures designed to prevent microbiological contamination of drug products to be sterile.*
- **Packaging / Labeling**. *Failure to include a specimen or copy of each approved label and all other labeling in the master production and control record.*
- **QC Organization**. *The quality control unit lacks responsibility to approve and reject all procedures or specifications impacting on the identity, strength, quality, and purity of drug products.*
- **QC Testing**. *E.G., Drug products failing to meet established quality control criteria are not rejected.*
- **Reporting**. *E.G., Failure to submit NDA/ANDA field alert reports (FARs) in the required time frame, within 3 working days of becoming aware of information concerning any significant chemical, physical, or other change or deterioration in the distributed drug product.*
- **Stability**. *Failure to assure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use by establishing an expiration date as determined by appropriate stability testing.*
- **Written Procedures**. *Your firm does not have adequate written procedures for production and process controls designed to assure that the drug products you manufacture have the identity, strength, quality, and/or purity they purport or are represented to possess.*

For More Information

To continue the conversation, contact Jessica Eure at jeure@clarkstonconsulting.com.

CLARKSTON CONSULTING

Headquarters
2655 Meridian Parkway
Durham, NC 27713
Phone: 800.652.4274
Fax: 919.484.4450

www.clarkstonconsulting.com

About Clarkston Consulting

Clarkston Consulting is a different kind of management and technology consulting firm. We deliver a unique experience for market leaders within the Consumer Products and Life Sciences industries. Considering professionalism, expertise, and value as prerequisites, we take service a step further through our unyielding commitment to the success of people as individuals, both our clients and our employees. By combining integrity, adaptability, and a whatever-it-takes attitude, we have achieved an extremely high rate of referral and repeat business and a 10-year average client satisfaction rating of 97%.