

NEW TECHNOLOGY AND INCREASED GLOBALIZATION:
ADDRESSING DIFFICULTIES PRESENTED IN THE
CURRENT FDA INSPECTION PROCESS

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I. INTRODUCTION

Christmas music played slowly in the background of a Toledo, Ohio hospital. Under the wistful drone of the music, Leroy Hubley stood next the bed of his wife Bonnie. Christmas music must have been present on many special occasions for Leroy and Bonnie; their kids opening presents, special family dinners, and perhaps happy trips in the car to visit relatives. But on this day, Christmas music marked the setting for the most somber of occasions. Leroy and his family were saying goodbye to Bonnie for the last time.

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Shortly after goodbyes and last kisses, Bonnie's breathing tube was removed and her pain shortly subsided. In a cruel twist, Leroy's seemingly unbearable grief was far from over. Only a few weeks later, Leroy's son, Randy, died in the same manner.¹

Randy and Bonnie Hubley suffered from a genetic kidney disease.² As a result of the disease, they routinely underwent dialysis. While not ideal, the disease was manageable with the correct medications and routine dialysis treatments. The tragedy Leroy Hubley experienced was not caused by a change in prognosis or an advancement of this genetic disease. Bonnie and Randy Hubley died because their life sustaining medication was contaminated.³

Approximately eighty-one deaths, including Bonnie and Randy Hubley, were the result of contaminated heparin produced by Baxter International during 2007 and 2008.⁴ Heparin is an anti-clotting prescription drug that is administered intravenously to help avoid blood clots. Heparin prevents blood clotting in patients undergoing open heart surgery, kidney dialysis, and a number of other serious surgeries or medical treatments.⁵

Baxter International used contaminated raw ingredients obtained from a Chinese manufacturer to produce the heparin that ultimately ended Randy and Bonnie's lives.⁶ As a result of the incident, the U.S. Food and Drug Administration ("FDA") was criticized for failing to prevent the tainted medicine from reaching the market. The FDA was forced to admit it failed to follow its own policies in

¹ Randolph Schmid, *Families of Contaminated Heparin Victims Tell Stories of Deaths*, USA TODAY (Apr. 29, 2008), http://www.usatoday.com/news/health/2008-04-29-3953029109_x.htm.

² *Id.*

³ *Id.*

⁴ Justin Blum, *China and U.S. Clash Over Cause of Heparin Deaths (Update 6)*, Bloomberg (Apr. 21, 2008), <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aUAE9VN4.xX0&refer=home>.

⁵ *Heparin (Intravenous Route, Subcutaneous Rout)*, mayoclinic.com, <http://www.mayoclinic.com/health/drug-information/DR601931> (last visited Oct. 03, 2012).

⁶ Blum, *supra* note 4.

regards to inspection of manufacturing plants.⁷ The FDA had never inspected the Chinese factory responsible for producing the tainted ingredient. The 2008 heparin tragedy forced the FDA to reassess current strategies and engage in a more active role monitoring overseas manufacturing facilities.⁸

Unfortunately, the heparin tragedy has not been an isolated occurrence in recent years. Several other similar incidents have transpired over the past few years. The FDA referenced several alarming occurrences in the 2011 Pathway to Global Product Safety and Quality Report: vegetable protein tainted with melonin killed many pets in the United States,⁹ counterfeit glucose monitoring test strips,¹⁰ Diethylene glycol tainted glycerin,¹¹ and titanium of low quality intended for medical implants.¹² In 2012, a fungal meningitis outbreak in eighteen states occurred as a result of contaminated steroid shots manufactured at a compounding pharmacy in Massachusetts.¹³ The tainted shots caused hundreds of infections and at least twenty-nine deaths.¹⁴

⁷ Gardiner Harris, *Tainted Drugs Put Focus on the F.D.A.*, NEW YORK TIMES (Mar. 17, 2008), http://www.nytimes.com/2008/03/17/health/policy/17fda.html?_r=0.

⁸ FDA Adopts New Strategies to Oversee Global Economy, PHARMACEUTICAL TECH., <http://www.pharmtech.com/pharmtech/Regulatory+Corner/FDA-Adopts-New-Strategies-to-Oversee-Global-Econom/ArticleStandard/Article/detail/781206?contextCategoryId=48564> (last visited October 3, 2012).

⁹ U.S. FOOD AND DRUG ADMINISTRATION, PATHWAY TO GLOBAL PRODUCT SAFETY AND QUALITY (2011) *available at* <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/GlobalProductPathway/UCM262528.pdf>.

¹⁰ *Id.*

¹¹ *Id.*

¹² *Id.*

¹³ *13,000 Received Potentially Tainted Steroid Shots, Risk Remains Uncertain*, FOX NEWS (Oct. 09, 2012), <http://www.foxnews.com/health/2012/10/09/13000-received-potentially-tainted-steroid-shots-risk-remains-uncertain/>.

¹⁴ *Meningitis Outbreak: 368 Cases, 29 Deaths*, Sydney Lupkin, ABC NEWS (Oct. 31, 2012), <http://abcnews.go.com/Health/Wellness/meningitis-outbreak-368-cases-29-deaths/story?id=17609742>.

A. Food and Drug Administration History

The United States government's regulation of food and drugs can be traced back to 1862 when President Abraham Lincoln appointed Charles M. Wetherill to serve in the newly created Department of Agriculture.¹⁵ Wetherill served in the Bureau of Chemistry which was the predecessor to the Food and Drug Administration.¹⁶

Since Wetherill's appointment, Congress has passed a series of laws designed to ensure the safety of U.S. food and drugs. Food and drug safety statutes have included: the Tea Importation Act in 1897, the Biologics Control Act in 1902 (the result of children receiving tainted vaccines),¹⁷ the original Food and Drugs Act in 1906, the Meat Inspection Act in 1906, the Gould Amendment in 1913, the Harrison Narcotic Act in 1914, and the McNary-Mapes Amendment in 1930.¹⁸ However, it was not until 1938 that Congress enacted legislation with expansive regulatory enforcement power. In 1938, Congress enacted the Federal Food, Drug, and Cosmetic Act ("FFDCA").¹⁹ Similar bills were previously introduced but were quickly scuttled by industrial interest groups. However, in 1937 S.E. Massengill Co. of Bristol, Tennessee marketed a tainted serum that resulted in the deaths of nearly 100 people.²⁰ The tragedy pushed Congress into action and the FFDCA was passed. From the time of the FFDCA's passage in 1938, the FDA was primarily concerned with adulterated food and ineffective medications.²¹

¹⁵ *Significant Dates in U.S. Food and Drug Law History*, U.S. FOOD AND DRUG ADMINISTRATION, <http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.htm> (last updated Mar. 25, 2014).

¹⁶ *Id.*

¹⁷ Sharon B. Jacobs, *Crises, Congress, and Cognitive Biases: A Critical Examination of Food and Drug Legislation in the United States*, 64 *FOOD & DRUG L.J.* 599, 601 (2009).

¹⁸ *Significant Dates*, *supra* note 15.

¹⁹ *Id.*

²⁰ Jacobs, *supra* note 17, at 602-06.

²¹ *Id.* at 599

The Food and Drug Act of 1938 contained many provisions that significantly expanded the regulatory role of the Federal Government in the food and drug industry. Some of the more notable provisions include: the authority to regulate cosmetics and therapeutic devices,²² a requirement that new drugs be proven safe before marketing is allowed,²³ removing the requirement to show intent to defraud in drug misbranding cases,²⁴ and implementation of standards for the identity and quality of food.²⁵ The statute also included the authority to inspect factories as well as quarantine drugs that did not conform to good manufacturing practices.²⁶ Section 374(a) of the Food and Drug Act provides:

For purposes of enforcement of this Act, officers or employees duly designated by the Secretary, upon presenting appropriate credentials and a written notice to the owner, operator, or agent in charge, are authorized (1) to enter, at reasonable times, any factory, warehouse, or establishment in which food, drugs, devices, or cosmetics are manufactured, processed, packed, or held, for introduction into interstate commerce or after such introduction, or to enter any vehicle being used to transport or hold such food, drugs, devices, or cosmetics in interstate commerce; and (2) to inspect, at reasonable times and within reasonable limits and in a reasonable manner, such factory, warehouse, establishment, or vehicle and all pertinent equipment, finished and unfinished materials, containers, and labeling therein.²⁷

²² Significant Dates, *supra* note 15.

²³ *Id.*

²⁴ *Id.*

²⁵ *Id.*

²⁶ *Id.*

²⁷ 21 U.S.C § 374(a) (2014).

In 1962, Congress amended the 1938 Act to “bring about better, safer medicine and to establish a more effective system of enforcement of the drug laws.”²⁸ The amendment to FFDCA was largely driven by increased drug safety scrutiny following a large number of birth defects in Europe caused by a thalidomide compound marketed by a German company, Gruenenthal.²⁹ Fortunately, the FDA prevented the Gruenenthal drug from being marketed in the United States due to diligent FDA agents, but some industry researchers claimed the thalidomide compound would have been compliant with the current U.S. drug laws. The extraordinary efforts of the FDA agents were the only reason the compound did not reach the U.S. market. Proponents of revising the FFDCA in order to expand the FDA’s regulatory authority latched onto these findings and used them to leverage the passage of an amendment.³⁰

The 1962 Amendment required any facility manufacturing or processing drugs to be registered with the Department of Health, Education, and Welfare (the precursor to the Department of Health and Human Services).³¹ Additionally, the Amendment strengthened the FDA’s inspection authority.³² The 1962 Amendment defined a drug as “adulterated” if it is not manufactured in conformance with “good manufacturing practices.”³³

Following the 1962 Amendment, Congress took actions that affect the role of the FDA on several occasions. The Infant Formula Act, intended to establish minimum nutrient requirements for infant formula and define adulteration, was passed in 1980.³⁴ Additionally, the Food and Drug Administration Amendments Act was passed in 2007 (“FDAAA”).³⁵ However, as a general rule, the

²⁸ Jacobs, *supra* note 17, at 608.

²⁹ *Id.* at 608-09

³⁰ *Id.* at 609-10

³¹ *Id.*

³² *Id.*

³³ Freddy A. Jimenez, *Enforcement of the Current Good Manufacturing Practices for Solid Oral Dosage Forms After United States v Barr Laboratories*, 52 FOOD & DRUG L.J. 67, 67 (1997).

³⁴ Jacobs, *supra* note 17, at 612.

³⁵ Jacobs, *supra* note 17, at 612.

foundation of the FDA's current system of inspection is based in the 1938 FFDCA and has expanded through statutory enactment over the years.

B. Inspection Process

The 1938 Act authorized the Federal Government to inspect manufacturers or processors of products that fall under the regulatory scope of the FDA.³⁶ Some examples of industries which fall under the inspection authority include: vaccine and drug manufacturers, blood banks, food processing facilities, dairy farms, and animal feed processors.³⁷ Additionally, the Federal Government inspects the following: facilities that conduct studies in people, such as clinical trials; laboratories that conduct studies in animals or microorganisms when the studies are used to apply for FDA approval of a medical product; foreign manufacturers and processors that sell FDA regulated products in the United States; and imported products at the border.³⁸

Under the authority of the 1938 Act, the FDA currently conducts several types of inspections of drug product manufacturers.³⁹ The FDA conducts pre-approval inspections ("PAI") upon submission of a new product application, including New Drug Applications, Biological Licensing Application, or Abbreviated New Drug Application.⁴⁰ If a manufacturer intends to market a drug product, it must first gain approval of the manufacturing facility from the FDA. The FDA attempts to ensure the manufacturing facility is capable of manufacturing the product in compliance with regulatory expectations.⁴¹

³⁶ *What Does FDA Inspect*, FDA.GOV, <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm194888.htm> (last updated Feb. 12, 2014).

³⁷ *Id.*

³⁸ *Id.*

³⁹ *Id.*

⁴⁰ *Id.*

⁴¹ *See* U.S. FOOD & DRUG ADMIN., COMPLIANCE PROGRAM GUIDANCE MANUAL, CHAPTER 46 – NEW DRUG EVALUATION 2 (2012) *available at* <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufa>

A second type of inspection is the “for cause” inspection. These inspections occur when a specific problem is called to the attention of the FDA.⁴² An example of a “for cause” investigation would be an inspection following consumer complaints or adverse reactions to a particular product.

The final type of inspection is a routine inspection. These are recurring inspections at facilities that manufacture, process, or hold FDA regulated drug products.⁴³ The purpose of a routine inspection is to ensure continued compliance with manufacturing regulations. The routine inspection process is subsequent to the PAI and is intended to prevent the need for a “for cause” inspection.

C. Regulations

The requirements for manufacturing FDA regulated drug products are known as current Good Manufacturing Practices (“cGMP”). The 1962 Amendment to the FFDCA established cGMPs as the standard by which to inspect FDA regulated facilities for compliance.⁴⁴

The cGMPs are a system of regulations that are intended to “assure proper design, monitoring, and control of manufacturing processes and facilities.”⁴⁵ The purposes of the regulations are to define the necessary quality systems that must be in place for a drug to be consistently manufactured in a safe manner. The FDA defines the cGMPs as:

Adherence to the cGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This

cturing/QuestionsandAnsweronCurrentGoodManufacturingPracticescGMP forDrugs/ucm071871.pdf.

⁴² *What Does FDA Inspect*, *supra* note 36.

⁴³ *Id.*

⁴⁴ *Facts About Current Good Manufacturing Practices (cGMPs)*, FDA.GOV, <http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm169105.htm> (last updated May 2, 2013).

⁴⁵ *Id.*

includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.⁴⁶

The cGMP regulations are the minimum regulatory requirements. It is not unusual for manufacturers to exceed the basic requirements outlined in the cGMPs.⁴⁷ The cGMPs are broadly written in order to allow individual manufacturers the freedom to establish scientifically sound strategies to comply with the requirements. Two different manufacturers may adopt different strategies that are both compliant. For example, cGMPs require manufacturers to establish procedures that keep microbiological contamination from entering sterile drug products.⁴⁸ One manufacturer may establish a process that waits until a drug has been packaged and then irradiates the drug inside the packaging to destroy any microbiological contamination. Another manufacturer may have a product that does not allow the irradiation approach so they choose to filter the product to remove any microbiological contamination prior to packaging. Both strategies conform to the cGMP requirements but are very divergent as strategies and processes.

The cGMPs are found in the Code of Federal Regulations (“CFR”). Title 21 of the CFR contains the cGMPs. Some examples of sections from Title 21 include: manufacturing, processing, packaging, holding drugs,⁴⁹ finished

⁴⁶ *Id.*

⁴⁷ *Id.*

⁴⁸ 21 C.F.R. § 211.113(b) (2014).

⁴⁹ 21 C.F.R. § 210, 225, 226 (2014).

pharmaceuticals (products such as heparin from Baxter International),⁵⁰ medicated feeds,⁵¹ type A medicated articles,⁵² and blood components.⁵³

The cGMP regulations outline the FDA's expectations of manufacturers in many areas. One area in which the cGMPs require compliance is documentation. There are cGMP requirements regarding how the data generated in the manufacturing process is to be documented and retained. There are also requirements for equipment and process validation. Validation is the documented evidence that a piece of equipment or a process achieves the intended results.

Additionally, the cGMPs establish requirements for the manufacturing facility itself. The facility must be capable of maintaining certain levels of cleanliness. Other requirements call for personnel to be appropriately trained for the tasks they will be performing and the training to be documented. Standard operating procedures ("SOP") must be in place and managed in an appropriate manner. There must be a system in place to track errors and how the company corrects and prevents errors from reoccurring in the future. The company also must conduct self audits to ensure compliance. These are just a few of the requirements the cGMPs require of drug product manufacturers.⁵⁴

The small "c" that begins the acronym "cGMP" stands for "current." This word is important because it allows each manufacturer the flexibility to establish his or her own scientifically sound strategies for manufacturing and/or processing drug products.⁵⁵ "Current" is necessary because technology is always evolving and strategies that may have been compliant with the cGMPs ten years ago may no

⁵⁰ 21 C.F.R. § 211 (2014).

⁵¹ 21 C.F.R. § 225 (2014).

⁵² 21 C.F.R. § 226 (2014).

⁵³ 21 C.F.R. § 606 (2014).

⁵⁴ CENTER FOR CELL AND GENE THERAPY, THE EMMES CORP., INTRODUCTION TO GMP & GTP 11, *available at*, https://secure.emmes.com/pactweb/system/files/gmp_gtp_training_022007.pdf.

⁵⁵ Facts About Current Good Manufacturing Practices (cGMPs), *supra* note 44.

longer be compliant today.⁵⁶ Current Good Manufacturing Practices vary in the amount of guidance given to manufacturers; the more risk a certain process presents to consumers, the more government oversight exists.⁵⁷

II. ANALYSIS

Based on the historical expansion of the FDA's regulatory powers and the current regulations (cGMPs), it would seem the FDA has the necessary authority to prevent incidents like Baxter's tainted heparin from occurring. However, the incident did occur despite the FDA's regulatory powers and current inspection scheme. Additionally, the reoccurrence of similar issues, such as the 2012 meningitis outbreak as a result of tainted steroid shots prompts the question, "what is hampering the FDA's effectiveness and how can it be improved?" The FDA is in a very difficult position because it receives little credit for the effective measures already in place that have prevented contaminated medication from reaching the marketplace but receives much of the blame when incidents such as Baxter's heparin occur. However, given the consequences that occur when the FDA does fail, the criticisms are arguably fair.

In this author's opinion, the most effective preventative step the FDA has at its disposal, to protect consumers from contaminated products, is "routine" inspections. "For cause" inspections are reactive. A "for cause" inspection is not conducted until after a problem has been identified. Of course, a "for cause" inspection may prevent the problem from being exacerbated or future issues from occurring, but generally there must be a problem before that type of inspection occurs. Drug pre-approval inspections ("PAI") are vitally important, but may not be as accurate a reflection of the manufacturing process as a routine

⁵⁶ *Id.*

⁵⁷ JILL WECHSLER, PHARMACEUTICAL TECH., FDA MOVES TO IMPLEMENT NEW GMP POLICIES 36 (2004), *available at* <http://www.pharmtech.com/pharmtech/data/articlestandard/pharmtech/452004/132382/article.pdf>.

inspection. Manufacturers have prepared for the inspection and know what will be expected. Going into a preapproval inspection, the “i’s” are dotted and “t’s” crossed. A “routine” inspection is generally unannounced and results in a more accurate reflection of the day-to-day manufacturing process. Additionally, a routine inspection differs from a PAI because it allows inspectors to track data over longer periods of time for potential negative trends or failure to properly correct errors that have occurred.

The FDA must effectively use its routine factory inspection process to protect U.S. consumers. However, the FDA does not have the resources to inspect every product that makes it to the consumer.⁵⁸ This would be logistically impossible. Given this reality, foods, cosmetics, and medicines must be organized on a continuum of risk to patients based on intrinsic characteristics of the products.⁵⁹

For many products that fall under the purview of the FDA, the risk of harm to people is mitigated by the presence of natural human defenses. The body has physical barriers that prevent bacteria, viruses, and pathogens from causing sickness and infection.⁶⁰ The immune system, skin, tears, mucus, cilia, stomach acid, and natural occurring microflora all help prevent infection.⁶¹ These physical barriers many times offset the danger of contaminated food or cosmetics.⁶² Typically, only people with compromised or underdeveloped immune systems, such as the elderly or children, are impacted by contaminated food or cosmetics.⁶³ The highest risk to U.S. consumers is either from drug products that contain toxins that will adversely affect the body, despite

⁵⁸ U.S. FOOD AND DRUG ADMINISTRATION, *supra* note 9.

⁵⁹ WECHSLER, *supra* note 57.

⁶⁰ *Immune System*, MICROBIOLOGY ONLINE, <http://www.microbiologyonline.org/about-microbiology/microbes-and-the-human-body/immune-system> (last visited April 9, 2014).

⁶¹ *Id.*

⁶² *Id.*

⁶³ Stephanie Armour et al, *Food Sickens Millions as Company-Paid Checks Find It Safe*, Bloomberg Markets (Oct. 11, 2012), <http://www.bloomberg.com/news/2012-10-11/food-sickens-millions-as-industry-paid-inspectors-find-it-safe.html>.

the body's physical defenses, or drug products that bypass the body's natural defenses such as injectibles.

When these types of high risk drug products are manufactured incorrectly, incidents such as the 2008 heparin outbreak and 2012 steroid meningitis outbreak can result. Heparin and steroid shots are drug products that are injected directly into the patient's blood stream or muscle tissue, bypassing the body's physical defenses. If injectable drug products contain even a trace amount of contamination, serious repercussions are usually to be expected.

As a result, manufacturing these medications is a very complicated and expensive process. Due to these risk factors, and a realization that the FDA has finite resources, the FDA has a strategy of concentrating more resources towards oversight, such as inspections, of manufacturers that produce high-risk goods, such as injectable medicines.⁶⁴

Despite the FDA's increasing regulatory power over the years, as well as its risk-based approach, this author believes certain trends have made it increasingly difficult for the FDA to regulate the industry and protect consumers. These trends include increased globalization of, and quickly evolving technology for, high-risk product manufacturing. These trends have created barriers to FDA inspections by increasing the jurisdiction the FDA must inspect and the depth of knowledge the inspectors must attain.

A. Globalization

Traditionally, pharmaceutical companies were highly centralized, and conducted the entire process of drug development, from research through manufacturing, domestically.⁶⁵ However, "[g]lobal production of FDA-regulated goods has exploded over the past ten years. In addition to an increase in imported finished products,

⁶⁴ WECHSLER, *supra* note 57; U.S. FOOD AND DRUG ADMINISTRATION, *supra* note 9.

⁶⁵ Rachna Pande, Globalization of Biopharmaceutical Manufacturing 15 (Sept. 2011) (unpublished S.M. thesis Massachusetts Institute of Technology) (on file with author).

manufacturers increasingly use imported materials and ingredients in their U.S. production facilities, making the distinction between domestic and imported products obsolete.”⁶⁶ Some estimates predict importation of FDA regulated goods will triple between 2007 and 2015 (a 15% annual growth rate).⁶⁷ From 2007 to 2011 FDA regulated shipments from China increased from 1.3 million to 2.1 million annually.⁶⁸ The number of foreign facilities making FDA regulated drugs has doubled between 2001 and 2007 (1282 – 2820).⁶⁹ Of the 2.1 million FDA regulated imports from China, 30% were drugs or medical devices (630,000).⁷⁰ New manufacturing facilities in China and India make up more than 40% of FDA-registered foreign pharmaceutical locations.⁷¹ Supply chains are becoming increasingly globalized and complex.⁷²

Additionally, increasing populations throughout the globe have resulted in increased demand in new markets for drug products. This new demand is one of the drivers for increased globalization in the food and drug industry manufacturing. Increased demand also presents a new challenge for the FDA because drug seizures or manufacturer closures may result in drug shortages worldwide. Drug shortages in the United States alone rose from 61 incidents in 2005, to 178 incidents in 2010.⁷³ In addition to the challenges of regulating a quickly globalized industry, the FDA now also feels the pressure to keep the “presses rolling” by not closing manufacturing facilities. The FDA is in the unenviable spot of attempting to regulate

⁶⁶ *FDA Unveils New Global Strategy to Help Ensure Safety and Quality of Imported Products*, U.S. FOOD AND DRUG ADMIN. (June 20, 2011), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2011/ucm259848.htm>.

⁶⁷ *FDA Fact Sheet: Increasing FDA Capacity in China*, FDA.gov, <http://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/ucm291754.htm> (last updated Feb. 13, 2012).

⁶⁸ *Id.*

⁶⁹ Pande, *supra* note 66, at 18.

⁷⁰ *FDA Fact Sheet*, *supra* note 68.

⁷¹ Pande, *supra* note 66, at 19.

⁷² *FDA Fact Sheet*, *supra* note 68.

⁷³ Pande, *supra* note 66, at 19.

food and drug products perfectly and without any similar instances as the problem with Baxter heparin, while at the same time not causing drug shortages in the process. Given this global trend, the FDA is facing a global regulatory challenge that requires new and creative approaches to maximize resources and increase regulatory effectiveness.

Increased globalization is a challenge for the FDA's inspection process because it has expanded the area in which regulated products are marketed. Fifty years ago, the FDA could inspect a factory and see the entire process, cradle to grave, in one location. Today, the manufacturing process may occur over several continents, as was the case for the Baxter heparin.⁷⁴ As a result, the number of facilities the FDA is required to inspect has significantly increased.

B. Industry Technology

Manufacturing of high risk drug products such as injectable drugs occurs in "clean rooms." Microbe-free clean rooms were first used in hospital settings in the late 1800's when there was increasing knowledge that bacteria caused surgical infections.⁷⁵ The first hospital clean room sprayed carbolic acid (phenol) into the air, and onto the surgeon's hands and tools to eliminate bacteria.⁷⁶ Throughout the early 1900's, more advances were made in aseptic gowning techniques for surgeons.⁷⁷ In 1961, Charnley and Howorth invented a "greenhouse" to provide clean, unidirectional air over a surgical operating table.⁷⁸ Charnley and Howorth also improved the design of fabric and clothing used in the "greenhouse" to prevent the dispersion of microbes.⁷⁹ As a result of Charnley and Howorth's discoveries, infections

⁷⁴ Walt Bogdanich, *F.D.A Tracked Poisoned Drugs, but Trail Went Cold in China*, N.Y. TIMES (June 17, 2007), http://www.nytimes.com/2007/06/17/health/17poison.html?_r=2&.

⁷⁵ WILLIAM WHYTE, CLEANROOM TECHNOLOGY: FUNDAMENTALS OF DESIGN, TESTING AND OPERATION 12 (2d ed. 2010).

⁷⁶ *Id.*

⁷⁷ *Id.* at 14.

⁷⁸ *Id.* at 17.

⁷⁹ *Id.* at 18.

during hip replacement surgeries, which used the “greenhouse,” went from 10% to less than 1%.⁸⁰

Industrial clean rooms were first established to improve manufacturing quality of gun, tank, and aircraft components during WWII.⁸¹ These rooms used non-shedding materials such as stainless steel for manufacturing.⁸²

Research relating to nuclear fission, biological weapons and chemical weapons drove the invention of High Efficiency Particulate Air (“HEPA”) filters.⁸³ These filters allowed extremely clean air to be showered over the area in which critical manufacturing was occurring.

The first room which put together all the components for microbial cleanliness was a Western Electric factory in North Carolina which built missile gyroscopes. The personnel wore non-shedding clothing; the room was built of materials that were non-shedding and easily cleanable; and the air was filtered through HEPA filters.⁸⁴ This strategy remains the current strategy in most FDA regulated clean rooms. After the Western Electric clean room, the next pivotal moment for clean rooms came in 1960 when Willis Whitfield organized a bank of HEPA filters that supplied air that flowed in a laminar direction.⁸⁵ Laminar (unidirectional) airflow creates a blanket of clean air that protects whatever is being processed within the area.

Much of the history of clean rooms is embodied in the cGMP regulations, and as such, is a standard by which the FDA measures manufacturer compliance. The FDA’s expectation is that manufacturing of high risk drugs such as injectables be done in a clean room where microbial contamination is controlled (See Image 1). The cGMPs do not specifically require all the strategies be employed in clean rooms, but the FDA releases guidance to the industry reports which explain the FDA’s minimum expectations in

⁸⁰ *Id.*

⁸¹ *Id.* at 19.

⁸² *Id.* at 20.

⁸³ *Id.*

⁸⁴ *Id.* at 21.

⁸⁵ *Id.* at 20.

manufacturing facilities (informal rules). The FDA cites other guidance documents such as the International Standards Organization (ISO) standards in their guidance to the industry for establishing the clean room expectations when manufacturing.⁸⁶

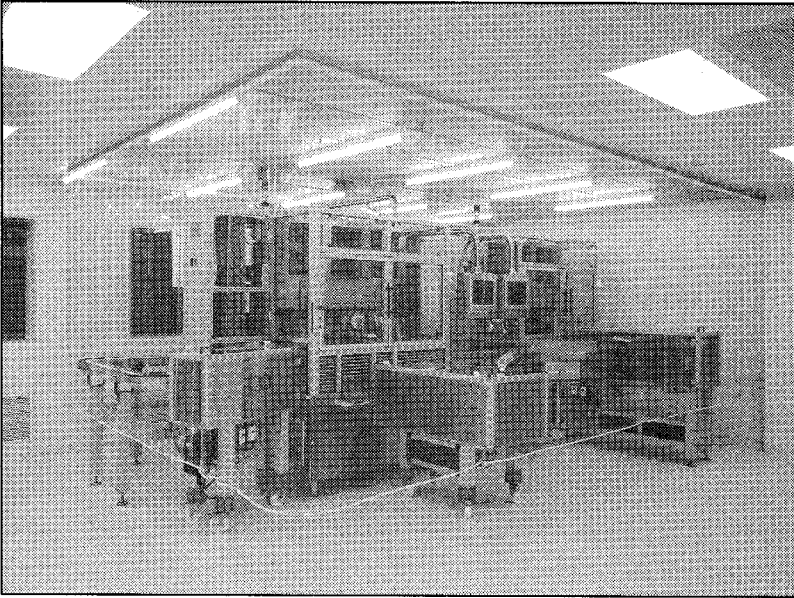


Image 1: Traditional Clean Room⁸⁷

However, new forms of equipment have allowed the industry to move away from the traditional “clean room” manufacturing strategy that the FDA has established as an expectation. Modern technology has allowed computers and machines to perform some of the roles previously conducted manually by humans (the greatest source of contamination in clean rooms). Equipment such as depyrogenation tunnels, automatic lyophilizer loading systems, clean-in-place/sterilization-in-place systems, and automated check/adjustment systems all reduce the human interaction

⁸⁶ U.S. DEPT OF HEALTH & HUMAN SERV. ET AL., GUIDANCE FOR INDUSTRY: STERILE DRUG PRODUCTS PRODUCED BY ASEPTIC PROCESSING – CURRENT GOOD MANUFACTURING PRACTICE, 5, (2004), *available at* <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf>.

⁸⁷ *Medical*, ADVALTECH, <http://www.styner-bienz.com/group/mediainfo/picture-archive/marketsproducts/medical.html> (last visited Jan. 11, 2013).

within the manufacturing environment.⁸⁸ Each of these automated pieces of equipment has subject matter experts employed by manufacturers to ensure the equipment is functioning properly and doing the job as intended. However, the FDA does not have the resources to inspect every facility with a similar subject matter expert for each piece of equipment. The automated equipment results in a better process, but a process that is much more complex and has to meet increased regulatory requirements such as computer system validations. This presents a challenge to the FDA's current inspection scheme by requiring inspectors to gain a much broader base of knowledge to properly inspect a manufacturer.

Some other examples of trends in manufacturing equipment that are different from the traditional manufacturing practices include isolators and restricted access barriers. Isolators are closed systems in which a bank of HEPA filters supplies air within a rigid walled "box" (See Image 2). All of the critical drug manufacturing steps occur within this "clean box." The only human interaction occurs through permanently mounted gloves that are accessed from the outside of the box. The advantage is the elimination of human interaction within the manufacturing areas. However, because there is no human interaction, there is an increase in automation and computer controlled systems. This results in a much more complex validation, complex SOPs, and complex quality systems. An inspector inspecting the facility must understand all of this complexity.

⁸⁸ James Akers & James P. Agalloco, *Clean Rooms, RABS and Isolators: Validation and Monitoring in the Diverse World of Aseptic Processing*, AM. PHARMACEUTICAL REV., May/June 2011 available at <http://www.americanpharmaceuticalreview.com/Featured-Articles/36878-Clean-Rooms-RABS-and-Isolators-Validation-and-Monitoring-in-the-Diverse-World-of-Aseptic-Processing/>.

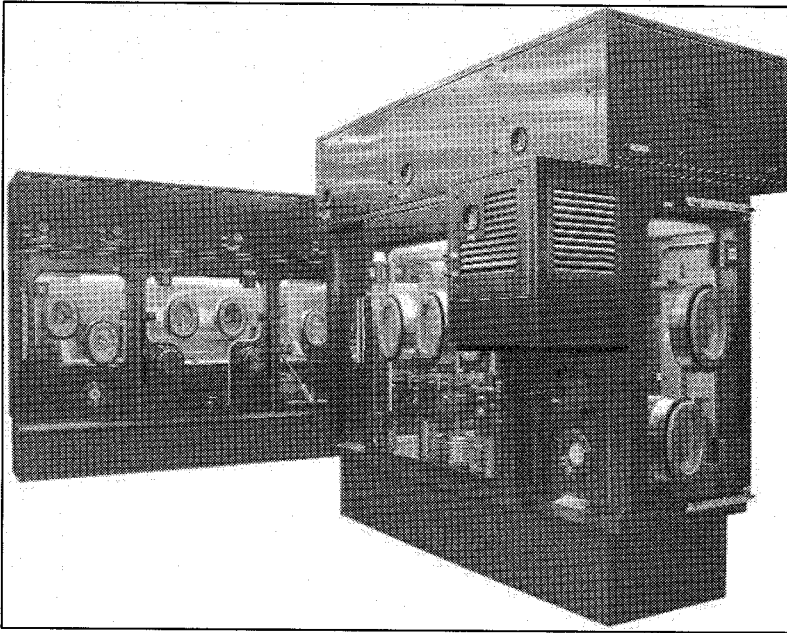


Image 2: Aseptic Isolator⁸⁹

An intermediary between the isolator and the clean room is the restricted access barrier (See Image 3). This system creates a containment box, which can be opened in some situations in order to perform manual manipulations. Once again, this is a challenge for an inspector. If a facility utilizes either an isolator or a restricted access barrier to manufacture drug products, the inspector must fully understand the requirements of, and differences in, each form of technology.

⁸⁹ Skan AG, *Isolator Technology*, PHARMACEUTICAL INT'L, (April 7, 2007, 12:33 PM), <http://www.pharmaceutical-int.com/article/isolator-technology.html>.

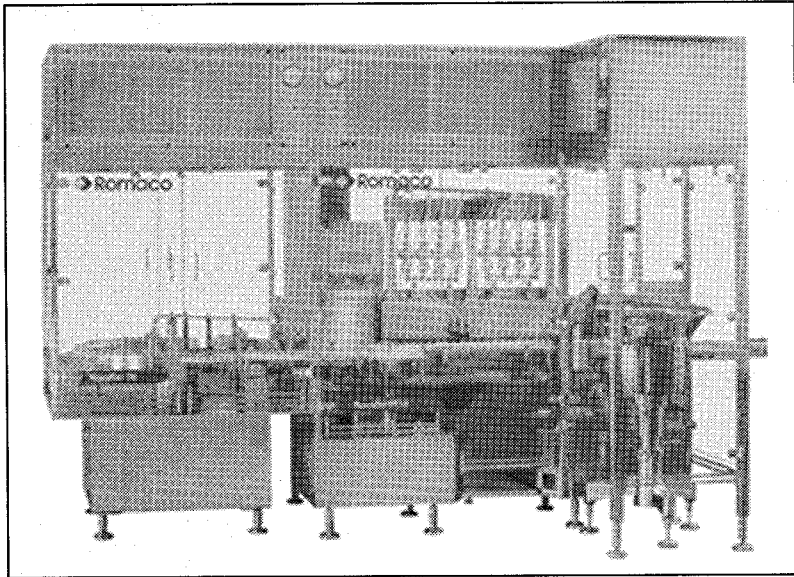


Image 3: Restricted Access Barrier⁹⁰

Additionally, new modes of medicine delivery are becoming more and more prominent. Traditionally, aseptic medicine was packaged in an ampoule from which the doctor would use a syringe to extract the medicine. Ampoules evolved into vials, and now, direct injection pens and pre-dosed cartridges are the trend.

Methods of analyzing data are evolving in the manufacturing industry as well. Recently the United States Pharmacopeia (“USP”), a non-profit publication that provides guidance to the industry by establishing documentary and reference standards for medicine, revised chapter 1116. Chapter 1116 is titled “Microbiological Control and Monitoring of Aseptic Processing Environments.” The chapter gives guidance on how manufacturers of high risk medication should monitor for microbiological contamination in clean rooms. Historically, 1116 set numerical limits on how much contamination could be recovered in clean rooms while still being considered in a state of control. However, the revised chapter advises a more holistic approach where recovery of microbiological

⁹⁰ *News & Events*, ROMACO, <http://www.romaco.com/gb/news/artikel/news/the-vf-18-aseptic-liquid-filling-machine.html> (last visited Jan. 11, 2013).

contamination is analyzed for negative trends rather than discrete occurrences. The FDA relies heavily on the USP when inspecting factories. Shifts in USP recommendations create new quality strategies in the industry. This requires additional knowledge and flexibility on the part of inspectors.

New methods of collecting data are also emerging. The traditional method of determining whether or not microbial contamination is present requires exposing a petri dish with an appropriate medium, such as trypticase soy agar, to the desired environment over a given period of time.⁹¹ The medium provides nutrients to any bacteria that fall onto the surface of the petri dish. After several days of incubation, bacteria on the surface of the petri dish will grow to a point where visible. A microbiologist will count the number of bacterial “colonies” and compare it to the allowable amount of contamination for the area to determine if the area was sufficiently clean during manufacturing activities. This approach is effective but time consuming. This method only reveals contamination several days after manufacturing has occurred.

New technology has recently been emerging that yields instant analysis of microbial contamination. One technology (of many that are being developed) uses an enzyme found in lightning bugs to create a chemical reaction when proteins from bacteria are present on a given surface. The tool measures the amount of light released in the chemical reaction and reports the results instantly. While this technology is still in its infancy, it could revolutionize the way manufacturers analyze the cleanliness of their facility. Another example of new technology that may revolutionize data collection is Azbil’s BioVigilant system. This system instantly detects both non-viable and viable particles using lasers and bioluminescence.⁹² The current guidance from the FDA

⁹¹ *Limitations of Traditional Microbiological Methods*, EHOW, http://www.ehow.com/info_8616775_limitations-traditional-microbiology-methods.html (last visited April 11, 2014).

⁹² *Azbil BioVigilant’s Instantaneous Microbial Detection System*, http://www.youtube.com/watch?v=I_2WBBfrf24 (last visited Feb. 05, 2013).

assumes the use of the traditional methods of microbial recovery. If a company invests in new technology, such as BioVigilant, there is no guidance to indicate what results would be deemed acceptable for a clean room environment. These new technologies are just one example of the complexity an FDA inspector must adapt to when conducting an inspection. New methods and technology are constantly emerging and the FDA must determine if it meets the intent of the cGMPs. These determinations require technical knowledge in multiple areas.

All of the examples of evolving technology present increased responsibilities for the FDA. This evolution and constant change requires the agency to be ahead of the curve and make regulatory decisions quickly in order to provide stability to the industry. The FDA hires exceptionally talented and bright individuals as inspectors. However, manufacturers employ subject matter experts in many different areas such as microbiology, engineering, validation, chemistry, etc. The FDA inspectors must understand the nuanced approaches each of these areas employs and determine if the strategy is sound and compliant with the regulatory requirements. This is a challenging task even for the sharpest inspector.

Modern technology that is being utilized in sterile manufacturing is consistent with the “c” in cGMPs. It is producing a cleaner way of making medicine. However, it poses a challenge for the FDA because it makes ensuring compliance harder. Complex systems require complex software, validations, cleaning, etc. The FDA must assess the current inspection scheme to maximize the specific talents of each inspector.

C. FDA's Response to Globalization and Evolving Technology

The FDA is not blind to the challenges it is facing. The agency has taken steps to address both increased globalization and the difficulty in regulating new technology and evolving processes.

Between 2007 and 2009, foreign manufacturing plant inspections have increased from 333 to 424.⁹³ The FDA has collaborated with other regulatory agencies around the globe by working on harmonizing regulations. The Pharmaceutical Inspection Cooperation/Scheme (PIC/S) is an informal organization of drug manufacturing inspectorates from 39 different countries.⁹⁴ The FDA obtained full PIC/S membership in 2010.⁹⁵ The goal of the PIC/S organization is to develop and disseminate consistent cGMP standards.⁹⁶ This will result in manufacturers being held to the same standards regardless of where the manufacturing occurs. Currently, regulations in China may differ from standards in the United States or Europe. This creates difficulty for manufacturers as well as inspectors. The FDA has moved to eliminate this hurdle by joining PIC/S.

Additionally, the Global Harmonization Task Force (“GHTF”) was created to provide a forum for medical device manufacturers.⁹⁷ The FDA is assembling global coalitions of regulators.⁹⁸ This strategy will provide global data information systems and networks so regulators worldwide can more easily collaborate in real time.⁹⁹ The FDA is attempting to modernize its IT capabilities, allowing easier communication and interaction with global manufacturers.¹⁰⁰ The FDA is also allocating agency resources on a risk based model.¹⁰¹ This allows the FDA to focus more resources on higher risk products.

⁹³ U.S. FOOD & DRUG ADMIN., *supra* note 9.

⁹⁴ *Id.* at 19.

⁹⁵ THOMAS PEITHER, FDA WILL OBTAIN FULL PIC/S MEMBERSHIP IN 2010, MAAS & PEITHER AG – GMP PUBLISHING (2010), at 1, *available at* <http://www.picscheme.org/bo/commun/upload/document/article-on-us-fda-pdf.pdf>.

⁹⁶ *Id.*

⁹⁷ U.S. FOOD & DRUG ADMIN., *supra* note 9.

⁹⁸ *Id.* at 24.

⁹⁹ *Id.*

¹⁰⁰ *Id.* at 20.

¹⁰¹ *Id.*

In 2011, the FDA Food Safety Modernization Act was enacted.¹⁰² Under the Act, importers now have the explicit responsibility to ensure the source of the imports have sufficient quality system controls in place.¹⁰³ This places the onus on the manufacturers to control their third party manufacturers that may be located outside of the United States. Additionally, the agency can now certify a third party system for inspecting foreign supplies of food, freeing agency resources.¹⁰⁴ This strategy is based on the risk model, that food products are generally lower risk than medicines, and therefore third parties can adequately verify the producers. Arrangements with foreign governments that leverage their resources are encouraged as well.¹⁰⁵

Despite these improvements to the FDA strategy, the FDA cannot keep up with the trend in globalization. It would take approximately nine years for the FDA to inspect every high risk drug manufacturing facility just one time.¹⁰⁶ It is expensive to inspect foreign facilities. The average cost of inspecting a domestic facility is approximately \$23,000 while the cost of inspecting a foreign facility is approximately \$52,000.¹⁰⁷

The FDA has also implemented changes to account for rapidly evolving technology in the industry. In 2002, the FDA announced a new program called the Pharmaceutical Current Good Manufacturing Practices for the 21st Century.¹⁰⁸ The new program was intended to modernize the cGMP regulations to account for new technology and practices. The new program encouraged manufacturers to use scientific rationale to create risk-based quality systems.¹⁰⁹

Additionally, as a response to increasingly complex manufacturing processes and technology, the FDA

¹⁰² *Id.*

¹⁰³ *Id.*

¹⁰⁴ *Id.*

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

¹⁰⁷ Pande, *supra* note 66, at 19.

¹⁰⁸ U.S. FOOD AND DRUG ADMINISTRATION, COMPLIANCE PROGRAM GUIDANCE MANUAL, *supra* note 41.

¹⁰⁹ *Id.*

developed the Pharmaceutical Inspectorate (PI). Certification for the program began in 1994.¹¹⁰ The program was initiated as a response to the industry asking for more consistency in the inspection process.¹¹¹ The program establishes three levels of certification for drug inspectors. Level I inspectors are newly hired inspectors, and certification requires intensive classroom training.¹¹² Level II inspectors require more in-depth knowledge of active pharmaceutical ingredient manufacturing, computer systems validation, industrial sterilizations, and drug manufacturing/quality control.¹¹³ The preeminent level is Level III. These inspectors comprise the Pharmaceutical Inspectorate.¹¹⁴ Eligibility to become part of the Pharmaceutical Inspectorate is based on a minimum of three years inspecting drug manufacturers, certification as a Level II, endorsement by management, and selection or nomination by the Level III certification board.¹¹⁵

The PI spends approximately 80% of his or her time participating in foreign and domestic drug inspections.¹¹⁶ Level III certified investigators are expected to be competent in the latest regulatory programs and procedures as well as technology.¹¹⁷ Level III certified investigators are also expected to develop and implement formal training for FDA, industry, and state/local officials.¹¹⁸

Additionally, there are many forums for the industry to present new strategies and receive feedback from regulatory agencies. This allows the FDA to stay up-to-date on the latest industry strategies and provide regulatory feedback. The Pharmaceutical Drug Association (“PDA”) hosts conferences in which many of the newest technological

¹¹⁰ RICK PERLMAN, WHAT’S NEW IN THE FDA’S PHARMACEUTICAL INSPECTORATE AND RISK BASED SYSTEMS INSPECTION, ASQ (2006), *available at* asq.org/fdc/events/ppt/200604-golden-gate-section-conference.ppt.

¹¹¹ *Id.*

¹¹² *Id.*

¹¹³ *Id.*

¹¹⁴ *Id.*

¹¹⁵ *Id.*

¹¹⁶ *Id.*

¹¹⁷ *Id.*

¹¹⁸ *Id.*

advances and strategies are presented. The FDA regularly attends and provides input to the industry.

Finally, the FDA has created several committees to advise the agency as well as the industry in regards to drug safety trends and strategies. In 2002, the Drug Safety and Risk Management Advisory Committee was formed. The committee is made up of experts in science as well as risk management. The committee “advises the Commissioner or designee in discharging responsibilities as they relate to helping to ensure safe and effective drugs for human use.”¹¹⁹ The FDA also created the Drug Safety Oversight Board. Members of the board are comprised of FDA personnel as well as other governmental agencies. The board’s purpose is to advise the FDA “on the handling and communicating of important and often emerging drug safety issues” and to provide “a forum for discussion and input about how to address potential drug safety issues.”¹²⁰

Beyond the difficulty faced by the FDA and other regulators, globalization and new technology has also presented challenges for the industry as they seek to manufacture goods that are compliant with cGMP regulations. One of the difficulties faced by manufacturers is that inspectors with technical expertise in a specific field are responsible for inspecting every aspect of a facility. This results in potential regulatory enforcement actions based on incomplete background knowledge of the particular area that is being assessed. Additionally, quickly evolving technology has created a multitude of strategies and it is difficult to know regulatory expectations until an inspection occurs. Finally, many manufacturers sell products globally; as a result, they must comply not just with the CFR

¹¹⁹ FDA, DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE CHARTER, FOOD AND DRUG ADMIN. (2012), *available at* <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/ucm094886.htm>.

¹²⁰ SUSAN THAUL, CONG. RESEARCH SERV., R41983, HOW FDA APPROVES DRUGS AND REGULATES THEIR SAFETY AND EFFECTIVENESS 9 (2012) *available at* <http://www.fas.org/sgp/crs/misc/R41983.pdf> (quoting *Drug Oversight Board*, FOOD AND DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucu082129.htm> (last updated Dec. 22, 2010)).

regulations. Companies must interpret the regulations from every country in which they sell products.

III. RECOMMENDATIONS

Based on the challenges facing the FDA along with the expectation from the public of perfect enforcement, the agency should consider new strategies for routine inspections that better utilize the agencies resources.

The primary driver for safe products is not necessarily the fear of enforcement proceedings from a regulatory agency. Manufacturers do consider regulatory compliance vitally important, but the primary driver for any manufacturer is the overall health of the business. If a business manufactures a product that harms consumers, there is little doubt they will falter and perhaps even fail as a business. If a manufacturer is not acting in good faith, there is a strong likelihood that no matter what the current regulatory guidance or inspection strategy entails, consumers will eventually be hurt. The FDA recognizes this truth and has indicated the belief that most manufacturers intend to comply with regulations. "A basic precept of FDA enforcement policy . . . that a majority of persons desire to comply with the law and will comply voluntarily when given information as what is required and what violations appear to exist."¹²¹

For situations where a manufacturer has not acted in good faith, the regulatory reaction must be swift and harsh to dissuade other companies that may consider similar actions in the future. This is the purpose of "for cause" inspections. The incidents that can be avoided are situations where manufacturers desire to comply, but may not have the proper guidance or knowledge to make proper strategy decisions. To provide the best guidance to manufacturers, and at the same time maximize resources, the FDA should consider separating a routine inspection into two parts, an onsite portion, as inspections occur now, as well as an online portion.

¹²¹ Marie A. Urban, *The FDA's Policy on Seizures, Injunctions, Civil Fines, and Recalls*, 47 FOOD & DRUG L.J. 411 (1992).

A. The Two Parts of a Routine Inspection

A typical routine facility inspection of a high-risk manufacturer, such as injectibles, consists of two parts, document review and facility tours. The document review portion of a routine inspection usually includes the examination of the facilities quality system, or how the manufacturer ensures the medicine is being manufactured safely and correctly. As part of that review, inspectors review raw data during the document review portions of an inspection. The inspector ensures the quality system and data align with the cGMP expectations outlined in the Code of Federal Regulations. The document review portion of the facility inspection is in general very predictable. Many of the same documents and strategies as well as certain data are consistently reviewed during document review. This is true regardless of which regulatory body is conducting the inspection, whether it is the FDA or a foreign agency such as the European Medicines Agency. The following paragraphs highlight a few of the subject areas that are typically covered in a routine inspection of a high risk manufacturer.

Inspectors will ensure the quality system is properly established by verifying a corrective action/ preventative action (“CAPA”) system has been defined and documented.¹²² It is not unusual for the CAPA system to be the first system reviewed during an inspection.¹²³ CAPA is an expectation established by the cGMPs.¹²⁴ A properly established CAPA system will investigate any failure or deviation in the manufacturing process, correct the failure, and prevent it from reoccurring. Preventative actions are also proactive by attempting to predict and prevent similar failures in the future. As part of the CAPA review, the

¹²² Ken Peterson, *Essential Elements of Effective CAPA Systems*, QUALITY DIGEST (Apr. 22, 2008), <http://www.qualitydigest.com/inside/fda-compliance-article/essential-elements-effective-capa-systems>.

¹²³ *Id.*

¹²⁴ 21 C.F.R. § 820.100(a) (2014).

inspector will ensure the appropriate root causes of the failures or deviations are identified and remediated.¹²⁵

Further, when reviewing the quality system, inspectors will typically review strategies to determine if quality and product information is trended and whether or not trends have been identified.¹²⁶ A properly established quality system will communicate data to the CAPA system in ways that are complete, accurate, and timely.¹²⁷ Inspectors will verify this expectation. Other expectations that the inspector will verify in regards to the quality system include: appropriate statistical methods are being utilized for trending quality issues, timelines for approval and execution of corrective and preventative actions follow logical sequences, procedures are followed which establish how to investigate failure or deviations, corrective and preventative actions are effective and verified, corrective and preventative actions are implemented and properly documented, and objective evidence is available to indicate management is actively engaged and notified.¹²⁸

In addition to the CAPA system, inspectors often review several other common areas. Media fills are reviewed during the document review portion of an inspection. A media fill is an exercise in which the entire manufacturing process is replicated using a liquid media that encourages bacteria to grow.¹²⁹ The medicine containers filled with liquid media go through the entire manufacturing processes and are then incubated to ensure no bacteria were introduced into the containers during the manufacturing process. This process demonstrates the facility has the capability of manufacturing without contaminating the product. Media fills are executed on routine intervals to

¹²⁵ *How to Prepare for an FDA Inspection*, PATHWISE, http://www.forumsci.co.il/Landau/General/how_to_prepare_for_an_fda_inspection.pdf. (last visited Mar. 5, 2014) [hereinafter *FDA Inspection*].

¹²⁶ *Id.*

¹²⁷ *Id.*

¹²⁸ *Id.*

¹²⁹ *Media Fill Trials as Process Simulations in Pharmaceutical and Biotech Manufacturing*, RAPID MICROBIOLOGY, <http://www.rapidmicrobiology.com/test-method/media-fill-trials-as-process-simulations-in-pharmaceutical-and-biotech-manufacturing/> (last visited Mar. 5, 2013).

continually prove the facility has maintained its ability to manufacture drugs properly.¹³⁰

Batch release strategies are also reviewed during the document review portion of a routine inspection. A batch release strategy ensures all of the necessary steps in the manufacturing process are completed and documented appropriately. Every batch of medicine is reviewed to ensure each step in the process was completed correctly within the appropriate time period. Batch release strategies are a final check prior to the release of medicine to the market which ensures the medicine is safe. The inspector takes particular interest in any deviation from the routine manufacturing process and analyzes any rationalization the manufacturer may have used to justify releasing the product to the market in those cases. The manufacturing of high risk medicine is a complex process and invariably there will be deviations from the prescribed process. A common example would be someone forgetting to place his or her initials in the appropriate location following the completion of a step in the process. The manufacturer must analyze such discrepancies during the batch review and determine the risk to the product caused by the deviation. If there is no risk to the product, the batch of medicine will likely be released onto the market. However, because a company has a financial interest in determining whether or not there is risk to the product, the FDA will typically review these justifications closely.

Validation of processes and equipment is another area that is typically reviewed during the document review portion of an inspection. Validation is the documented evidence that the equipment or process is performing as it is intended. The FDA has released specific guidance to manufacturers regarding the expectation of process validation.¹³¹ Some process validations that may be reviewed during an inspection of a high-risk manufacturer include the process of making and transporting the bulk

¹³⁰ *Id.*

¹³¹ U.S. DEPT OF HEALTH AND HUMAN SERVS. ET AL., GUIDANCE FOR INDUSTRY PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES (2011).

medicine and the process of cleaning and installing the filling equipment. Some examples of other validations that may be reviewed include: filling equipment, cleaning equipment, data collection equipment / systems, computer software systems, the environment inside the manufacturing area, air flow patterns in the critical manufacturing zones, and utility systems such as water, gas, and steam.

Several other things that may be reviewed include: laboratory testing methods, methods of tracking out of specification data results, systems to check the quality of incoming materials, systems to ensure appropriate packaging and labeling, organizational charts, standard operating procedures, customer complaints, and whether appropriate training is completed for people conducting critical activities.

The document review portion of an inspection will also typically involve the review of raw data and any investigations conducted into non-conforming data. This review includes data collected to ensure the manufacturing areas comply with the requirements of cleanliness as well as data around the manufacturing process itself. Data review will allow inspectors to verify specific cGMP expectations, such as data integrity, good documentation, facility cleanliness, and utility system control have been met. These are just a few examples of subjects typically covered in the document review portion of the inspection process.

The other half of the inspection process typically involves facility and area tours. Facility tours allow the inspectors to observe the conditions of the manufacturer's production area. The inspectors will observe whether or not the personnel are acting appropriately, such as moving slowly and deliberately inside clean rooms. The inspectors will be able to observe whether the facility is adequately clean, whether the laboratories have the appropriate equipment to do testing, and any other criteria expected of manufacturers that must be observed in person.

B. Separation of Inspection Components

The FDA can offset the challenges and costs faced by globalization and technology by separating document review audits from facility tour audits. A common thread that runs through all of document review portions of inspections is that all of the information can be inspected from a remote location.

Evolving technology can be leveraged by the FDA to be in constant contact with manufacturers from a centralized location. Web based “clouds” allow easy and safe document exchange and online meetings allow face to face interactions from remote locations. Collaborative websites could be used for fast, easy, and organized document exchange. An example of how a remote inspection may occur would be to allow the manufacturer to upload strategy documents, validation protocols, and even raw data to a website which they control the access. The FDA could be given access, upon notice, to review the requested documents. It might also be possible for the FDA to access secured websites and see data streaming in real time. Of course, the FDA would need to provide notice before accessing the data, but it would allow for efficient, impromptu checks without any of the current travel time and expenses.

Remote meetings are no longer a concept from science fiction movies. Most businesses, especially those that have international suppliers or third party manufacturers, have the capability of conducting remote, online meetings. This technology should be utilized by FDA inspectors to meet with manufacturers to discuss strategies and data.

Remote interaction with the FDA is not a novel concept for manufacturers and is not an unreasonable burden upon manufacturers. Manufacturers are currently required to interact with the FDA for several reasons following the approval to manufacture drugs. In each of these instances the obligation is on the manufacturers to initiate the required interactions. The Code of Federal Regulations requires manufacturers to notify the FDA if there are any changes to the agreed terms in the new drug application

(“NDA”).¹³² Additionally, manufacturers must notify the FDA if they make any changes to labeling on drugs.¹³³ This includes any changes to actual labeling or even promotional material. The manufacturers must also submit an annual report that includes all labels and promotional material that is being utilized for a given product.¹³⁴ Manufacturers must submit any changes to the manufacturing process to the FDA for review.¹³⁵ Under 21 CFR 314.80, the manufacturers are required to report any adverse events that are associated with the use of the manufacturer’s drug in humans.¹³⁶ Finally, manufacturers are required to submit an annual report to the FDA to summarize any new information regarding the drug to which the manufacturer received NDA approval.¹³⁷

These interactions are typically formal submissions that occur in preapproved formats. For minor changes, an annual report is sufficient and drugs can be marketed without waiting for the annual report to be filed.¹³⁸ Moderate changes require the submission of a CBE-0 or CBE-30 reports.¹³⁹ Marketing is delayed until either the submission of the report or 30 days following the submission.¹⁴⁰ Major changes require the submission of a Prior Approval Supplement (“PAS”) change.¹⁴¹ Marketing of the drug can only occur following the approval of the report for major changes.¹⁴²

Given the fact that manufacturers currently interact with the FDA remotely, it is not too burdensome to additionally require manufacturers to submit to inspections

¹³² PETER BARTON HUTT ET AL., *FOOD AND DRUG LAW* 735 (3d ed.2007).

¹³³ *Id.*

¹³⁴ *Id.*

¹³⁵ *Id.*

¹³⁶ *Id.* at 136.

¹³⁷ *Id.* at 137.

¹³⁸ Arthur B. Shaw, *Drug Master Files*, *FOOD AND DRUG ADMIN.* 46 <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ucm103534.pdf> (last visited Mar. 5, 2014).

¹³⁹ *Id.*

¹⁴⁰ *Id.*

¹⁴¹ *Id.*

¹⁴² *Id.*

remotely as well. The current submissions to the FDA occur on predetermined forms and typically occur at set frequencies or following changes made by the manufacturer. This allows the process to move deliberately and slowly. This would be different than an inspection that would occur remotely. Manufacturers would not have the same amount of time to prepare as they typically do for a submission to the FDA. However, it should not be any more of a burden than when an impromptu inspection occurs at the facility itself.

C. Creation of FDA Hubs

Beyond remote inspections, and in order to account for rapidly changing technology, the FDA should establish specific groups of inspectors to look at subsets of a manufacturer's process in which those inspectors are experts such as PI inspectors. This would be a change from the current strategy of allowing several inspectors to review every aspect of a manufacturer's process. For example, inspectors who have science backgrounds will evaluate the laboratory controls of a company. Engineering inspectors will evaluate facility design and equipment validation. IT inspectors will inspect the data integrity and computer software systems used by companies. These expert subsets of inspectors can form specific hubs that are centrally located, such as in Washington D.C. Each hub would be made up of experts in a specific subject area that is required by cGMPs. The hubs would allow inspectors to focus on one particular subject area and increase their knowledge base in that field. Hubs would help the FDA stay up to date on the most current trends in the industry for particular subject areas. Hubs would also allow proliferation of strategies that are being utilized by the industry as a whole. Proliferation would occur because the inspectors would be very familiar with their particular area of expertise and the various strategies being employed throughout the industry. Using remote inspections, the inspectors can either schedule a meeting to ask questions of the manufacturer

regarding a specific strategy or require the manufacturers to submit strategy documents or data.

This strategy would also allow manufacturers to decentralize their response to an inspection. When an inspection occurs, there is typically an entire group of people that put everything on hold to accommodate the inspection. This group includes facilitators which act as hosts for the inspectors and coordinate the logistics of the inspection.¹⁴³ Additionally, an inspection team will include scribes and runners to write down observations and requests an inspector may have and relay that information to the appropriate parties.¹⁴⁴ Subject Matter Experts are also part of the inspection team. These individuals can speak to specific processes and strategies the manufacturer employs.¹⁴⁵ The inspection team also includes control room staff and members of management.¹⁴⁶ Rather than have a single group that coordinates an inspection, each individual subject area within the manufacturer would be responsible for coordinating the inspection for their particular area with the FDA hub. For example, the manufacturing group that is responsible for assuring the sterility of the facility and processes would interact directly with the FDA hub tasked with inspecting sterility assurance strategies. A microbiologist from the FDA, in this case, would be interacting with a microbiologist from the manufacturer. As a result of this strategy, resolution to questions the inspector may have regarding data or strategy would come more quickly because the FDA hub and the subject matter expert would be speaking the same language. The FDA and the manufacturer's subject matter experts could discuss disagreements or FDA observations. This would save the time it would take for an inspector, who may have a background in a different area, to understand the strategy employed by the manufacturer's microbiologist and determine if that strategy is appropriate under the cGMPs.

¹⁴³ *FDA Inspection, supra* note 125.

¹⁴⁴ *Id.*

¹⁴⁵ *Id.*

¹⁴⁶ *Id.*

In order to maintain the approval to manufacture, manufacturers should be required to gain approval from each hub at a predetermined frequency. In order to maintain a license to manufacture approved products, the manufacturer would have the responsibility of showing that each hub has approved the strategies employed by the manufacturer.

A proposal for the hub groups: Quality Control Laboratories, Validation, Engineering, Manufacturing/Technology, Batch Disposition, Materials Management, Operations, Facilities, and Environmental Monitoring and Sterility Assurance.

Each hub would be responsible for developing expert inspectors in specific subject areas. The Quality Control Laboratories hub would review method transfer protocols, data and transfer reports, method validations, method history, stability data, release data, out of specification results, consistency of data between batches, and lab equipment. The Validation hub would be responsible for reviewing cleaning validations, sterilization strategies, media fills, and cross contamination controls. The Engineering hub would be responsible for calibrations and preventative maintenance, facility drawings, and the fit and finish of the facility. The Manufacturing and Technology hub would be responsible for reviewing process validations, changes to the areas, and risk assessments. The Batch Disposition hub would review the strategies each company employs for final release. The Materials Management hub would review the quality strategies for incoming material as well as labeling and packaging of outgoing materials. The Operations hub would review the standard operating procedures for manufacturing as well as review any deviations from those procedures. The Facilities hub would review the design, validation, and data around facility systems such as clean steam and high purity water. The Environmental Monitoring and Sterility Assurance hub will review qualifications of the environment, data trending, and deviations in environmental results.

Rather than a one or two week audit that occurs bi-annually, the FDA hubs would provide notice regarding

their desire to review various strategies, documents, or data at any point in time. This request would be accommodated by scheduling online meetings or requesting specific documents from a collaborative website. Additionally, the FDA could schedule an online meeting if a question arises regarding the information they may have been initially provided following a request. On many occasions, this process is how a normal inspection occurs in practice. An inspector will ask for documents or data at the end of the day. The inspector will review the requests that evening and ask follow-up questions the next day. All of the review is done remotely, outside of the presence of the manufacturer.

This strategy will require the manufacturer to take responsibility for gaining approval rather than the FDA showing up at the manufacturer's door for inspections. The FDA hubs would allow one set of inspectors to evaluate strategies from many companies both domestic and foreign. This strategy would allow more consistent guidance in particular areas as well as become an effective means to disseminate the latest strategies being used by the manufacturing industry. An inspector may review the sterility assurance control strategies from a manufacturer in Kansas during the morning and then the strategies of a manufacturer from Shanghai during the afternoon. Based on strategies seen in Kansas, the inspector may have some meaningful feedback for the Shanghai manufacturer in regards to areas where their strategies may no longer meet the "current" requirements of cGMPs.

D. Onsite Inspection Strategy

The FDA should use the tradition inspection model for Facility and Area tours. Employing this strategy would cut down on the time needed to conduct an inspection. It would also allow for more impromptu checks. An inspector would likely be able to complete an onsite inspection in several days rather than a week or two. Additionally, on-site inspectors could be in communication with the FDA hub inspectors to be given guidance regarding specific areas or

actions that should be observed based on perceived weakness in the manufacturers overall strategies.

Another option available if the FDA were to separate inspections into two parts would be the use of private, third party inspectors for facility inspections. This strategy is not unprecedented. The food industries already rely heavily on third party inspections.¹⁴⁷ However, third party inspectors have never been utilized to inspect high risk drug manufacturers. Given the criticality of the process and the complex regulations, the FDA has retained the responsibility of inspecting high risk facilities. However, Congress has indicated it supports the use of third party inspectors. The 2002 Medical Device User Fee and Modernization Act required the FDA to accredit third party inspectors for Class II and Class III devices.¹⁴⁸ Additionally, the 2011 Food Safety Modernization Act establishes a system of third party certification for imported foods.¹⁴⁹ Albeit, both of these examples are for instances that are considered low risk. The FDA may feel more comfortable supporting third party inspections of high risk manufacturers if the agency retains a portion of the inspection process itself, which it would with the FDA hubs. With hubs, the FDA would still directly inspect the strategies, processes, and data of high risk manufacturers. The third parties would be verifying the conditions of the facility which is a much more objective measurement.

The manufacturing industry, rather than the FDA, would be responsible for funding the third party inspections. The FDA should establish an expectation of frequency for onsite inspections. In addition to approval from each FDA hub, the manufacturer should be required to pay for a third party inspection of their facility at the frequency established by the FDA. The onsite inspection

¹⁴⁷ *The Value of Third Party Audits*, AIB INTERNATIONAL, <https://www.aibonline.org/press/ValueofThirdPartyAudits.html> (last updated Sept. 9, 2009).

¹⁴⁸ HUTT, *supra* note 132, at 1244.

¹⁴⁹ *Background on the FDA Food Safety Modernization Act (FSMA)*, FDA, <http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm239907.htm> (last updated Mar. 18, 2013).

will be an additional responsibility of the manufacturers in order to maintain the approval to manufacture. The FDA was given authority to certify third party manufacturers in the 2011 Food Modernization Act.¹⁵⁰ The FDA should request similar authorization from Congress to certify inspectors of high risk products as well.

IV. CONCLUSION

Given the challenges facing the FDA's inspection process, the agency should consider revamping their routine inspection process to become more efficient, nimble, and consistent. This can be accomplished by separating facility inspections into two parts, onsite and online, and segregating inspectors into specialized hubs that concentrate on inspecting specific areas.

Would this particular strategy avoid the Baxter heparin incident? No one can say, but there are two reasons to think it might have. First, it may have increased the availability of FDA resources to inspect the Chinese plant manufacturing the tainted ingredient. Inspections could have occurred by a group of inspectors sitting in Washington D.C. Secondly, it may have resulted in a dissemination of better methods for testing for adulterants. The method used by Baxter was not sensitive enough to recognize the adulterated ingredient and was expensive.¹⁵¹ If the FDA had been functioning as a hub, perhaps that particular hub would have been aware of the need for a better methodology. Regardless, limited resources and an expanding jurisdiction demand new and creative ideas for inspections. Separation of the inspection process is a step in that direction.

¹⁵⁰ HUTT, *supra* note 132, at 1244.

¹⁵¹ Kathy Jones, *Improved Test for Adulterated Heparin*, MEDINDIA (Sept. 23, 2011, 6:47 PM), <http://www.medindia.net/news/Improved-Test-for-Adulterated-Heparin-90995-1.htm>.

