Improving the Quality of Generic Drugs

White Paper
Improving the Quality of Generic Drugs

White Paper

January 2015

Contributors

Robert G. Bell, Drug and Biotechnology Development, LLC
Anthony DeStefano, Consultant, University Research Co., LLC (URC)
Martin Jeiven, Jeiven Pharmaceutical Consulting, Inc. (JPC)
Neeraj Kak, University Research Co., LLC (URC)
Stacy Kancijanic, University Research Co., LLC (URC)
Anil Kaul, Oklahoma State University, Center for Health Sciences (OSU)
Refoloe Matji, University Research Co., LLC (URC)
Giorgio Roscigno, Network of Excellence in People Centered Testing and Treatment (NEXT)
Ashutosh Sharma, Jeiven Pharmaceutical Consulting, Inc. (JPC)
Alisha Smith-Arthur, University Research Co., LLC (URC)
Vince Suneja, TwoFour Insight Group
Barbara Turner, University Research Co., LLC (URC)
# Table of Contents

Acronyms ................................................................................................................. iv

**Purpose and Scope** ............................................................................................... 1

**Background and Introduction** ............................................................................... 1
  - US Situation – Strong Drug Regulatory Environment ........................................ 2
  - US Situation – Robust Supply Chain ................................................................. 2
  - Global Considerations – Issues for Receiving Countries .................................... 3
  - India – A Key Contributor to the Generic Industry .............................................. 4
  - Root Cause Discussion – Drivers To and Away From Quality ............................. 5

**Key Stakeholders** ................................................................................................. 7
  - Policy Makers .................................................................................................... 7
  - Programmatic Suppliers ..................................................................................... 7
  - Industry ............................................................................................................. 8
  - Civil Society ..................................................................................................... 8
  - Auditors ........................................................................................................... 8

**Best Practices – The Prevention and Remediation of Issues** ............................... 9
  - Quality Management System ........................................................................... 9
  - Best Practices – Some Detailed Examples ....................................................... 9
  - cGMP Training .................................................................................................. 9
  - Auditing ............................................................................................................ 10
  - Warning Letter Remediation .......................................................................... 10

**Benefits and Impact** ......................................................................................... 11

**A Single Quality Standard?** ............................................................................ 11

**Concluding Remarks** ...................................................................................... 12

**References** ........................................................................................................... 13
## Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAPS</td>
<td>American Association of Pharmaceutical Scientists</td>
</tr>
<tr>
<td>ANDA</td>
<td>Abbreviated New Drug Application</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>ASTM</td>
<td>American Society for Testing and Materials</td>
</tr>
<tr>
<td>CAPA</td>
<td>Corrective and Preventive Action</td>
</tr>
<tr>
<td>CDSCO</td>
<td>Central Drugs Standard Control Organization, India</td>
</tr>
<tr>
<td>cGMP</td>
<td>Current Good Manufacturing Practice</td>
</tr>
<tr>
<td>DIA</td>
<td>Drug Information Association</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GDUFA</td>
<td>Generic Drug User Fee Amendments of 2012</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use</td>
</tr>
<tr>
<td>ISO</td>
<td>International Organization for Standardization</td>
</tr>
<tr>
<td>NDA</td>
<td>New Drug Application</td>
</tr>
<tr>
<td>NOSQ</td>
<td>Not of Standard Quality</td>
</tr>
<tr>
<td>OSU</td>
<td>Oklahoma State University</td>
</tr>
<tr>
<td>PDA</td>
<td>Parenteral Drug Association</td>
</tr>
<tr>
<td>PQM</td>
<td>Promoting the Quality of Medicines, USAID</td>
</tr>
<tr>
<td>PQRI</td>
<td>Product Quality Research Institute</td>
</tr>
<tr>
<td>QA</td>
<td>Quality Assurance</td>
</tr>
<tr>
<td>QbD</td>
<td>Quality by Design</td>
</tr>
<tr>
<td>QC</td>
<td>Quality Control</td>
</tr>
<tr>
<td>QMS</td>
<td>Quality Management System</td>
</tr>
<tr>
<td>RLD</td>
<td>Referenced Listed Drug</td>
</tr>
<tr>
<td>SFFC</td>
<td>Spurious/Falsely-Labeled/Falsified/Counterfeit</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
</tr>
<tr>
<td>URC</td>
<td>University Research Co., LLC</td>
</tr>
<tr>
<td>USAID</td>
<td>U.S. Agency for International Development</td>
</tr>
<tr>
<td>USP</td>
<td>U.S. Pharmacopeial Convention</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Purpose and Scope

This white paper reviews the present state, current challenges, and recommended best practices for improving the quality of prescription pharmaceuticals, with an emphasis on generic pharmaceuticals. This white paper covers the following topics:

- Quality Management Systems
- Quality Control
- Public health impact
- Regulatory guidelines
- Auditing/Inspections

This white paper addresses key policy issues, best practices, and key challenges around the pharmaceutical value chain that has an impact on quality of pharmaceuticals available to patients. This white paper also discusses the key stakeholders involved in the quality of medicines (i.e. regulatory bodies, policymakers, and drug manufacturers) and recommendations for future actions.

Background and Introduction

Pharmaceuticals, especially generic drugs are a key component to containing healthcare costs around the world, including the United States (US). It is estimated that generic drugs saved the US healthcare system approximately $1.2 trillion between 2003 and 2012.¹ The global market for generic drugs was approximately $150 billion in 2013 and is growing at a compounded annual growth rate of 8.4%.² Over the next five years, it is estimated that generic drugs in emerging markets will grow at a rate of 15-20% and in mature markets they will grow at a rate of 6-10%.³ This growth is fueled by the anticipated loss of patent protection between 2010 and 2017 of blockbuster drugs with sales of over $150 billion.⁴

The robust growth of the generic drug industry has been based on the premise that generic drugs provide the same efficacy and safety as branded drugs, but at a substantially reduced cost. In the U.S., equivalent safety and efficacy is ensured by the submission of an abbreviated new drug application (ANDA) or a 505(b)(2) application to the Food and Drug Administration (the “FDA”), who verifies that the generic or 505(b)(2) drug has bioavailability that is equivalent to that of the Reference Listed Drug (“RLD”) prior to granting marketing authorization to the applicant. Maintenance of equivalent and consistent safety and efficacy hinges in the long run on consistent quality and manufacturing. Consistent quality is maintained by management commitment, a strong quality management system that is continuously updated and works in close coordination with manufacturing and other disciplines within the company, adherence to the principles of current Good Manufacturing Practices (cGMPs) and routine audits, both internal and by FDA to assure compliance and point out issues needing attention.

Currently, an estimated 80% of active pharmaceutical ingredients (APIs) and 40% of drug products are manufactured overseas, primarily in India and China.⁵ For US physicians, consumers and payers to have confidence in the quality of drugs, whether generic or branded, it is important that inspection findings both in the US and overseas drug manufacturing facilities demonstrate compliance with cGMPs and that drug substances and drug products are produced with the expected quality and consistency demanded by the USFDA and patients.

Much of the drive to move drug manufacturing overseas, especially generic drug manufacturing comes from the desire to reduce costs in an effort to produce drug products at the lowest practical cost in light of the commercial market in the U.S. procuring generic drugs on essentially a commodity basis. Generics are now on the market almost the day after the brand drug patent expires or successfully challenged and the first to challenge a patent listed in the so-called Orange Book covering the brand reference listed drug (RLD) is eligible for a six-month exclusivity period. This exclusivity period may be shared with an authorized generic (an unbranded version of the brand product that the brand company typically licenses out to a partner) or other ANDA or 505(b)(2) filers. After this time, other generic bioequivalent versions are allowed on the market and that typically results in a rapid decrease in the price of generic drugs. The net result for small molecule drugs is that within a year or two after generics come on to the market for a particular brand drug, the generic drug is priced at a commodity level rather than at the level of a brand pharmaceutical that may have attributable cost over one billion dollars to bring onto the market.

The introduction of generics in the US has been critical to ensuring that important medicines are available at an affordable cost. More broadly, affordable drugs have improved public health globally, as drugs become available that were previously financially out of the reach of many people in both developing and developed countries. Similar to other industries, pharmaceutical companies in India and China have been able to supply pharmaceutical raw materials and finished drug products at prices that are not typically available for the same generic drug product manufactured in the US or another developed country.
However, in order for the sales of generic drug products to remain strong, it is critical that regulatory agencies, physicians and consumers have confidence in the ongoing quality of these products. The quality of a drug is often critical to its performance. In the U.S., a drug might be substandard (e.g., variable potency, variable levels of impurities), misbranded (contains a false or misleading label), adulterated (inadequate manufacturing controls) or counterfeit (without authorization has a trademark, trade name or other mark owned by the legitimate manufacturer of the product). Of particular interest are sterile (e.g., IV) drugs, where lack of sterility can be life threatening, and drugs with narrow therapeutic indices (e.g., Digoxin or Warfarin) that require batch-to-batch consistency of the product in order to ensure an appropriate response. If physicians or consumers lose confidence in generic drugs, they would essentially lose confidence in USFDA, which would result in potentially causing a shift back toward branded drugs, increasing overall costs and decreasing the rate of growth in the volume and profit of generic drugs, to the detriment of both the generic industry and public health.

**US Situation – Strong Drug Regulatory Environment**

The regulatory landscape regarding generic drug quality is essentially identical to that of the branded-drug manufacturer. The chart below lists some of the key quality attributes that FDA looks for. As can be seen, the expectations are identical whether the drug product is a branded or generic. FDA inspects facilities that produce APIs and drug products prior to approval of the application, to ensure that the firm is capable of meeting the commitments of the application and can manufacture the product consistently. In addition, the law allows FDA to audit firms unannounced, on a biennial basis, and conduct unannounced audits at any time for cause. Typically, the thoroughness of the audits and knowing that there will be unannounced audits at a minimum of every other year requires firms to develop robust Quality Management Systems that ensure that their standards regarding drug manufacturing facilities are at or above the minimum cGMP expectations. This is not always the case – there have been several instances involving both oral medications and sterile medications where FDA has found serious quality/compliance issues in the last few years for both brand and generic drug manufacturers. Some of these issues have led to extensive product recalls and loss of business for the companies involved.

**US Situation – Robust Supply Chain**

The number of cases where the drug is legally in the supply chain yet may be substandard is difficult or impossible to quantify since there is not a systematic check of individual lots of materials that enter the supply chain either nationally or globally. However, protection of the supply chain remains a major concern in the US as witnessed by recent testimony by Howard Sklamberg, Deputy Commissioner for Global Regulatory Operations and Policy at FDA to the US House of Representatives. In contrast, the number of cases of counterfeit material, either generic or brand, found

**Table 1. Brand and Generic Drug Product Quality Attributes**

<table>
<thead>
<tr>
<th></th>
<th>Brand Name Drug</th>
<th>Generic Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>For reformulations of a brand-name or generic versions of a drug. FDA reviews data showing the drug is bioequivalent to the one used in the original safety and efficacy testing.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA evaluates the manufacturer’s adherence to good manufacturing practices before the drug is marketed.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA reviews the active and inactive ingredients used in the formulation before the drug is marketed.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA reviews the actual drug product.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA reviews the drug’s labeling.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Manufacturer must seek FDA approval before making major manufacturing changes or reformulating the drug.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Manufacturer must report adverse reactions and serious adverse health effects to the FDA.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA periodically inspects manufacturing plants.</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>FDA monitors drug quality after approval.</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
for materials entering the US through the regulated supply chain remains very low, with Avastin® (Bevacizumab) perhaps being the most well-known example of a counterfeit product that was able to enter the legitimate supply chain. Nevertheless, a lack of confidence in the reliability of the supply chain, whether from counterfeit, substandard, misbranded or adulterated drugs, can cause physicians to change their prescribing habits, and cause patients to be reluctant to take certain generic drugs, potentially leading to increased costs or drug supply disruption.

Global Considerations – Issues for Receiving Countries

While the Avastin® (Bevacizumab) case represents one of the most prominent rare breaches of the US drug supply chain, the same is not true across the globe. Many developing countries have drug regulatory environments and supply chain controls that are far weaker than those in the International Conference on Harmonization (ICH) countries (i.e., US, Europe and Japan). This makes them vulnerable to counterfeit or suppliers of intentionally-not of standard quality (“NOSQ”) drugs that are selling worthless material or otherwise legitimate companies that are trying to procure materials from suppliers that are engaged in such illegitimate activity. The percentage of drugs (APIs and finished drug products) distributed globally that are counterfeit or intentionally NOSQ is unknown. In addition, it is nearly impossible to have international concurrence on the definition of terms such as counterfeit, substandard, spurious, falsified or adulterated that would be required to identify the real extent of the problem. However, it is estimated that the incidence of spurious/falsely-labeled/falsified/counterfeit (SFFC) drugs is less than 1% of market value for industrialized countries with effective regulatory systems, but in African countries, in parts of Asian, Latin American countries and countries in transition, the incidence of SFFC drugs may be much higher.12

The drug regulatory, quality and supply chain controls are critical to ensure patient safety, however, the lack of oversight and enforcement due to resource constraints continues to grow and cause a great deal of harm. This is an area whose control is typically managed by regulators or law enforcement, both country specific and global, and by brand pharmaceutical companies with an interest in maintaining the integrity of their brands. There are significant roles for global health professionals in this arena, especially as it relates to the training and equipping of regulators to find and combat substandard drugs. An example is the United States Pharmacopeia (USP)/USAID Promoting the Quality of Medicines (PQM) program, aimed at helping developing countries address issues related to poor quality medicines through training of regulators, testing of medicines in the market and sharing standards. Other examples include private consultants skilled in analytical technologies and regulatory science and organizations such as the UL Eduneering program (www.uleduneering.com).

The factors that encourage the intentional distribution of spurious or falsified drugs are many. Some identified by the WHO13 include:

- Lack of political will and commitment – Minimizing the problem requires strong government will and commitment to establish and operate a strong national drug regulatory authority. Without a strong regulatory authority, stopping the entrance and penetration of SFFC drugs is very difficult.
- Lack of appropriate drug legislation – In many countries, sanctions imposed on suppliers of spurious drugs are, in most cases, no deterrent. The absence of deterrent legislation encourages these suppliers since there is no fear of being apprehended and prosecuted.
- Weak enforcement and penal sanctions – Lenient punishments for offenses tend to encourage criminal activities such as medicines’ falsifying, particularly when the penalties for falsifying non-medical products are more severe.
- Absence of or weak drug regulation – Ensuring that drugs are safe, efficacious, and of high quality requires competent national drug regulatory authorities. At present, out of the 191 WHO member states about 20% are known to have well developed drug regulation. Of the remaining member states, about 50% implement drug regulation at varying levels of development and operational capacity. The remaining 30% either have no drug regulation in place or a very limited capacity to regulate drugs.
- Corruption and conflict of interest – The efficiency of personnel is adversely affected by corruption and conflict of interest resulting in laws not being enforced and criminals not being arrested, prosecuted and convicted for their crimes.
- Demand exceeding supply – In situations where demand for medicines exceeds supply, criminally minded people profit by manufacturing and distributing spurious medicines as a substitute for genuine medicines.
- High prices of medicines – When prices of medicines are high and price differentials between identical products exist, there is a greater incentive to supply cheap spurious medicines.
- Inefficient cooperation between stakeholders – Cooperation between regulatory authorities, police, customs services and the judiciary is essential for effective control of the national drug market and enforcement of drug legislation.
Equally, the cooperation of the pharmaceutical industry, wholesalers, and retailers to report to the national drug regulatory authority cases of SFFC drugs is necessary in combating SFFC drugs.

- **Lack of regulation by exporting countries and within free trade zones** – Pharmaceuticals made for export are not regulated by many exporting countries to the same standard of quality as those produced for domestic use.

- **Trade through several intermediaries** – Currently, trade in pharmaceuticals often takes place through one or more intermediate countries or trading houses. Activities in trading houses may sometimes involve repackaging and re-labeling which may be carried out without any controls under conditions that do not comply with good manufacturing practices’ requirements. This is exacerbated by the lack of an interoperable track and trace system for pharmaceuticals.

Tackling the issues related to the encouragement and enabling of the sale of spurious or substandard drugs can be seen to be a very complex task involving a wide range of stakeholders ranging from governments, pharmaceutical companies, to pharmacies, and even nongovernmental agencies and patient advocacy groups. Some specific strategies are discussed later in the paper.

India – A Key Contributor to the Generic Industry

India is a key contributor to the success of the global generic drug industry. Figure 1 shows some highlights of India’s contributions to global pharmaceuticals.\(^\text{14}\)

Clearly many firms in India have a very high commitment to quality systems, quality products, and the production of first-rate drug substances and drug products.

Unfortunately, several firms have recently come under the scrutiny of developed country regulators that has led to a focus on the quality of APIs and finished drug products coming from India. One example is the increase in FDA audits conducted in India over the last two years, in part as a result of the FDA Safety and Innovation Act of July, 2012.\(^\text{15}\) The user fees collected as part of the Generic Drug User Fee Amendments of 2012 (GDUFA) have allowed FDA to increase its overseas inspections, moving towards parity in inspections between firms in India and the US and required identification of facilities involved in the manufacture of generic drugs and associated APIs. FDA has also promised that by 2017, risk-based biennial inspections similar to what occur now in the US would be the norm in other countries as well.

**Figure 1. India’s Pharma Market**

- As per ‘Pharma vision 2020’ the Indian government aims at making India a global leader in end-to-end drug manufacture
- The Indian government plans to set up a USD 640M VC fund to boost drug discovery and strengthen the pharma infrastructure
- Increased government expenditure on healthcare could create an over USD 4.5B market for pharmaceuticals in the next few years
- Government-sponsored programmes expected to provide health benefits to over 380 million people below poverty line
- Market size of BIOSimilars USD 200M as of 2008 and government plans to allocate USD 70M for local players to develop biosimilars

** Pharma Manufacturing & Patents**

- The manufacturing cost in India is 65% lower than the US and 50% lower than Europe.
- The Indian Pharma Sector produces 60,000 generic brands across 60 therapeutic categories also manufactures more than 500 different APIs.
- Higher spending on R&D, owing to products patents have made India a major destination for generic drug manufacture
- Following the introduction of product patents, several multinational companies are expected to launch patented drugs in India
- India has over 120 USFDA approved and 84 UK MHRA approved manufacturing facilities
In 2013, FDA issued seven Warning Letters to firms in India. Some key observations from the Warning Letters included issues such as:

- Failure to investigate batch failures
- Failure to investigate media-fill failures
- Discarding of raw laboratory data, both paper and computer forms
- Lack of data audit trails
- Not recording data directly into a notebook
- Back dating information
- No investigation of quality related complaints
- Failure to monitor environmental conditions
- Failure to use sporicidal disinfectant in class 100 cleanroom
- Using “trial” QC tests as official data
- Failure to follow written procedures for QC testing
- Inadequate stability testing
- Inadequate facilities
- No procedures to prevent microbial contamination of drug products

These observations are certainly not limited to firms in India, as demonstrated by other FDA Warning Letters, nevertheless they should pose a cause for concern. The issues are broader still in that many firms in India have multiple facility sites, some of which, like those that received the Warning Letters, have higher standards so that they may be able to meet current FDA/ICH standards while others work to lower standards and market to India and developing countries (such as those in Africa) with potentially lower standards.

FDA has heightened its interest in working more globally with the counterpart regulators as well as local industries to improve overall regulation of drug product quality and FDA Commissioner Dr. Margaret Hamburg earlier in 2014 visited India to discuss this issue with Indian drug authority representatives directly. The issue is not simply that some Indian drug companies do not comply with US FDA standards. It is more systemic in that regulators at the highest levels have stated clearly that they do not have the necessary resources to consistently and comprehensively ensure the same level of regulation and oversight. From a recent FiercePharma article:

“G.N. Singh, the Drug Controller General of India, told Reuters that he sees some areas where the FDA and India’s Central Drugs Standard Control Organization (CDSCO) can cooperate toward improvements. But he was adamant that Indian regulators do not have to maintain the same standards as the FDA when regulating drug makers’ products for the Indian market. “We don’t recognize and are not bound by what the U.S. is doing and is inspecting,” Singh said. “The FDA may regulate its country, but it can’t regulate India on how India has to behave or how to deliver.”

Even though DCGI Singh issued a clarifying statement, this does highlight how drug regulatory systems around the world can differ depending on the level of risk the country deems acceptable.

Accordingly, the remarks by DCGI Singh are true for essentially all countries, but unfortunately there are apparently different levels of quality for different regions of the world, depending, in part, on the level of strength and resources of their national drug regulatory authority as well as their comfort around the level of acceptable risk to their patient population. This could be acceptable, if there were a global standard as to what is minimally acceptable coupled with sufficient resources to enforce the standard, with other countries perhaps requiring a higher bar. Without a minimum for what is acceptable, a quality level below what is currently recommended in the various ICH guidelines is viewed by many as unacceptable.

**Root Cause Discussion – Drivers To and Away From Quality**

Independent of country, the issues driving firms toward quality or away from ensuring consistent quality typically have similar root causes. Some of these include:

**Lack of understanding of the cost of not meeting quality standards** – The goal of many firms is to maximize their profit margin. This is understandable in terms of survival of the firm, but if quality is not taken into account, serious issues can occur. Too much emphasis on output at the expense of quality can lead to a series of issues that may result in cGMP violations:

- Overworked employees, who may be prone to more errors or who may not follow or fully understand standard operating procedures (SOPs), batch records or other written instructions
- Rewarding output instead of quality, potentially leading to taking shortcuts in cGMP requirements (e.g., poor, incomplete or missing documentation) or lack of SOPs and sufficiently detailed manufacturing and testing instructions
- Neglect of routine maintenance and inadequate repair of poorly performing equipment, potentially leading to lack of sterility, inaccurate or imprecise data
Neglect of facilities, leading to potential poor sanitary conditions, product contamination, or insect infestations

Lack of cleaning of equipment, leading to potential cross-contamination

The above issues are often issues of omission, where the drive for output leads to unintended errors or neglect. Some of the issues are deliberate attempts to hide issues, which can seriously jeopardize patient safety and the brand of the company. At the bench level, issues that can tend to be attributed to lack of training and/or understanding of consequences by employees, include:

- Writing over initial computer files
- Faking numbers
- Tearing out notebook pages
- Back-dating information
- Blending failed and passed batches so that test results meet specifications
- Not enabling or turning off audit trails to change data
- Retesting products using same or different test methods until compliant data are produced

At the management level, there can be a lack of an overall Quality System culture. This leads again to opportunities for employees to take short cuts with quality or the inability to identify compliance issues if they occur. Some of these include:

- Lack of an overall Quality Management System and a Quality by Design (QbD), process-based approach to quality production and manufacturing leading to lack of employee knowledge, poor cGMP knowledge or execution and no mechanism for learning and continuous improvement.
- An attitude of punishing employees for lack of quality rather than rewarding the discovery and resolution of issues
- Inefficient processes that increase workload to the point where administration, documentation and best practices fail
- Multiple quality standards across the globe causing confusion and inefficiencies
- Lack of procedures to systematically investigate and analyze batch failures
- Lack of audit trails, thus allowing multiple users with the same password, lack of software systems that do not enable data to be changed
- Lack of procedures to investigate and analyze product complaints

Lack of procedures to monitor environmental conditions

Lack of adequate equipment and facilities to perform the work

Poor housekeeping and sanitation leading to potential product contamination

A culture of fear and a fear of failure are key causes of many quality failures. One set of issues can be caused by an inappropriate reporting structure between Quality Assurance (QA) departments and Manufacturing departments or senior management. Pressure from these groups to increase throughput can conflict with quality practices when there are not sufficient resources, systems or cultural norms in place to assure that proper quality standards are followed, leading to the QA department overlooking or ignoring critical quality issues.

A fear of failure can result in other issues such as not writing numbers directly into notebooks, “trial” Quality Control (QC) runs, turning off audit trails, not speaking up when there are problems or management not being receptive to employee suggestions for improvements. More broadly in this culture there is a:

- Fear of offending superiors
- Fear of challenging the status quo
- Fear of failure
- Fear of acceptance of ideas
- Fear of producing data that contains errors
- Fear of poor performance rating

This attitude is less prevalent in Western culture where suggestions for improvements are expected, accepted, encouraged and often rewarded. In addition, in the U.S., whistle-blower status protects employees that report improper behavior and employees are not as fearful of retaliation. In some Eastern cultures, these same traits are often seen as insubordination and viewed as not acceptable. Management establishing a culture of quality, and encouraging employees to improve processes and find issues without fear, will be one important key to breaking out of this culture and establishing a culture of quality. Management needs to see high quality, process-driven systems that get the task done properly and in a well-documented way as a way to maximize profits by avoiding rework. Warning Letters or other issues that ultimately lead to expensive delays, recalls, or adverse publicity.
Key Stakeholders

Almost everyone has a stake in the production of high-quality medicines. This starts with those groups that make regulations, policy, or guidelines (e.g., FDA, EMA, WHO, ICH), followed by those tasked with providing the supporting methods and procedures for these policies (e.g., the compendia, ISO, and others), industry itself, which needs to live with and abide by the policies, civil society (e.g., learned intermediates such as physicians and pharmacists, patient advocacy groups and patients) and finally auditors (e.g., third party or regulators) that oversee the industry to help ensure compliance. These will be discussed in turn below.

Policy Makers (FDA, EMA, WHO, ICH, State Dept., Office of Science and Technology)

The policy makers are responsible for establishing and enforcing a system that encourages high quality without imposing requirements that do not add value. This is often a difficult path to follow, and regulators typically use what they observe in the field to adjust the cGMP to reflect the current situation. For example, many years ago water flowing through iron or lead-containing pipes required special consideration, while it is essentially a non-issue now in developing countries, while microbial or other contamination in sterile products has grown in importance as injectable drugs have become increasingly important, particularly as essential medicines.

Regulators in the US are responsible for overseeing the entire supply chain, from raw materials, to the drug substance, the drug product, packaging, labeling, storage, handling, and shipping. Each is critical to the successful delivery of a safe and efficacious product to the patient. US regulators have avoided writing manufacturing quality regulations or guidelines that are overly specific (step-by-step instructions). Rather, they have preferred to write higher-level documents that allow room for good science, common sense and continuous improvement, yet are sufficiently specific to allow for robust inspections. The extent to which each country’s regulatory body regulate the entire supply chain is quite country dependent.

Rules around good documentation practices are especially important for regulators to be able to re-create what happened during any given process. Lack of an audit trail is seen as negligent at best, and as an attempt to deceive the inspectors or high poor quality at worst. A robust Quality Management System (QMS) with good SOPs, a process-based, Quality by Design (QbD) approach to quality rather than a check-box approach, and management commitment to quality make it easier for drug manufacturers to comply with the regulations and for the regulators to ensure compliance. Lack of compliance can lead to recalls, drug shortages, and drugs doing harm to patients, all in direct contradiction to everyone’s goal of improving patient health.

More globally and more broadly, organizations such as USAID and WHO provide healthcare programs for developing countries, many with drug regulatory systems that are not as robust their counterparts in developed countries such as the U.S. These organizations rely on obtaining high-quality medicines to deliver to patients that are often in remote locations. Supply chain issues (e.g., lack of refrigeration, chain of custody) make the job very challenging. Unfortunately this is compounded by the presence of spurious drugs and/or falsified materials in these markets, which are introduced by companies intentionally taking advantage of the weaker regulatory environment.

Programmatic Suppliers (e.g., Compendia, ISO)

While regulators provide policy, they are not in a position to say how to do it, nor are they in a position to set individual material specifications. While this is ultimately the responsibility of the individual firm, there are organizations that provide levels of standardization and training. The pharmacopoeias (e.g., USP, EP, BP and JP) are an example. They provide methods, procedures and acceptance criteria (specifications) and physical reference materials for hundreds of drug substances, drug products and excipients for a significant number of the overall marketed drugs in their respective markets, and do this in a public fashion. Public specifications differ from company-generated specifications that occur at the new drug application (“NDA”) or ANDA phase, since those specifications are private and known only to the firm and the regulators. Public specifications allow independent third parties to verify the quality of a given material. Ultimately, public specifications rely on firms working closely with the pharmacopoeias to publish these specifications and keep them current.

Other organizations, such as ISO, ASTM, and NSF also provide both written specifications and reference materials, and firms and the pharmacopoeias provide extensive training courses to help firms understand the uses and limitations of the procedures. All these organizations are developing specifications and performance standards that ultimately help set the bar for many of quality attributes, and help the regulatory agencies update cGMPs while having a baseline against which to enforce their policies.
Industry

Industry must ultimately live with the regulations, guidelines and policies. Firms do have “a seat at the table” at the level of the pharmacopoeias, where the specifications set are reviewed by industry members that are actively involved in their fields. Regulators hold scheduled public meetings and workshops (e.g., through Drug Information Association [DIA], Parenteral Drug Association [PDA], American Association of Pharmaceutical Scientists [AAPPS] or Product Quality Research Institute [PQRI]) where current thinking is discussed and public comment is welcome.

Regulations add costs to the process of developing, manufacturing, and marketing drugs. It has been estimated that this overhead approaches 25%. This is one of the drivers for some firms to attempt to cut corners and do the minimum or less to get their products on the market. The most successful firms, however, have gone in the other direction. They have developed systems and processes that do, in fact, ensure that all efforts are expended to produce the right material, under the right conditions, the first time. This Right First Time approach to quality, coupled with a QbD approach that drives an in-depth understanding of the critical parameters and how to control them, leads in the end to a system where there are minimal deviations, batch failures, and quality deficiency observations. This leads to faster approvals and few (if any) recalls, public relations or public health issues as well as overall savings for the firm in the long run.

Most firms now go well beyond monitoring and controlling the work and have expanded their monitoring of quality to include their supply chain. Rx360, a pharmaceutical industry consortium, has examined the issue of supply chain control and has set the stage for some standardization in this area through a proposed supply chain monitoring system that includes a spreadsheet to track shipping channels among the supply chain steps and a product supply chain map to serve as a process flow diagram.22

There remain some firms, however, that have not bought into the concept of process-driven quality, QbD, and continuous improvement. They still attempt to do the least amount possible to pass, and may be more prone to occasionally bend the rules to sell their product. In the long run, this can lead to entire plants being barred from distributing and/or selling material to the US consumer.23 As important, it casts a shadow on the entire drug industry, especially the overseas plants, and can lead to a decrease in the overall use of certain drugs made in a particular country. If physicians and consumers lose confidence in the same quality – lower price paradigm, the entire industry will suffer.

The issue of what level of quality is sufficient is also one that countries such as India that export materials to many different countries must deal with. As discussed above, some firms supply material that is made to higher standards to countries with higher expectations and sell a different grade of products to other countries. This gives the appearance that different quality materials are acceptable depending on the end-market. Material that fails to meet its safety, efficacy and quality expectations is never acceptable in any market. A minimum standard of quality against which firms could be held and could work to, would be helpful in establishing if the product produced by a firm meets sufficient quality standards for release globally.

Civil Society (Patient Advocacy Groups, Physicians, Pharmacists, Patients)

Patients expect their medicines to be safe, efficacious, of the proper quality, and to deliver consistent doses each time taken or administered. Interchangeability of medicines requires that they perform equivalently to the previous dose (e.g., batch to batch of either the brand or generic). This is especially critical for drugs with a narrow therapeutic index (e.g., blood thinners, oncology drugs), where small differences in dose can cause injury or death. Patient advocacy groups exist for many serious illnesses (e.g., diabetes, leukemia, breast cancer) and these groups pay careful attention to patient outcomes. Poor performance by a drug from a particular manufacturer is often spotted, and word spreads quickly. Similarly, doctors and physicians are attuned to patient outcomes. In the US, if a patient is readmitted to the hospital within 30 days of release, this is recorded as an issue and the physician and hospital can be held accountable. For example, physicians dealing with, for example, heart disease can see quickly if a patient responds quickly, consistently and as expected to diuretics, or if there are issues. There are anecdotal cases where physicians switch a drug from one supplier to another (same active, same dose) or from one batch to another of the same company’s drug (brand or generic). This is especially critical for drugs with a narrow therapeutic index (e.g., blood thinners, oncology drugs), where small differences in dose can cause injury or death. Patient advocacy groups exist for many serious illnesses (e.g., diabetes, leukemia, breast cancer) and these groups pay careful attention to patient outcomes. Poor performance by a drug from a particular manufacturer is often spotted, and word spreads quickly. Similarly, doctors and physicians are attuned to patient outcomes. In the US, if a patient is readmitted to the hospital within 30 days of release, this is recorded as an issue and the physician and hospital can be held accountable. For example, physicians dealing with, for example, heart disease can see quickly if a patient responds quickly, consistently and as expected to diuretics, or if there are issues. There are anecdotal cases where physicians switch a drug from one supplier to another (same active, same dose) or from one batch to another of the same company’s drug (brand or generic) and see marked changes in response. This information spreads quickly, leading to fewer sales for the company’s drug in question. When these incidences occur with a generic drug, the generic industry is more suspect to the physician abandoning the use of any company’s generic drug for the indication and instead switching the patient to the brand drug.

Auditors (Regulators, Third Parties)

Auditors or inspectors have the responsibility of policing the system to ensure that the quality standards have been adhered to. This function relies on the ability to follow a paper or electronic trail from the start of the process to the end. An auditor typically will
begin with the start of the process (for example, receipt of raw materials) and follow it through to its logical progression to the end (i.e., distribution). Breaks in the audit trail, or places where the audit trail may be compromised (e.g., ability to write over electronic results or not entering results directly into a notebook) are serious violations. Most firms are very helpful during inspections, bringing the inspectors the needed documents in a timely way. Some firms, however, appear to be hindering the inspection, perhaps by not providing documents, or in the worst cases, actually destroying documents, including notebook pages. The USFDA in October 2014 issued an updated guidance making delaying, denying, limiting or refusing a drug inspection cause for regarding a material as adulterated (i.e., in violation of the cGMPs).24

Third party auditors play an important role as well, although there does not exist a system to certify these auditors for competency. They may be hired by firms to assess the current state of cGMP compliance, do specific training, or to help with remediation in cases of FDA Form 483 inspectional observations, Warning Letters or Consent Decrees. There are also programs provided by groups such as NSF25 or USP26 that can help provide assurance to firms and purchasers of material that proper cGMP procedures have been followed during manufacturing and that the firm is capable of producing material that is consistent with its specifications. Finding and remediation of issues and training are important for developing and updating Quality Systems, but most important is a commitment to quality. Auditors and inspectors are not on site full-time and can only provide a “snapshot” of the quality situation. A Quality Management System needs to be in place to ensure that quality is a priority and is maintained at a high level when the auditor or inspector leaves.

**Best Practices – The Prevention and Remediation of Issues**

The best way to avoid issues is to have in place a strong, well established system for ensuring that full efforts are made to getting things done right the first time. This includes the right SOPs; the right people, proper training; the right equipment, properly calibrated and maintained; and a quality management system to assure long-term commitment to continuous improvement. Also important is the initial and ongoing training of employees, and auditing, by both internal and external experts, to ensure systems and people are up to date and all working in unison. In some cases, issues are found. Some are simple FDA Form 483 inspectional observations, others are more serious, ranging up to Warning letters and Consent Decrees resulting in loss of the right to export to or sell material in the United States. These points are discussed briefly below.

**Quality Management System**

A well-functioning Quality Management System (QMS) is critical for the long-term establishment and maintenance of quality. Quality is an on-going process with a tendency to slip or degrade if not actively maintained. The key elements of pharmaceutical quality management are embodied in guidance by, among others, USFDA27 and ICH28. The details of a good QMS are beyond the scope of this document, but require detailed QA processes including a functioning corrective and preventive action (CAPA) program, a commitment to QbD to fully understand the factors impacting manufacturing, and most importantly, a company-wide commitment to quality beginning at the highest levels of management.

**Best Practices – Some Detailed Examples**

There are three levels at which detailed assistance can be provided by outside personnel. These include:

- cGMP systems training. For example
  - Good Document Procedures (paper and computer)
  - Good Analytical Laboratory Practices
  - Process and Production Controls
  - Quality Systems
  - Good Clinical Practices
  - Compendial or other standard product testing
  - Proactive continuous improvement program
- Auditing or QC of samples to assess compliance with standards
- Warning Letter or Consent Decree remediation

For an outside group to be of any help to any organization, whether individual firm, trade organization or government entity, there needs to be a clear commitment to quality standards and a desire on the part of the group involved to want to improve their systems. Some companies have made clear commitments beyond the minimal quality standards. An ex-Indian company with facilities in India exporting to the U.S., such as Mylan is an example of a company with a strong compliance record to date.29

**cGMP Training**

As in the US, there is a continuing need for ongoing cGMP training. Most US firms have an ongoing training program where key issues are emphasized and it is demonstrated that the firms have a commitment to continuous quality improvement. There is certainly room in India and China for this sort of training, since it is likely that only the largest of Indian firms are firmly grounded in USFDA’s current thinking on cGMPs, QbD and the concepts of continuous improvement as embodied by documents such
as ICH Q8, Q9, Q10 and Q11. This type of activity can at first be
staffed from US-based personnel but to be successful in the long
run likely needs to be run from India or the country in question. In
India, it may be possible to reach out to companies that have good
reputations and a vested interest in developing and maintaining
the reputation of the Indian pharmaceutical community for
producing materials of high quality. Unease is growing among US
doctors regarding the quality of drugs from India and this has the
talent to be a real problem for the industry, impacting even
those that are producing very high quality materials.30

Auditing

Another point of potential intervention is inspection at the level of
the supply chain. This can be done at any of a number of levels,
from spot checking/QC at an individual firm to pulling samples
from the field or working with customers to assess whether the
drugs they are receiving meet quality standards. Ideally, testing
would best be done at the local level in a laboratory that has the
appropriate ISO or WHO certifications, although initially there are
a number of well-established firms that can help in this area.31

Warning Letter Remediation

The training area is a prospective intervention aimed at
preventing problems before they occur, while the auditing area
is aimed at finding a problem that may exist. Warning Letter
remediation goes a step further and addresses a problem that
is known to have occurred. An example of the USFDA strongly
suggesting that an outside auditing firm get involved with quality
remediation is presented from the Wockhardt Warning Letter:32

“We highly recommend that you hire a third party auditor, with
experience in detecting data integrity problems, to assist you
with this evaluation and to assist with your overall compliance
with cGMP. It is your responsibility to ensure that data generated
during operations is accurate and that the results reported are a
true representation of the quality of your drug products. Provide a
list of all the lots of drug products shipped to the U.S. market that
relied upon missing, inaccurate, or unreliable test data.

The cGMP expert should:

1. Perform a comprehensive inspection of the facilities, method,
and controls used to manufacture drugs, and determine
whether your facilities, method, and controls used to
manufacture drugs are in compliance with cGMP requirements.
2. Evaluate whether your facilities have established and implemented
a comprehensive written QA/QC program that is adequate to
ensure continuous compliance with cGMP’s requirements.
3. Evaluate whether your facilities have established and implemented
an adequate stability program that accurately
measures the stability characteristics of drug products.
4. Evaluate whether your firm has established and implemented
a comprehensive written program to maintain production,
control, and other records and to ensure the authenticity and
reliability of all data reflected in those records.
5. Evaluate adequacy of data integrity training for all staff
who perform cGMP activities. Identify gaps and implement
ongoing training modules on the responsibility of all staff to
assure authentic records. This training should also instruct
your firm’s managers in detection of data integrity and
manipulation practices. At minimum, staff from development,
quality, operations, and regulatory affairs should be trained.

The data integrity consultant should (Note – can be the same as
the cGMP expert):

1. Identify any historical period(s) during which inaccurate data
occurred at your facilities.
2. Identify and interview your current employees who were
employed prior to, during, or immediately after the relevant
period to identify activities, systems, procedures, and
management behaviors that may have resulted in or
contributed to inaccurate data reporting.
3. Identify former employees who departed prior to, during, or
after the relevant period and make diligent efforts to interview
them to determine whether they possess any relevant
information regarding any inaccurate data reporting.
4. Determine whether other evidence supports the information
gathered during the interviews, and determine whether
additional facilities were involved in or affected by inaccurate
data reporting.
5. Use organizational charts and SOPs to identify the specific
managers in place when the inaccurate data reporting
was occurring and determine the extent of top and middle
management involvement in or awareness of data manipulation.
6. Determine whether any individual managers identified in item
(5) of this subparagraph are still in a position to influence
data integrity with respect to cGMP requirements or the
submission of applications: and establishing procedures to
expand the internal review to any other facilities determine to
be involved in or affected by the inaccurate data reporting.”33

There are many firms that engage in Warning Letter or Consent
Decree remediation. This process can take many months and
involves careful coordination between the manufacturer, the
remediation firm and FDA to establish root cause issues, develop plans to ensure the problems have been addressed and will not reoccur, and to assess the impact of the issues on products still on the market, and determine if recalls are needed or other safety notifications are required to be provided to healthcare providers and/or patients. Again it should be noted that these consultants have no formal certification process and care should be taken in selecting them. Ideally, consultants should be qualified through a supplier/vendor qualification program so their suitability for the project can be assured.

Benefits and Impact
An ongoing commitment to quality has broad ranging impact. From a public health perspective, the benefits include:

- Consistent safety and efficacy across products and regions of the world
- Confidence in the use of generic drugs as cost-effective alternatives to branded drugs
- Lower regulatory costs due to a decrease in the intensity of audits, when a risk-based audit approach is used
- A drug supply that does not contain not of standard quality products and that is less subject to shortages due to poor product quality
- Better and more consistent patient outcomes

From an industry perspective, the benefits are many as well. They include:

- Consistent quality of raw materials and finished products, resulting in fewer failed batches, leading to reduced cost of goods sold and operating costs
- Confidence in testing, because the procedures are well validated and the materials are of sufficient quality
- Confidence during audits because systems are in place, are working, and are well documented
- Few if any product recalls, critical and major FDA Form 483 inspectional observations, or Warning Letters
- Stronger physician and patient confidence in the generic drug system leading to higher sales
- A reputation as a good manufacturer, leading to the firm being a “go to” firm when quality products are needed

The above list is, of course, just the “tip of the iceberg” in terms of benefits to the public and to the manufacturers of a highly-functioning QMS. The key point is that the value proposition is quite clear. An early investment in quality will pay off throughout the development, manufacturing and marketing cycle, whether final output is an API or a drug product. Lack of quality can lead to product failure, extensive rework, and added cost of goods sold. There are massive inefficiencies due to trying to save batches or committing cGMP violations in an attempt to disguise problems either with the product or its testing, and there is an overall increase in operating costs because the processes are not well managed and in control. The FDA regulators are going to be on site more regularly. They have audited a sufficient number of sites to know issues when they are there, and they know the procedures that firms use to try to hide issues. In the long run, it is far better to invest in developing systems, understanding processes and materials, training personnel, keeping equipment running well and generating good data than it is trying to fix things later and risk recalls, loss of market share, and developing a reputation as a company that cannot be trusted.

A Single Quality Standard?
The issue of differing quality standards across the globe remains a major one. It is often far more inefficient to have multiple standards of quality than just one. The U.S., Europe, and Japan have harmonized the majority of the quality standards for drug substances and drug products adopted by ICH. The standards have attracted the interest of other countries as well, and ICH continues to expand its influence. Its meetings now have observers from many countries, and it is actively engaged in discussions as to how to embrace the views of these other countries. If ICH is successful in broadening its global scope, those countries that now have issues with ICH standards will have a seat at the table where these issues are discussed, and perhaps accommodation can be made to bridge the gaps. WHO also has a set of standards that are helpful, and it appears that ICH and WHO standards are converging.

The key issues link quality, safety, efficacy and economics. Is the high quality standard imposed by ICH imposing sufficient price impacts that certain developing countries cannot afford the medication? Is it really the quality standard that is causing the price issues, or issues such as distribution costs or even marketing costs? If the minimum quality standard were to be lower, what would the savings be, and why? What would the impacts be on safety and efficacy? Clearly lack of content uniformity, or variable dissolution (and by implication bioavailability) results may be acceptable in some cases, but in many cases, wide variability leads to differing safety and efficacy outcomes batch to batch, and this would not be acceptable.
Patients have the right to expect that their medicines will work as expected, consistently, batch to batch and manufacturer to manufacturer. If this is not true, the entire pharmaceutical model, especially the utilization of generic drugs to lower costs begins to fall apart. It is up to each country interested in establishing a recognized standard of quality to either adopt their own standards and publicize them openly, adopt existing ICH, WHO or other international standards, or have a seat at the table and help lead the broader group to a standard all find acceptable.

**Concluding Remarks**

Quality of pharmaceutical manufacturing, especially generic drugs is a complex issue. It is influenced by a wide variety of issues, including individual country regulatory structure, manufacturing capabilities, measurement capabilities, storage and handling conditions, supply chain management, and government policies ranging from free market enterprise to strict price controls. In any event, the bar to safety and efficacy is set by the branded-drug manufacturer, through a set of standards, including quality standards, agreed to between the manufacturer and the competent regulatory body that approved the product. Any generic drug is expected to be bioequivalent to the branded drug and interchangeable with it (switchable with the branded drug or other generics even during a course of treatment).

Key quality attributes (e.g., content uniformity, dissolution, assay and identity) must be well enough controlled to not impact the clinical safety and efficacy outcomes. Practically, this means adhering to international standards of quality, unless it can be demonstrated that going outside these standards produces no important safety or efficacy differences. It also means being able to produce material, either API or drug product, to a consistent standard, and having systems in place to demonstrate to third-party auditors and inspectors that this can be done. A strong regulatory system with clear expectations and a strong quality management system with management commitment to quality and continuous senior level improvement and a commitment to the principles of quality by design (building in quality rather than testing in quality) are key to achieving these objectives and ensuring the consistent safety and efficacy of medicines across the globe.
References

2 http://www.slideshare.net/AiswariyaChidambaram/pharma-tech-2013-aiswariya-chidambaram-fs
3 Ibid.
4 Ibid.
5 http://www.fda.gov/NewsEvents/Testimony/ucm387449.htm
6 What You Want to Know about Generic Drugs. www.fda.gov
7 http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm246685.htm
8 http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm281843.htm
9 http://www.fda.gov/drugs/drugsafety/ucm291960.htm
10 http://www.aei.org/events/2013/12/02/dangerous-drugs-in-your-medicine-cabinet-a-whistleblowers-account-of-indias-troubling-exports/
11 http://www.who.int/mediacentre/factsheets/fs275/en/
12 PQM: Promoting the Quality of Medicines in Developing Countries | U.S. Pharmacopeial Convention
13 http://www.who.int/medicines/services/counterfeit/overview/en/index1.html
14 http://www.brandindiapharma.in
16 http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376913.htm
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm369407.htm
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm365428.htm
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm365427.htm
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm361928.htm
http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm355294.htm
17 What You Want to Know about Generic Drugs. www.fda.gov
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm246685.htm
18 FDA’s Hamburg comes back from India with high hopes about quality standards - FiercePharma Manufacturing
19 Ibid.
21 ICH Quality Guidelines, www.ICH.org
22 http://hosted-p0.vresp.com/427409/0cddf6275/ARCHIVE
23 See Endnote 16.
24 Guidance for Industry - Circumstances that Constitute Delaying, Denying, Limiting, or Refusing a Drug Inspection, www.fda.gov
http://www.nsf.org/regulatory/regulator-nsf-certification/
26 http://www.usp.org/usp-verification-services
28 Good Manufacturing Practice Guide For Active Pharmaceutical Ingredients Q7, www.ICH.org
Pharmaceutical Development Q8(R2), www.ICH.org
Quality Risk Management Q9, www.ICH.org
Pharmaceutical Quality System Q10, www.ICH.org
Development And Manufacture Of Drug Substances (Chemical Entities And Biotechnological/Biological Entities) Q11, www.ich.org
29 http://www.mylan.com
30 See Endnote 29.
31 http://www.jeiven.com/pages/auditing/15
http://www.nsf.org/services/by-industry/pharma-biotech/pharma-consulting/
32 http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm361928.htm