Development of General Guidelines for the Pharmaceutical Manufacture Company Reaction to a Consent Decree Emitted by the Federal Drug Administration (FDA)

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***Abstract* —** *Consent Decrees have been very popular lately. The consent decree mandates that a company start initiating change, and that change is usually associated with the way the company is manufacturing a product; and, it will involve the company re-constitute the manufacturing practices to bring it in alignment with the Food and Drug Administration (FDA's) Good Manufacturing Practices. This project main purpose is to give guides on how pharmaceutical industries should react when a Consent Decree is given. Based on all information gathered from different sources, the consequences that bring the consent decree, the review of FDA inspectional process, and the hints required to effectively interact with the FDA are given. Finally, the guide will assist the companies to manage important events regarding compliance with the Good Manufacturing Practices and with the requisites of the consent decree.*

Key Terms *— cGMP, consent decree, FDA inspections, regulatory issues, warning letters.*

INTRODUCTION

This project explains in many ways why is very important that all pharmaceutical industries must comply with the regulations of the Food and Drug Administration (FDA). Consent Decrees (CD) are a negative impact because the company must work to restore the faith of customers and stockholders as well as FDA officials. When a CD is given, a fine and other consequences may result. It is a kind of opportunity that industries have in order to demonstrate that they can make a tremendous effort to contribute to a better performance and that they are in accordance and comply with the law.

Once the court emits a Consent Decree, one or a few persons are assigned to monitor that employees are making their work properly and that methods, procedures, and controls in the manufacture of each plant comply with the GMP's and with the requisites of the CD. People must perform GMP required activities, and also should be appropriately qualified. This is achieved with the presence of auditors and the monitoring of different activities. Without a robust internal audit system, the company is at the mercy of regulators and, increasingly, customers to discover GMP deviations which the company should have known about and addressed. A good internal audit group not only will point out problems, but also will affirm which actions are working well. This project will help pharmaceutical industries not to fall in the same mistakes than those industries with Warning Letters (WL) and CD. A WL is an informal advisory, to a firm or clinical investigator, communicating the agency's position on a matter but does not commit FDA to taking enforcement action. A WL is issued for significant regulatory violations that require prompt and adequate corrective actions. [6]

Consent Decree

CD is the decree entered by a court that is determined by the parties' agreement, the pharmaceutical industry and the governmental regulatory agency. This is a decree by which the accused agrees to cease alleged illegal activities without admitting guilt.

Once a Consent Decree exists the following happens:

- The company agrees to correct deficiencies in its affected operations as soon as possible.
- The corrections are overseen by outside experts hired by the company who will certify to the FDA that corrections are being made.
- These personnel are assigned to monitor that employees are making their work properly and that methods, procedures, and controls in the manufacture of each plant comply with the GMP's and with the requisites of the CD. This is achieved with the presence of auditors and the monitoring of different activities.

FDA

The Food and Drug Administration (FDA) main objective is to protect citizens from products that are inherently unsafe or that make claims of effectiveness that cannot be substantiated. [3] The FDA has the power to regulate a multitude of products to ensure the safety and the effectiveness of marketed food, medical and cosmetic products. The FDA also sets the standards under which individuals may be licensed to prescribe drugs or other medical devices.

Background on Drug Safety

Modern drugs provide unmistakable and significant health benefits. It is well recognized that FDA's drug review is a gold standard. FDA grants approval to drugs after a sponsor demonstrates that they are safe and effective. Unless a new drug's demonstrated benefit outweighs its known risk for an intended population, FDA will not approve the drug. An adverse drug reaction can range from a minor, unpleasant response to a drug product, to a response that is sometimes life threatening or deadly. Such adverse drug reactions may be expected (because clinical trial results indicate such possibilities) or unexpected. It may also result from errors in drug prescribing, dispensing or use. The issue of how to detect and limit adverse reactions can be challenging; how to weigh the impact of these adverse drug reactions against the benefits of these products on individual patients and the public health are multifaceted and complex, involving scientific as well as public policy issues.[7]

How to Ensure Good Manufacturing Practices

Over the years current good manufacturing practice (cGMP) violations in the pharmaceutical industry have increased at an alarming rate, and penalties imposed by FDA have failed to alleviate the problem. The problem, therefore, is twofold: FDA is obliged to monitor companies because they keep breaking the rules, and companies as well keep breaking the rules because they are preoccupied with addressing the symptoms and not the causes. [4]

Raising awareness and promoting understanding will require significant education and training. By committing to a quality systems initiative, manufacturers develop the capability and capacity to improve. They can still address symptoms of problems they experience, but they will have the systems that can resolve them permanently. This alone will help them avoid high-profile penalties. Combined with a change in FDA's approach, quality systems will have a dramatic impact on the industry.

Pharmaceutical Quality and the Customer

A major reason for the federal role in regulating pharmaceutical quality is that the customers are often not able to independently assess the quality of the drugs they use. The historical literature of drug regulation verifies this, telling a story of tragedies that occurred when unsuspecting health professionals treated patients with contaminated or improperly labeled drugs and of the subsequent laws enacted to prevent recurrence.

For people taking medicines, however, more is at stake than just their money: their health or even their lives could be jeopardized by a drug quality problem. [2]

FDA Requirements

The FDA has legal authority to gain access to all regulated companies' facilities and to vehicles

that carry regulated products and to records for particular types of products. The FDA has the authority to inspect records, files, papers, processes, controls, and facilities' bearing on whether prescription drugs are adulterated or misbranded or is otherwise violative. [1]

FDA conducts inspections for many reasons:

- Routine GMP audits: to make sure that employees are making their work properly and that methods, procedures, and controls in the manufacture of each plant comply with the GMP.
- A directed inspection for a specific reasonA re-inspection after a WL to make sure that deficiencies are being fixed.
- A recall effectiveness check for the purpose of verifying that the recalling firm's consignees have received notification about the recall and have taken appropriate action.
- A pre-approval inspection as a requirement for the manufacture of a new product. [1]

Warning Letters (WL)

The Warning letter was originally intended to be a letter warning the firm to take corrective actions or face regulatory action including the possibility of a seizure, injunction or prosecution. Warning Letters are required to be responded to in 15 days. In the case of a serious violation, the Agency would not issue a WL but proceed straight to an enforcement action. FDA will likely issue a WL if response to the FD483 is considered inadequate or not provided; deficiencies are sufficiently serious that FDA is prepared to proceed with further enforcement action. A WL indicates that higher-level FDA officials have reviewed the inspection findings and have concluded that the findings warrant further formal notification to the inspected company that FDA believes serious violations may exist.

FDA Enforcement Actions

WL are typically sent to the CEO, President or others senior official. A CD is basically a resolution of the initial compliance effort.

In order to comply with GMP/QS requirements, companies must perform a number of steps to ensure the quality of their final products including implementing laboratory controls, writing standard operating procedures, conducting internal audits, investigating adverse events, hiring qualified employees and training employees, validating manufacturing processes, and maintaining records. If the FDA finds violations of the Food, Drug and Cosmetic Act through inspections or other means, the agency has several means available to enforce its authority under the FD&C Act including seizures; recalls; injunctions/consent decrees; rejection of regulatory submissions or withdrawal of approval for a product; WL; and, in severe cases, criminal prosecution.

Consent Decrees

Frequently, the decree requires the use of outside, independent consultants to review the facilities, audit reports to be provided to FDA, payment or fines per day for failing to meet schedules proposed by the consultants and approved by FDA, and disgorgement of profits. A CD impact because it implies re-inspections within 6-12 months, loss of credibility with FDA, a negative effect on stock price, employee departures or firing sand low company morale, and delay of product approval or shipment. Consent Decrees are becoming more popular with FDA. Many companies that have had poor inspections are proactively initiating their own corrective action plans, such as those that would be required in a consent decree. If a company further violates these GMP requirements, FDA may seek the court to hold the company in civil or criminal contempt of the decree. If FDA determines that a plant identified in the consent decree is not in compliance with GMPs in the future, FDA may order the company under the terms of this decree to immediately cease the plant's operation.

METHODOLOGY

The study design of this project was divided in different steps. The first step included the identification gathered and examination of all information available in the FDA web page [5]. It was accessed from the period of 2004-2005 and 2008-2009.

A subsequent systematic literature search was conducted in the Internet, books and in the Polytechnic University of Puerto Rico Library electronic database from the period of 2004-2005 and 2008-2009, searching for any regulatory issue related to the investigational topic.

The aims that were used as a baseline for this project were:

- Provide guides on how pharmaceutical industries should react when a CD is emitted by the court.
- Explain the consequences that bring a CD to industries.
- Explain the actions that the FDA takes in order to give a CD to a company and the consequences that it brings on from the company perspective.
- Review of FDA Inspectional Process.
- Development of Quality Model to anticipate and manage FDA inspections.
- Review of skill sets required to effectively interact with FDA field investigators.

RESULTS AND ANALYSIS

As a significant step for the commitments that the corporations has to address in order to comply with the requirements of the FDA regarding the remediation of specific GMP issues, the corporations has to provide internal target dates for the completion of each task before they reach the specific deadlines. The company should submit a timetable only with respect to the significant steps identified in the work plans. It does not require a timetable for all of the subordinate tasks that lead up to a significant step. Thus, the dates associated with projected completion of such subordinate tasks have to be used by the company as management milestones to be used for internal project management. The company should set out the dates to improve its cGMP compliance status with a comprehensive system-based approach. As explained, a significant amount of work has to be completed, structural and organizing changes have to be implemented, management controls have to be strengthen, and controls have to be in place to assure the quality of marketed products while improvements to quality management system are implemented.

In response to FDA comments and concerns about prompt compliance and about the length of time proposed by the company to implement system improvements, the company has to carefully review the priority sequence and amount of time to complete each of the projects identified in the work plans. The company has to re-challenge each of its proposed timelines and if possible has to move up the dates for completion of significant steps, where practicable. When the entire scope of work to be accomplished is considered, the company has to believe that the timing for each project is appropriate, indeed should be aggressive. However, the company has to be mindful of the need to be as realistic as possible in terms of calculating the amount of time a particular project will require, the priority that should be assigned to the project, the resources required for the project, and the foundation work required. Thus, the company should attempt to schedule the projects in a manner that is consistent with their priorities in terms of overall GMP compliance. Even the nature and scope of the work to be performed and the number of sites involved, the company might believe it as an aggressive yet achievable schedule. Progress made on identified GMP issues, interim controls, and consent decree requirements all will serve to provide assurance of GMP compliance of presently manufactured products. The completion of a particular group of in-progress commitments represents a single significant step.

The company should take a number of actions (Table 1) to address these issues such as:

- Quality Unit Effectiveness: Hire new qualified personnel in different areas such as lab supervision, quality assurance, and quality services. The council reviews key quality and compliance metrics, identifies action plans for corrective and preventive actions, ensures resource availability, and helps to ensure high priority for compliance among senior management.
- Equipment and Facilities: Establish an Equipment Qualification Group and Equipment Qualification Review Board. The site has to revise key procedures on the equipment qualification process and document control. These procedures will improve the detail, accuracy, and effectiveness of equipment setup and operating procedures.
- Process Validation: Validations should be conducted in accordance with the company's worldwide quality standards. The Site Validation Review Board acts to approve plans, protocols, variances, and summary reports.
- Investigations: Improve the investigation systems in terms of its procedures, trainings, and the metrics that will be used to monitor performance.

Table 1
Key Issues that Might Rise by Audit Observations

Key Issues	Example
Quality Unit Effectiveness	Leadership and Oversight
Equipment and Facilities	Qualification acceptance criteria, Documentation
Validation	Process and cleaning validation, acceptance criteria, documentation, timeliness.
Investigations	Variances, preventive actions, partial batch release.

Improvements within the Quality Unit: In case there's need to improve the organization in the Quality Unit, action has to be taken to address the key issues that may rise by FDA observations:

- Laboratory: It is very important to strengthen the leadership and organization of the area. Job descriptions have to be reviewed and revised. Training matrices for analyst qualification have to be established and execution has to be tracked.
- Validation: As a recommendation, the corporation can create a local Validation Review Board to provide high level oversight of the validation process by Senior Management, focusing on such areas as approval of protocols, deviations, and protocol aging.
- Training: Create a new training department. Job descriptions should be revised and/or created as necessary. The Isotrain Tracking System should be validated and in use.
- Documentation: The Corporation should create a system for handling and custody of cGMP documents. Records should be readily retrievable and securely stored. Access to the records has to be under the custody of the Quality Unit, and access has to be controlled.

Table 2
Other Key Issues that Might Rise by Audit Observations

Observations	Examples
Laboratory	Out of Specification Investigations, method validation, Instrument qualification, data archival and security, compliance to USP requirements and stability.
Validation	Process consistency, critical process parameters, critical quality attributes and associated ranges, acceptance criteria, sampling plans, and lack of validation plans.
Trainings	A tracking system, and a system to measure training effectiveness.
Documentation	Handling and control of cGMP documents.

Guides for the Work Plan Development after a Consent Decree

The work plan team members are a new plan that is introduced in order to transform a company in a company of trust. Each member will be

responsible to outline the significant steps to ensure that the covered facilities are and will be continuously maintained in compliance with cGMP's. They will be in charge of summarizing the in-progress commitments that must be completed. The workplan team members would provide the significant steps and scheduled completion dates on an annual basis. Once a completion date for a significant step needs to be revised, the company should notify the FDA. It is important to recognize that significant steps may be subject to potential change based on technical, logistical, and/or other anticipated events.

How to Manage an Inspection

Some preparation measures are needed to survive an inspection and develop procedures for managing inspections. This should address policies such as: receiving investigators, access to clean rooms, photocopy and collection of records, copy and collection of electronic records, affidavits, and photography. Once you know that an FDA inspection is coming, prepare in advance, arrange for a location, establish housekeeping needs for the inspection (ex: train personnel on how to answer questions, be honest, do not guess), get prepared on how to react, how questions might be asked or phrased by the inspector, ask for clarification if requests are unclear. There should be an adequate infrastructure such as: phone, seating, ventilation, lighting, conference table, and a nearby staging area.

Mock Inspection Program

The Mock Inspection program simulates a regulatory sponsor inspection, and "Auditors" act as FDA investigators and asks questions posed during an inspection. (Observe company personnel response and reaction). This helps to identify areas for improvement and also helps to keep good practice. When conducting a Mock Inspection, the personnel feel more prepared and this helps to remove the "fear" factor. The people involved knows the importance on why inspections are needed, they learn how to respond to inspectors' questions, how to escort/host an inspector, how to provide copies of documents to the inspector, and how the interviewer will conduct during an interview.

Subject Matter Experts (SMEs)

SMEs are the persons most knowledgeable of a particular process, area, problem or subject who are also able to perform effectively under stressful interview circumstances. It is important to determine subject matter experts in advance, and rehearse the SMEs. Note: The most technically knowledgeable person is not always the one you want to put in front of the FDA.

Answering Questions

All FDA investigator questions should be accurately and concisely answered. Response information is limited to that which is necessary to answer the question. Don't answer if uncertain of the correct answer. A question that cannot be answered can be directed to the appropriate personnel.

Staging Room

While in the staging room, make sure to obtain all needed documents, locate and brief SMEs, keep a list of all items requested and provided (This includes documents, people (SMEs). Review all documents before delivery. This is very important for example to check for sticky notes and missing pages. Also, look for any obvious document deficiencies. If on time this can be corrected. In the staging room make sure the following technologies are available: Computers with intra and Internet access, printers, phones, fax machines, copy machines, white boards, and office supplies.

Annotating the 483

The company has a choice to either Annotate or Not Annotate. The annotation is provided to each of the 483 items. It is the company's response. There are only three options for annotation: Corrected and Verified, Corrected, Not verified, and Promised to Correct. Some investigators will

request that you annotate with a time frame for promised corrective actions, but the Investigator's Operations Manual (IOM) does not require this.

After the Inspection

Possible Outcomes of the Inspection might be: no 483 is issued; 483 with minor issues which means that there is no history of non-compliance and no warning letter; 483 with major issues which results in warning letter; and 483 with major issues, and past history of non-compliance including warning letter that leads to further enforcement action such as injunction, seizure, civil money penalties, and/or, import detection). After the Inspection, create a corrective action plan to address any 483 observations. If corrective/preventive action will take time, identify timelines, objectives, and milestones. It is better to take the time to do it right. FDA is generally very open to providing time as long as there is a reasonable plan with a reasonable timeframe and appropriate attitude. Attempt to provide written response to the 483 with evidence of corrective actions or plans for corrective actions within 15 days. Timeframe is important; a good response could head- off a Warning Letter. When responding to a 483, provide a cordial cover letter, restate each observation and provide your response below it. State facts clearly, provide objective evidence of corrective action, attach copies of objective evidence, do not take an argumentative stance, demonstrate that corrective actions are been taken systemically, address the root cause of the problem (training and/or resources), and finally, provide enough information so that the agency understands the observation does not directly impact product safety and effectiveness.

CONCLUSION

A comprehensive guide on how the pharmaceutical industry will react to a consent decree was developed. It includes the actions that should be provided and the way to conduct the process from the perspective of the pharmaceutical industry. This recommendations were the results of an extensive literature review published by the governmental institutions (mainly the Food and Drug Administration [FDA]) and others experts on this topic. The goal to focus on the Agency's cGMP requirements was achieved. The causes or factors that can result in a Consent Decree were explained, as well as its consequences, not limiting to issues that might rise by an audit observation. This guide includes areas that are not common in the regulations, in part because the regulations are presented from the enforcement agency and not by the affected counterpart. Some of these areas are focus on the personnel or response team preparation and conduct. Also, the guide mentioned those areas or documents not subject to FDA review during the inspection and the possible outcomes after the inspection. This project represents a great contribution and assistance for companies under a Consent Decree or those that will like to develop procedures or politics to manage those important events.

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