THE FDA AND THE PHARMACEUTICAL INDUSTRY: IS REGULATION CONTRIBUTING TO DRUG SHORTAGES?

*Aubrey Roman*

I. INTRODUCTION

Rebecca Robinson was a thirty six-year-old historical interpreter when she was diagnosed with Angiosarcoma, a rare blood-based soft tissue cancer, in February of 2010. Over the next year and a half, after receiving five Doxil chemotherapy treatments at the Dana Farber Cancer Center in Boston, Rebecca’s cancer had weakened and her prognosis was positive. But, in July of 2011, Rebecca’s condition took an abrupt and unexpected turn for the worse because she could not receive her sixth life-saving Doxil chemotherapy treatment. As her doctors explained, “there was no more Doxil available.” Similarly, at the young age of nine, Alyssa Divers was diagnosed with Osteosarcoma, a rare and aggressive cancer. After many sessions of chemotherapy to fight this vicious disease, Alyssa found out that her next chemotherapy appointment might be delayed because the hospital had a shortage of methotrexate—the “cornerstone of therapy” for Osteosarcoma. Alyssa knew that her tumors would double every thirty four days without methotrexate treatments, but in the case of a shortage there was nothing she or her doctors could do to get her the medication that she needed to

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3 Park, supra note 1.

4 See id.

5 Id.

6 Id.

7 Id.
stop the proliferation of her cancer.\textsuperscript{8}

Over the last decade, these stories have become increasingly common in the United States because we are experiencing an unprecedented drug shortage pandemic.\textsuperscript{9} Recently, the term “drug shortage” has become prolific; the term appears in newspaper headlines, hospital forms, and pharmaceutical paperwork informing practitioners and patients alike that the drugs needed to keep patients alive are indefinitely unavailable.\textsuperscript{10} The facts are glaring. The number of drugs in short supply has quadrupled from 2005 to 2011, jumping from sixty one drugs to a staggering 251.\textsuperscript{11} Ominously, in 2010 and 2011, almost seventy five percent of the drugs in short supply were sterile injectable agents, which are the foundation of life-saving cancer treatments, antibiotics, and emergency room medications.\textsuperscript{12}

These startling figures, along with stories like those of Rebecca and Alyssa, seem to implore the inquiry: why are so many of these critical drugs suddenly and simultaneously unavailable? The reason for the shortage of sterile injectable drugs is an exceedingly complex issue and there is no prevailing consensus with regard to why these drugs are in short supply.\textsuperscript{13} The origins of this pandemic can be traced to a variety of factors, including: industry consolidation, production delays due to quality and manufacturing

\textsuperscript{8} See id.
\textsuperscript{12} \textit{Examining the Increase in Drug Shortages: Hearing Before the Subcomm. on Health of the Comm. on Energy & Commerce}, 112th Cong. 7 (2011) [hereinafter Koh Testimony] (statement of Howard K. Koh, Assistant Sec’y of Health, Dep’t of Health & Human Servs., concerning the percentage of drugs in short supply that were sterile injectable agents in 2010); \textit{Frequently Asked Questions About Drug Shortages}, supra note 11 (“In 2011, there were 251 drug shortages reported, 183 [72.9 percent] of which involved sterile injectable drugs.”).
\textsuperscript{13} Koh Testimony, supra note 12, at 13.
challenges, discontinuations, small profit margins, shortages of the necessary raw materials, changes to inventory practices, unanticipated increase in demand, a public shift in policy within the Food and Drug Administration (FDA) regarding its compliance mechanisms, and an increase in the prosecution of high-level corporate managers for statutory violations.14 Despite disagreement among commentators as to the cause of the crisis, it is indisputable that the drug shortage is having devastating effects on both patient care and our health care system as a whole, and the problem must be remedied.15

The next Part of this article sets out the current drug shortage problem by analyzing data compiled by the FDA and the American Society of Health-System Pharmacists (ASHP). Within this part, we focus on the submarket that accounts for most of the current drugs on shortage, sterile injectable drugs. Part III discusses the FDA’s current policy initiatives concerning regulatory compliance in the pharmaceutical industry. Part IV discusses one device that the FDA is using with extraordinary frequency to carry out its compliance policy—the issuance of warning letters that mandate that companies correct all violations within fifteen days or face forced closure. Next, Part V explores the resurrection of the Park doctrine, a legal device used by the FDA and the Department of Justice (DOJ) to criminally prosecute corporate executives whose companies are not in strict compliance with FDA regulations or the Food, Drug, and Cosmetic Act. In conclusion, Part VI suggests that the FDA’s movement to overhaul the pharmaceutical industry has had an unintentional and dramatic effect on the supply of critical life-saving drugs because many manufacturers are “voluntarily” closing their plants, or shutting down production lines in order to avoid the very real possibility of forced plant closures and/or the criminal prosecution of their corporate executives.

14 See id. at 13–14, 15.
15 See Hensley, supra note 9 (indicating the severity of the drug shortages and quoting one FDA official’s description of it as a “dire public health situation”).
II. CURRENT STATE OF THE DRUG SHORTAGE PROBLEM

A. Drugs in Short Supply in the Pharmaceutical Market as a Whole

There are two major organizations that compile drug shortage data—the FDA and the ASHP.16 Although both of these organizations produce drug shortage data, it is important to recognize that they formulate their data based upon different methodologies.17 The FDA, through the Center for Drug Evaluation and Research (CDER), 18 defines a drug shortage as “[a] situation in which the total supply of all clinically interchangeable versions of an FDA-regulated drug is inadequate to meet the current or projected demand at the user level.”19 This narrow definition focuses only on medically necessary drugs which are used to “treat or prevent a serious disease or medical condition . . . [for which] there is no other available source of that product or alternative drug that is judged by medical staff to be an adequate substitute.”20

In contrast, the ASHP defines a drug shortage broadly as “a supply issue . . . [that] affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.”21 Due to this definitional difference, it is important to recognize that ASHP data will typically produce a higher quantity of drug shortages at any given time than CDER data.22 For example, the CDER reported 178

17 Id.
18 About the Center for Drug Evaluation and Research, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/default.htm (last updated Nov. 25, 2013). CDER is a subset of the FDA which “regulates over-the-counter and prescription drugs” and ensures that the drugs which American consumers are purchasing are safe and effective. Id.
19 MANUAL OF POLICIES AND PROCEDURES, supra note 10, at 7.
21 Id. at 2 (quoting Fox et al., supra note 20, at 1400). The Drug Information Service at University of Utah Health Care manages the ASHP data and further analyzes drug shortage data based upon the same methodologies as the ASHP. See Ventola, supra note 16, at 740.
22 See FDA REPORT, supra note 11, at 9; Ventola, supra note 16, at 740. This paper will, at times, reference data compiled by both of these organizations. All data referenced within the
drug shortages in 2010\textsuperscript{23} while the ASHP reported 211.\textsuperscript{24} Similarly, in 2012, the CDER reported 117 drug shortages\textsuperscript{25} while the ASHP reported 204.\textsuperscript{26}

There are two common data measurements referenced when discussing drug shortage figures: “new” drugs on shortage, and “active” drugs on shortage.\textsuperscript{27} Both the FDA and the ASHP measure new drugs on shortage on a yearly basis.\textsuperscript{28} This figure includes all drugs that go on shortage from January first of any given year through December thirty first of that same year.\textsuperscript{29} This figure is commonly referenced in order to determine the current state of the drug shortage crisis.\textsuperscript{30} However, this figure cannot be read in isolation. The second measurement, active drug data, depicts the number of existing drugs on shortage over time.\textsuperscript{31} The ASHP measures active drug shortages on a quarterly basis for a more accurate depiction of the total number of drugs on shortage at any given time.\textsuperscript{32} Therefore, if the number of total new drugs on shortage declines in any given year, but the number of active drugs on shortage either remains constant or increases, the outlook is not as optimistic as the new drug data may suggest, because this indicates that drugs are remaining in short supply for extended periods of time.

For example, from 2006 through 2011, the number of new drugs increased every year.\textsuperscript{33} In 2012 the number of new drugs on shortage decreased by sixty three, falling from 267 new drugs on shortage in 2011 to 204 in 2012.\textsuperscript{34} However, this figure should not provoke too much enthusiasm because the number of active drugs

\textsuperscript{23} FDA REPORT, supra note 11, at 9.
\textsuperscript{24} See infra Appendix Figure 1.
\textsuperscript{25} 2012 year-end data obtained from the CDER via the FDA. About the Center for Drug Evaluation and Research, supra note 18.
\textsuperscript{27} See Appendix Figure 1 and Figure 2 for an example of the different results produced by the two measurement strategies.
\textsuperscript{28} Fox & Wheeler, supra note 26.
\textsuperscript{29} See id.
\textsuperscript{30} See id.
\textsuperscript{31} See id.
\textsuperscript{32} For a graphical representation of the ASHP’s quarterly active drug measurements for 2012 through 2014, see Appendix Figure 2.
\textsuperscript{33} See infra Appendix Figure 1.
\textsuperscript{34} See infra Appendix Figure 1.
on shortage in 2012 increased from 260 in the first quarter to 299 in the fourth quarter. In addition, from the first quarter of 2010 through the fourth quarter of 2012, the number of active drugs on shortage had risen from 152 to 299. This means that even though the number of new drugs reported to be in short supply in 2012 decreased, the number of existing drugs on shortage that actively remained on shortage had steadily increased throughout the year, leaving many hospitals and pharmacies without critical life-saving drugs.

The drugs on shortage cover a wide variety of drug classes including those used in oncology, antibiotics, and nutritional and hormonal supplements. As of August 2011, the FDA found that the highest percentage of drugs in short supply were those used for cancer treatment, followed next by antibiotics. If the FDA were to categorize drugs by way of administration, an overwhelming number of the current shortages would be drugs administered by sterile injection.

According to a March 2011 survey of 311 pharmacy experts representing 228 hospitals and other healthcare facilities, “89 percent experienced shortages that may have caused a medication safety issue or error in patient care,” and fifty three percent experienced six or more drug shortages that led to “a medication safety issue or error in patient care.” Furthermore, “80 percent [of respondents] experienced shortages that resulted in a delay or

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35 See infra Appendix Figure 2.
36 See infra Appendix Figure 2. As of August 28, 2013 the Drug Information Service at University of Utah has announced the first quarter figures for 2013. It has been reported that there has only been forty new drugs to go on shortage during the first quarter of 2013. See Greg Rockers, Drug Shortage Update 2013, JCB LABS BLOG (Aug. 15, 2013, 1:47 PM), http://www.jcblabs.com/blog/bid/185437/Drug-Shortage-Update-2013. However, as shown above, the number of active drugs on shortage through the first quarter of 2013 remains almost unchanged, at 295. Id. Again, this signifies that although new drugs are not going on shortage with the same frequency as they were over the last five years, drugs are not reentering the market.
37 Hoffman, supra note 20, at 3 (quoting FDA REPORT, supra note 11, at 3).
38 See infra Appendix Figure 3.
39 See infra Appendix Figure 4. As Figure 4 shows, from 2010 through 2011, sterile injectables have accounted for almost eighty percent of the drug shortages. Id. Further, from January of 2012 through November of 2012, a majority of the drugs on shortage continued to be sterile injectable drugs. See infra Appendix Figure 5.
41 Id.
cancellation of a patient care intervention."\(^{42}\)

The current drug shortage pandemic is far-reaching and continues to cause life-threatening situations in many of our nation’s health care facilities.

**B. A Closer Look at the Market for Sterile Injectable Drugs and Why These Drugs Constitute Such a High Percentage of the Drugs on Shortage**

Injectable drugs account for a disproportionately large share of the total drugs in short supply.\(^{43}\) This is a frightening fact because sterile injectables are often critical life-saving drugs; they are the source of many oncology drugs such as Leucovorin and Doxil, as well as Naloxone, which is commonly used as a rescue drug, and Furosemide, a frequently used diuretic.\(^{44}\) It is important to point out that sterile injectable drugs on shortage are frequently older drugs,\(^{45}\) which have been off patent for many years, meaning that the shortages are concentrated in the generic market for sterile injectable drugs.\(^{46}\) Generic drugs, by their very nature, are expected to be more readily available and more moderately priced than drugs on patent because pharmaceutical companies are “free to market copycat versions” of the original drug at reduced prices,\(^{47}\) which is why this particular shortage is unusual.\(^{48}\)

\(^{42}\) Id.


\(^{44}\) Id. at 3.

\(^{45}\) See IMS INST. FOR HEALTHCARE INFORMATICS, DRUG SHORTAGES: A CLOSER LOOK AT PRODUCTS, SUPPLIERS AND VOLUME VOLATILITY 8 (2011), http://www.imshealth.com/deployedfiles/ims/Global/Content/Insights/IMS%20Institute%20For%20Healthcare%20Informatics/Static%20Files/IHII_Drug_Shortage_Report.pdf [hereinafter IMS REPORT] (explaining that fifty eight of the drugs on shortage in 2010 were introduced to the market in the 1980s and thirty one of them entered the market in 1979 or earlier).

\(^{46}\) See JOHN R. GRAHAM, THE SHORTAGE OF GENERIC STERILE INJECTABLE DRUGS: DIAGNOSIS AND SOLUTIONS 3 (2012), http://www.mackinac.org/archives/2012/2012-04SterileInjectables.pdf; see also IMS REPORT, supra note 45, at 5 (indicating that as of October 7, 2011, 139 of the 168 drugs on shortage were sterile injectables, and eighty three percent of the drugs on shortage were generic); see infra Appendix Figure 5.

\(^{47}\) GRAHAM, supra note 46, at 2. Note that the fact that these drugs are generic in-and-of itself is one contributing factor to the shortage in this market because there is no longer an incentive to manufacture these products that hardly produce a profit in the face of regulatory sanctions by the FDA. This issue however is not addressed in this article.

\(^{48}\) Id. at 2. In addition to this natural decline in prices, the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 indirectly encourages hospitals to prescribe brand-name instead of generic drugs because the higher the drug costs, the more
There are many reasons why such a high proportion of drug shortages can be traced to the market for sterile injectable drugs notwithstanding the fact that they are often generics. One of the reasons for the major drug shortages being experienced by the sterile injectable market is, as their name itself indicates, they must be *sterile*. Sterile drugs are governed by a very complex regulatory scheme that requires either terminal or aseptic sterilization. Terminal sterilization means that once the product and the container have been brought together to their final form, the entire unit is sterilized. Alternatively, aseptic sterilization is time consuming, very expensive, and extremely detailed because aseptic sterilization requires not only the drug product itself to be sterile, but also the container and the closures must be separately sterilized before coming together in a sterile environment.

In addition to the expense of sterilization, sterile injectable drugs are composed of living components, and therefore producers must ensure that the product remains stable after it is manufactured. This means that the pharmaceutical companies are forced to use “significantly greater” levels of care when transporting and storing these drugs than when handling the average prescription drug. The costs incurred ensuring that these drugs are both sterile and the hospital will be reimbursed. This means that because the cost of generic sterile injectables is already so low, this Act may in fact have the unintended consequence of giving sterile injectable producers an incentive to end the production of these drugs out of a fear that they will not be able to turn a profit. See Hoffman, *supra* note 20, at 7. The MMA has been analyzed as a contributing factor to the drug shortage crisis in the sterile injectable market but this analysis is outside of the purview of this article.

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*Free from living microorganisms, i.e., of bacteria, fungi, protozoa, spores, viruses, and other living organisms. Taber's Cyclopedic Medical Dictionary* (21st ed. 2010).


*See id. at 2–3 (“[G]lass containers are subjected to dry heat; rubber closures are subjected to moist heat; and liquid dosage forms are subjected to filtration.”).

*Sterile injectables are unique because they “are not made from inert chemicals, but from livings things, such as bacteria,” which makes the injectables difficult to produce. Graham, *supra* note 46, at 2.

*Id.* These manufacturers have very rigid guidelines that must be complied with in order to ensure that their products remain sterile throughout the production process, and storage.
stable may be too high to justify the business decision to continue production if a company is faced with the mandate to remodel their facilities in order to comply with the web of FDA regulations governing this product.

Additionally, the market for sterile injectable drugs is highly concentrated.\textsuperscript{55} Five manufacturers of sterile injectable drugs make up a large percentage of the market.\textsuperscript{56} The FDA and the IMS Institute for Healthcare Informatics estimate that the top five manufacturers in this field produce over eighty percent of the market supply of sterile injectable drugs and in 2010 accounted for seventy three percent of the dollars made in sales.\textsuperscript{57} Moreover, the top three manufacturers “held 71% of the market” from 2001 to 2010.\textsuperscript{58} In addition to the high level of concentration in this market, these manufacturers are producing at their maximum capacities and do not have the ability to increase production of any particular drug without sacrificing another.\textsuperscript{59} Therefore any market change in demand will affect the sterile injectable market substantially more than a market without a concentrated, maximum-operating, manufacturing base. Because there is a limited supply of alternative manufacturers in the market for sterile injectable drugs, if one manufacturer needs to halt production, or decides to leave the market, there is no alternative facility with the ability to increase production to make up for the lost supply, causing shortages to occur more easily in this unique market.

Another reason that there are a disproportionately large number of sterile injectable drugs in short supply is the inability of manufacturers to switch production of these drugs to alternative production lines, either within their facility or to outside manufacturers, when a specific line has to be temporarily shut

\textsuperscript{55} Id. at 3.
\textsuperscript{56} Compare \textsc{Staff of H.R. Comm. on Oversight & Gov’t Reform, 112th Cong., FDA’s Contribution to the Drug Shortage Crisis}, 15 (Comm. Print 2012) [hereinafter \textsc{FDA’s Contribution to the Drug Shortage Crisis}] (listing the five major manufacturers: APP Pharmaceuticals, Bedford Laboratories, Hospira Pharmaceuticals, Sandoz Pharmaceuticals, and Teva Pharmaceuticals), with \textsc{Haninger et al., supra} note 43, at 6 (claiming that there are seven primary manufacturers), and \textsc{Ilisa B.G. Bernstein & Connie T. Jung, FDA Update 42} (2012), http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM299785.pdf (detailing that some people believe \textit{seven} manufacturers control the sterile injectable market, not only five).
\textsuperscript{57} \textsc{FDA Report, supra} note 11, at 30.
\textsuperscript{58} Id.
\textsuperscript{59} See id. at 32.
down for renovations or maintenance. As mentioned above, sterile injectable drugs are made with live ingredients such as bacteria, which lead to a much more complex production line for these drugs than for a tablet or solution. Due to the variety of injectable drugs, and the fact that they must remain sterile, most manufacturers have designated equipment and production processes for different types of injectable drugs. The specialization of production lines means that if manufacturers have to shut down a line for any given reason, there is no alternative mode of production. Moreover, each individual company typically produces ninety percent of any given sterile injectable drug. The specialization of production equipment increases the likelihood that there will be a shortage of sterile injectable drugs even if there is only a minimal increase in demand or a temporary production suspension.

For all of these reasons, the market for sterile injectable drugs is especially susceptible to market shortages. Even minor interruptions in production can be felt in hospitals and pharmacies across the country. The FDA should give more weight to these supply factors when determining the appropriate time to bring regulatory enforcement proceedings against sterile injectable manufacturers, which may lead to production halts.

III. WHY THE FDA’S CURRENT MISSION TO BRING STERILE INJECTABLE FACILITIES “UP-TO-CODE” HAS RESULTED IN SUPPLY DISRUPTIONS

There has been much speculation about the origin of the current pharmaceutical drug shortage crisis. Suggested causes include: the adverse impact that the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA) has had on profit margins for sterile injectable drugs, contract practices for purchasing within the industry, the economic downturn, new production opportunities

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60 See id.
61 See GRAHAM, supra note 46, at 2.
62 See FDA REPORT, supra note 11, at 32.
63 See id.
64 See id. at 4.
65 See id. at 23–24, 32.
at aging manufacturing sites,\(^67\) unanticipated demand, manufacturing errors, and “regulatory policies with unintended consequences.”\(^68\) However, there is no debate that the mass closure of leading manufacturing facilities is the primary cause of a large percentage of the shortages in the sterile injectable drug market.\(^69\)

The crisis in this market will not subside until manufacturing facilities are back up and running at full capacity, so it is prudent to look at the reasons behind the closures to ensure that such widespread facility shutdowns do not reoccur. It appears that the widespread facility closures in the sterile injectable market are, at least in part, a result of the intensified regulatory enforcement policy by the present FDA, coupled with the FDA’s simultaneous


\(^68\) Hoffman, supra note 20, at 1.

\(^69\) S.L. Kweder & S. Dill, Drug Shortages: The Cycle of Quantity and Quality, 93 No. 3 CLINICAL PHARMACOLOGY & THERAPEUTICS 245, 247–48 (2013) (describing that fifty six percent of the sterile injectable shortages are due to quality problems during the manufacturing process); Woodcock & Wosinska, supra note 67, at 171 (same); FDA’s CONTRIBUTION TO THE DRUG SHORTAGE CRISIS, supra note 56, at 5. Four of the five major producers of sterile injectable drugs experienced plant closures or production delays after FDA inspections of their facilities. See, e.g., Angela Townsend, FDA Taking Steps to Increase Flow of Vital Cancer Drugs, PLAIN DEALER (Cleveland, Oh.), Feb. 22, 2012, at A6 (“In an effort to ease a shortage of critical cancer drugs caused by the manufacturing shutdown of Bedford-based Ben Venue Laboratories, Inc., the U.S. Food and Drug Administration . . . announced several measures.”) (emphasis added); JoNel Aleccia, Bugs in sterile drugs? Behind the shortage of critical meds, NBCNEWS.COM (Feb. 29, 2012, 2:52 PM), http://www.nbcnews.com/health/bugs-sterile-drugs-behind-shortage-critical-meds-260229 (stating that APP Pharmaceuticals received a warning letter during 2012 forcing the company to undergo plant renovations); Thomas Gryta, Teva resumes manufacturing at Irvine, Calif plant, WALL ST. J. (MARKETWATCH) (Apr. 26, 2011, 10:53 AM), http://www.marketwatch.com/story/teva-resumes-manufacturing-at-irvine-calif-plant-2011-04-26 (detailing that Teva closed its manufacturing plant in April of 2010 and reopened a year later with minimal production capabilities); Dan Stanton, Propofol Lethal Injections Blocked as Teva and Hospira Re-Enter Market, IN-PHARMATECHNOLOGIST.COM (Mar. 26, 2013), http://www.in-pharmatechnologist.com/Processing/Propofol-Lethal-Injections-Blocked-as-Teva-and-Hospira-Re-Enter-Market (“Hospira's Clayton, NC plant closed-down last year due to manufacturing issues highlighted in a US FDA . . . warning letter in 2010.”). See also FDA REPORT, supra note 11, at 4 (confirming that forty three percent of drug shortages from 2010 through 2011 were due to manufacturing facility problems, and fifteen percent were due to delays in production).
failure to encourage companies to commence plant renovation one firm at a time in order to ensure that an adequate supply of sterile injectable drugs remain available to the public.\textsuperscript{70}

A. When and How Did the FDA Change its Regulatory Policy?

President Obama’s nominee, Dr. Margaret Hamburg, became the Commissioner of the FDA in May of 2009.\textsuperscript{71} During her confirmation hearings, Dr. Hamburg “emphasized that she want[ed] to restore confidence in the agency” and that in order to accomplish that goal, the FDA would “need[] an overhaul.”\textsuperscript{72} Two months after Dr. Hamburg assumed her role at the FDA, she stated that her priorities during her tenure were to significantly increase the FDA’s regulatory enforcement activity within the pharmaceutical industry and to act “swiftly and aggressively” to accomplish regulatory compliance.\textsuperscript{73} She explained:

Through regular inspections and follow-up on signals indicating problems, the FDA must work to identify and resolve problems early. Sometimes problems can arise despite the best of intentions and efforts to adhere to best practices. When this is the case, our expectation is that companies will work to quickly and thoroughly correct deficiencies and ensure safety. Companies must have a realistic expectation that if they are crossing the line, they will be caught, and that if they fail to act . . . we will.

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When the FDA finds that a firm is significantly out of

\textsuperscript{70} Drug Shortage Crisis, supra note 67, at 28–29 (statement of Scott Gottlieb, M.D., Resident Fellow, American Enterprise Inst.) (“With its vigilance heightened, the FDA has required manufacturers to undergo major plant renovations, suspend facilities or stop shipping goods from suspect production lines. The FDA and the manufacturers often don’t understand the drug-production processes well enough to detect the root cause of problems. Instead of calling for targeted fixes of troubled plants, the agency has often required manufacturers to undertake costly, general upgrades to facilities. As a result, in 2010, product quality issues—and the subsequent regulatory actions taken by FDA to address these problems—were involved in 42% of the drug shortages.”); see also FDA’S CONTRIBUTION TO THE DRUG SHORTAGE CRISIS, supra note 56, at 15 (discussing the FDA’s role in causing drug shortages).


\textsuperscript{72} Id.

\textsuperscript{73} Margaret Hamburg, M.D., Comm’r of the U.S. Food & Drug Admin., Address at the Food and Drug Law Institute: Effective Enforcement and Benefits to Public Health (August 6, 2009).
compliance, we expect a prompt response to our findings. Once the FDA provides inspection findings identifying a serious problem, the firm will generally have no more than fifteen working days in which to respond before the FDA moves ahead with a warning letter or enforcement action.\footnote{Id. (emphasis added).}

Dr. Hamburg emphasized that she was interested in starting a “new era” for drug safety.\footnote{U.S. Food & Drug Admin., Strategic Priorities 2011–2015: Responding to the Public Health Challenges of the 21st Century 24 (2011), http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/uCm252092.pdf.} She stressed that in order to ensure that the consumers of drugs were going to remain safe, the FDA would need to implement procedures that would guarantee pharmaceutical companies were operating in strict compliance with safety regulations.\footnote{See id. at 11.} Events following this speech confirmed that the FDA would use the full range of administrative compliance mechanisms available to them to ensure strict regulatory compliance in the sterile injectable market, including warning letters\footnote{The FDA defines a warning letter as: [A] correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency’s principal means of achieving prompt voluntary compliance with the Act. U.S. Food & Drug Admin., Regulatory Procedures Manual, Exhibit 4-1(4.1) (July 2012), http://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM176965.pdf.} and other investigatory tactics.

IV. THE FIRST TOOL THE FDA IS USING TO ENSURE STRICT REGULATORY COMPLIANCE: WARNING LETTERS AND FORM 483S

Within the first year after Commissioner Hamburg’s speech referenced above, the FDA increased the number of warning letters sent to producers of FDA regulated drugs by forty two percent.\footnote{FDA’s Contribution to the Drug Shortage Crisis, supra note 56, at 5.} From 2010 to 2011, the number of warning letters increased 156 percent.\footnote{Id. at 5. Note that these warning letter figures are not confined to the sterile injectable market, but rather, they represent the total number of warning letters sent by the FDA in the respective years. They still indicate a dramatic change in the FDA’s regulatory enforcement} Many of these warning letters have caused companies to
“voluntarily” halt manufacturing in order to eliminate the concerns voiced by the FDA and to renovate and update their manufacturing facilities and/or individual production lines.\textsuperscript{80}

Because the market for sterile injectable drugs is mainly limited to five producers,\textsuperscript{81} any disruption in supply must be carefully coordinated to ensure that the demand for these drugs can still be satisfied. However, the FDA’s regulatory sanctions have caused synchronized shut downs and/or production delays at four out of these five production companies within the same year.\textsuperscript{82} The FDA’s decision to synchronize its regulatory enforcement activity instead of distributing this process over a longer period of time caused an insufficient supply of sterile injectable drugs to be produced while renovations were under way.\textsuperscript{83}

Before the FDA ramped up its regulatory citations, four of the major generic injectable producers produced close to one billion units of generic injectable products in a year.\textsuperscript{84} As of June 2012,
those same four companies had a thirty percent decrease in manufacturing capacity and their production lessened substantially. The U.S. House of Representatives Committee on Oversight and Government Reform determined in February 2012 that fifty eight percent of the drugs on shortage were produced by “at least one facility undergoing FDA remediation.”

Although the FDA claims that it has not formally mandated that any of the producers of sterile injectable drugs close their plants, the agency has initiated regulatory enforcement procedures that have resulted in manufacturing plants closing or temporarily suspending production lines. The warnings, whether in the form of an FDA Form 483, or an official warning letter, are becoming

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Id. at 5.

See Letter from Jeanne Ireland, Assistant Comm’r for Legislation, Dep’t of Health and Human Servs., to Honorable Elijah E. Cummings, Ranking Member, House of Rep. Comm. on Oversight and Gov’t Reform 3 (July 23, 2012) [hereinafter Ireland Letter].

FDA’s CONTRIBUTION TO THE DRUG SHORTAGE CRISIS, supra note 56, at 5 (finding increased enforcement by FDA to be responsible for the shutdown of a substantial amount of manufacturing). FDA inspections of sterile injectable facilities were described by J. Woodcock and M. Wosinska as the following:

The FDA assesses whether a facility is in a state of control through periodic inspections that provide an evaluation of a firm’s manufacturing operations, including their system for quality management. Almost all major sterile-injectable manufacturing facilities producing for the US market are inspected at least every 2 years, because they are based domestically. Between inspections, the FDA relies, in part, on firms to be forthcoming about their quality problems, which they report by issuing defect reports (Field Alert Reports and Biological Product Defect Reports).

Defects in sterile injectable products can be difficult to detect because microbial contamination may be non-uniform and episodic. This lack of uniformity can confound conventional sampling plans. In addition, microbial contamination can increase after production, which means that more sensitive testing must be done at production time. For these reasons, the FDA has made attempts over the last few years to enhance its audit of a site’s state of control and quality problems by developing a cadre of highly trained and experienced inspectors to conduct inspections of complex facilities such as those that produce sterile injectables.

Woodcock & Wosinska, supra note 67, at 172.

“A FDA form 483 is issued to firm management at the conclusion of an inspection when an investigator(s) has observed any conditions that in their judgment may constitute violations of the Food Drug and Cosmetic [] Act.” FDA Form 483 Frequently Asked Questions, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ICECI/EnforcementActions/ucm256377.htm (last updated Mar. 13, 2012). The purpose of a Form 483 is to put companies on notice of any conditions present in their facilities which may be objectionable, in order to incentivize voluntary alterations and prevent formal FDA action. See id. The Food Drug and Cosmetic Act authorizes the FDA to perform inspections of drug manufacturing facilities. See 21 U.S.C. § 374(a)(1) (2013). The stated purpose of these inspections is to “ensure[] the quality of drug products” by monitoring a firm’s compliance with Current Good Manufacturing Practices (CGMP) regulations. See Drug Applications and Current Good Manufacturing
increasingly predictable because the FDA is referencing many of the same regulatory violations in their communications to these firms.

Receipt of a Form 483 notice or a warning letter is a serious matter because if the violations do not cease before the next inspection, the FDA can force closures of the plants, and possibly pursue criminal sanctions against the corporate executives. This knowledge is why the majority of firms in the sterile injectable market are now “voluntarily” closing their plants upon receipt of one of these enforcement documents—to avoid sanctions.

Since 2006, the CDER has released annual “Inspectional Observation Summaries” regarding the issuance of FDA Form 483s. These summaries include a detailed breakdown of Form 483s issued to members of different FDA centers throughout each fiscal year and reveal which regulatory sections are most likely cited against manufacturing companies. Section 211.22(d) of Title 21 of the Code of Federal Regulations (CFR) was the most cited regulatory violation within Form 483s issued for drugs in 2009, 2010, and 2011, which indicates that manufacturing companies are

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A warning letter is a more serious enforcement procedure than a Form 483, and is utilized by the FDA after a firm fails to implement procedures to resolve the potential regulatory violations listed in their Form 483. Warning letters require a response by the firm to the FDA within fifteen days stating how the firm intends to remedy the observations noted in the form. Aleccia, supra note 69. The FDA in a recent presentation suggested that a timely, well-executed response could be the most effective way for a firm to avoid a formal warning letter. See Jean Mulinde, U.S. Food & Drug Admin., View from a Regulator: Clinical CAPAs and Their Role in Your Overall Compliance Model 54–55, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM337109.pdf (last visited Mar. 22, 2014).

Warning letters are immediately published on public domains so companies' reputations are immediately affected. In addition, warning letters can be used in court when manufacturing companies are being accused of conducting improper practices within their facilities. See Aaron Davidson et al., You've Been Warned: FDA Warning Letters Are Not Final Agency Actions, But They Carry More Risk Than Ever, BAKER BOTTS LLP (Feb. 28, 2012), http://www.bakerbotts.com/file_upload/Update_2012_02LifeSciencesNewsletterYouveBeenWarned.htm.

See infra Part V.A.

See infra Part IV.A.


For example, foods, drugs, devices, veterinary medicine, and Radiological health, among others. FY 2013 Inspectional Observation Summaries, U.S. Food & Drug Admin., http://www.fda.gov/ICECI/EnforcementActions/ucm381526.htm (last updated Jan. 15, 2014).
not ensuring that their products are free from error before leaving the production facility.\textsuperscript{96} In addition, section 211.67(a)–(b) of Title 21 of the CFR, which outlines requirements for maintenance of machinery,\textsuperscript{97} was one of the top ten regulations cited on Form 483s during that same time period.\textsuperscript{98} Interestingly, this data also shows


(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.

(b) Adequate laboratory facilities for the testing and approval (or rejection) of components, drug product containers, closures, packaging materials, in-process materials, and drug products shall be available to the quality control unit.

(c) The quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product.

(d) The responsibilities and procedures applicable to the quality control unit shall be in writing; such written procedures shall be followed.

21 C.F.R. § 211.22 (2013). The Quality Control Unit is defined in 21 C.F.R. § 210.3 as “any person or organizational element designated by the firm to be responsible for the duties relating to quality control.” 21 C.F.R. § 210.3(b)(15) (2013).

\textsuperscript{97} 21 C.F.R. § 211.67 details the following requirements for equipment cleaning and maintenance:

(a) Equipment and utensils shall be cleaned, maintained, and, as appropriate for the nature of the drug, sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

(b) Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:

1. Assignment of responsibility for cleaning and maintaining equipment;
2. Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules;
3. A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance;
4. Removal or obliteration of previous batch identification;
5. Protection of clean equipment from contamination prior to use;
6. Inspection of equipment for cleanliness immediately before use.

21 C.F.R. § 211.67(a)–(b) (2013).

\textsuperscript{98} See FDA 2011 Summary, supra note 96; FDA 2010 Summary, supra note 96; FDA 2009 Summary, supra note 96. Although there is no data source analyzing the regulations that
that the number of Form 483s issued since 2006 has hardly changed, nor have the regulations cited in those forms varied in any major way; instead the number of warning letters issued has increased dramatically. This means that, under the previous FDA commissioner, the issuance of a Form 483 did not necessarily mean that a formal warning letter would follow, whereas under the current administration, warning letters are being sent at a noticeably higher rate. The warning letters also contain new language making it very clear to recipients that the FDA will pursue legal and injunctive action if manufacturers fail to immediately resolve regulatory violations.


Each of the warning letters sent out under Dr. Hamburg’s supervision contain the following threat of formal enforcement action: “You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice including, without limitation, seizure and injunction...” APP Warning Letter, supra note 98; Hospira Warning Letter, supra note 98; Teva Warning Letter, supra note 98; see also Novartis Warning Letter, supra note 98 (stating similar language to that quoted above). The following was posted by Barnes & Thornburg, LLP in an effort to update their clients on the FDA’s change in warning letter policy:

FEMA ANNOUNCES NEW WARNING LETTER PROCESS FOR ALL FDA-REGULATED PRODUCTS

See infra Appendix Figure 6 (showing only a slight increase in Form 483s issued in recent years).

Manufacturing companies are aware of the current FDA administration’s shift in regulatory enforcement policy to ensure product safety.\textsuperscript{102} This in-and-of-itself is not a bad thing—manufacturing companies should be required to supply the market with only safe drugs. As stated above, the problem is not the shift of the FDA’s policy toward strict regulatory compliance, but rather, the manner in which it was implemented to simultaneously affect all companies across the market without proper consideration of the implications the enforcement actions would have on the supply of life-saving drugs.

The next subsection will explore the sterile injectable drug Leucovorin, as it is a prime example of a sterile injectable drug currently experiencing a shortage because the main manufacturers of Leucovorin have closed their plants, or temporarily suspended production, due to receiving Form 483 notices and warning letters from the FDA.

\textbf{A. A Case Study: Leucovorin Calcium Injection}

Leucovorin is a drug within the “class of medications called folic acid analogs.”\textsuperscript{103} Leucovorin is most commonly used by cancer patients who receive methotrexate\textsuperscript{104} as part of their chemotherapy.

On Aug. 6 2009, the new FDA Commissioner, Dr. Margaret Hamburg, outlined the FDA’s new post-inspection deadline and warning letter process. According to Dr. Hamburg, when the FDA finds that a firm is significantly out of compliance the FDA will expect a prompt response to its findings. Once the FDA provides inspection findings identifying a serious problem, the firm will generally have no more than 15 working days in which to respond before the FDA moves ahead with a warning letter or enforcement action. This will help FDA issue warning letters on a timely basis and facilitate prompt corrective action. The FDA will be prepared to act swiftly and aggressively to protect the public. The FDA will no longer issue multiple warning letters to noncompliant firms before taking enforcement action. If the FDA finds that it must move quickly to address significant health concerns or egregious violations, it will consider immediate action—even before it issues a formal warning letter. This new process is scheduled to begin on Sept. 15, 2009 and will be re-evaluated after 18 months.


\textsuperscript{102} See Barnes & Thornburg LLP, supra note 101 (informing companies of the FDA’s change in policy).


\textsuperscript{104} “Methotrexate exerts its chemotherapeutic effect by being able to counteract and compete with folic acid in cancer cells resulting in folic acid deficiency in the [cancer] cells and causing their death. This action also effects [sic] normal cells which can cause significant side
medication and as a result have very low levels of folic acid, a necessary vitamin for the survival of cells. Leucovorin is considered a “rescue” drug because it reinvigorates the body with necessary folic acid to prevent good cells within the body from dying, and prevents, or at minimum significantly mitigates, the harsh side effects of the chemotherapy drug methotrexate. Leucovorin is typically administered approximately twenty four hours after methotrexate has been administered to a patient in order to give the methotrexate an appropriate amount of time to kill cancer cells.

Prior to the drug shortage crisis, Leucovorin was mainly produced at two facilities: Bedford Laboratories and Teva Pharmaceuticals. However, when both Bedford and Teva temporarily suspended production of Leucovorin due to manufacturing equipment going offline, two additional manufacturers were compelled to step in and ramp up supply: APP Pharmaceuticals and Sagent Pharmaceuticals. But these extra facilities do not have the effects in the body, such as: low white, red and platelet blood cell counts, hair loss, mouth sores, difficulty swallowing, diarrhea, liver, lung, nerve and kidney damage.”


capacity or capability to produce the level of Leucovorin demanded. The following depiction of what happened to Teva and Bedford, and what caused those plants to suspend production of Leucovorin, will shed light on what is happening to most major sterile injectable drug producers and why most plants have decreased their production capacity in recent years.

The FDA, under the leadership of Dr. Hamburg, first inspected Teva Pharmaceuticals, a main producer of Leucovorin, in July 2009 after reports surfaced that Teva’s sterile injectable drug Propofol was causing sporadic illnesses. As a result of that inspection, the FDA issued a warning letter to Teva on December 11, 2009, citing numerous manufacturing practices that did not conform to the Current Good Manufacturing Practices (CGMP) found in Title 21 of the CFR. In this 2009 warning letter, Teva was cited for thirteen different regulatory violations ranging from “[f]ailure to define the responsibilities and procedures applicable to the quality control unit in writing,” to “[f]ailure to clean and sanitize equipment and utensils at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug.” In response to receiving this warning letter, Teva voluntarily shut down its Irvine, California manufacturing facility—which produces all of the company’s sterile injectable drugs—on April 16, 2010, and the plant remained closed for more than one year.

Teva reopened its California plant in April 2011 with a significantly reduced production capacity and it was estimated that its manufacturing capacity would not reach pre-closure levels for at least one year. After spending a reported $375 million to upgrade

112 See Ireland Letter, supra note 87, at 4 (citing reports of serious injuries as cause for the July 2009 inspection); Teva Warning Letter, supra note 98. Please note that although this warning letter was sent to Teva Parenteral Medicines, Inc., this company is a subsidiary of Teva Pharmaceuticals, specifically the subsidiary that manufacturers and markets sterile injectable pharmaceuticals, located in Irvine, California. See History of Teva US Generics, TEVA PHARM. USA, http://www.tevagenerics.com/default.aspx?pageid=3404 (last visited Jan. 22, 2014).
113 See Ireland Letter, supra note 87, at 4; Gryta, supra note 69.
114 Teva Warning Letter, supra note 98.
115 See supra note 109.
116 See Ireland Letter, supra note 87, at 4; Gryta, supra note 69.
117 See Gryta, supra note 69.
their Irvine facility, Teva’s production capacity has still not returned to the level it was pre-closure.118 In February of 2013, Teva Pharmaceutical’s CEO Jeremy Levin announced the sale of Teva’s Irvine, California facility.119 Although Levin did not directly link the FDA-propelled closure to the sale of the facility, there is no doubt that Teva’s profit margin decreased dramatically120 in 2012.121

Similarly, Dr. Hamburg’s inspectors first visited the Bedford Laboratories subsidiary Ben Venue Labs, a sterile injectable producer, from May 2, 2011 through May 25, 2011, while Teva was still operating at significantly reduced production capacity and not yet producing Leucovorin.122 As a result of this inspection, Ben Venue was issued a Form 483 on May 25, 2011, which totaled thirty three pages in length and referenced forty eight different deficiencies.123 Many of these observations were related to aseptic processing weaknesses that affect the sterility of the injectables produced at the facility, rather than life-threatening deficiencies.124 Six months later, in early November, the FDA returned to Ben Venue Labs and inspected the property through December 2, 2011.125 The Form 483 issued as a result of this inspection was only eleven pages in length, but cited many of the same observations

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119 Id.


121 Id. Teva has stated that it will work with the FDA to prevent shortages of the sterile injectable drugs that they currently produce in Irvine, CA while their facility is in transition to another drug manufacturer. Id.


123 See MAY 2011 BEN VENUE FDA FORM, supra note 122, at 33.

124 See, e.g., id. at 5–9.

from the previous investigation. The observations documented ranged from failing to present documentation to the FDA inspector to prove that the media fill process complied with aseptic processing to a lack of testing to ensure that the facility complied with environmental monitoring requirements.

Instead of waiting for the second inspection of their facility to conclude, Ben Venue took preemptive action and voluntarily shut down their facility on November 19, 2011. The suspension was due to “significant manufacturing and quality concerns” and the company announced that they could not remediate all of the deficiencies cited by the FDA in the Form 483 while simultaneously manufacturing drugs and therefore they were forced to close. Although not publically stated, Ben Venue likely closed at the time it did, prior to receiving its second Form 483, to prevent the anticipated follow-up warning letter and subsequent forced closure.

Almost one year after Ben Venue Laboratories closed its doors, and after spending over $300 million to upgrade its facility, the company announced that it was reopening a limited number of production lines to produce the most needed sterile injectable drugs. The company still has not reached full production capacity. This case study detailing the effect of the FDA’s warning letters and Form 483s on the main manufacturers of Leucovorin demonstrates how these tactics have spurred the shortages of many sterile injectable drugs.

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126 Compare id. at 1, with MAY 2011 BEN VENUE FDA FORM 483, supra note 122, at 1 (“However, the following observations document a lack of adequate oversight by the Quality Unit to approve or reject the products manufactured and processed, as well as, approve or reject the established procedures and/or specifications impacting the quality of the drug product.”).

127 DECEMBER 2011 BEN VENUE FDA FORM 483, supra note 125, at 4.

128 Id. at 6.


130 Id.


V. THE SECOND TOOL THE FDA IS USING TO ENSURE STRICT REGULATORY COMPLIANCE: THE PARK DOCTRINE

A. Criminal Sanctions Can Arise Out of FDCA Violations

In addition to increasing the quantity of warning letters submitted to pharmaceutical companies to ensure regulatory compliance, the FDA has recently revived a dusty doctrine that puts corporate executives and officers of pharmaceutical companies in the line of fire for criminal prosecution. The primary purpose of the Food, Drug, and Cosmetic Act (FDCA) of 1938 is to protect the safety and health of the public by preventing adulterated and/or misbranded articles from coming into the stream of interstate commerce and to the homes of American citizens. The language of the FDCA notifies all persons regulated under this Act that if they or their companies conduct any of the prohibited acts listed in 21 U.S.C. § 331, they can personally face criminal misdemeanor or felony charges under 21 U.S.C. § 333(a), in addition to injunctions or seizure of their adulterated or misbranded good(s).

In order to enforce these laws, the FDA established the Office of Criminal Investigations (OCI) in 1992 to “conduct and coordinate investigations of suspected criminal violations [of the FDCA] and to

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134 See 21 U.S.C. § 331 (2012) (listing reasons why articles/products would be prohibited from entering the stream of commerce); see also United States v. Dotterweich, 320 U.S. 277, 280 (1943) (“The purposes of this legislation thus touch phases of the lives and health of people which, in the circumstances of modern industrialism, are largely beyond self-protection.”); United States v. Eight Unlabeled Cases, 888 F.2d 945, 946 (2d Cir. 1989) (“[The FDA may] regulate food, drugs and cosmetics for the purpose of safeguarding the public health from deleterious, adulterated and misbranded articles.”).
136 This section states that:
(a) Violation of 21 USC § 331; second violation; intent to defraud or mislead.
(1) Any person who violates a provision of section 301 [21 USC § 331] shall be imprisoned for not more than one year or fined not more than $ 1,000, or both.
(2) Notwithstanding the provisions of paragraph (1) [of this section], if any person commits such a violation after a conviction of him under this section has become final, or commits such a violation with the intent to defraud or mislead, such person shall be imprisoned for not more than three years or fined not more than $ 10,000 or both.
21 U.S.C. § 333(a) (2012). Note that this provision not only makes a misdemeanor a strict liability crime, it also subjects repeat offenders to felony charges without the requisite proof of intent to defraud or mislead.
collect evidence to support successful prosecutions” through the federal or state court systems as appropriate. If OCI determines that the evidence they collect would support a successful prosecution, they will then refer the case to the Department of Justice (DOJ), generally via the U.S. Attorney’s Office in the jurisdiction of the alleged criminal violation. It is then left to the sole discretion of the U.S. Attorney’s Office whether to proceed with filing criminal charges against alleged violators.


140 See John W. Lundquist & Sandra L. Conroy, Defending Against Food & Drug Prosecutions, THE CHAMPION (1997), available at http://www.nacdl.org/CHAMPION/ARTICLES/97jul02.htm. Before submitting a case to the DOJ for criminal prosecution, the FDA has the power to provide a potential defendant with notice and an opportunity to be heard in what is known as a “Section 305 hearing.” Id.; see 21 U.S.C. § 335 (2012). The Section 305 hearing gives the FDA a better opportunity to understand the circumstances surrounding the regulatory violations and the potential defendant’s involvement in order to give the FDA a full opportunity to determine how to proceed with the disposition of the charges. Inspections, Compliance, Enforcement, and Criminal Investigations: § 6-5—Prosecution, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176977.htm (last updated Mar. 19, 2013). The compliance officer holding the hearing will then determine whether to submit the case for prosecution, non-prosecution, or to hold the case in abeyance, and notify the subject of the hearing of her determination. Id. At the beginning of the Park doctrine proceedings, Section 305 hearings were almost always held before charges were filed; however, in the last twenty years they have very rarely been invoked because the Supreme Court has held that it is not mandatory for the FDA to hold a Section 305 hearing before recommending a case for prosecution to the DOJ. United States v. Dotterweich, 320 U.S. 277, 279–80 (1943).

Additionally, in January of 2011, the FDA updated its Criminal Prosecution Guideline manual and removed from it the provision that suggested that compliance officers hold a Section 305 hearing, an action that gave the FDA the ability to refer a case to the DOJ without prior notice. John T. Bentivoglio et al., FDA Revamps Criminal Prosecution Guidelines and Expands Health Care Fraud-Related Investigations, SKADDEN, ARPS, SLATE, MEAGHER & FLOM LLP (Feb. 9, 2011), http://www.skadden.com/newsletters/FDA_Revamps_Criminal_Prosecution_Guidelines.pdf. This underruts the due-process protections provided to people under the FDCA.

141 See Lundquist & Conroy, supra note 140.
B. The Park Doctrine, aka “Responsible Corporate Officer”

In 1943, the Supreme Court of the United States first recognized that an officer of a corporation, not just the corporation itself, may be prosecuted under the FDCA for introducing misbranded and/or adulterated articles into interstate commerce.\textsuperscript{142} In \textit{United States v. Dotterweich}, the president and general manager of Buffalo Pharmacal Company, Inc., was charged with three counts of pharmaceutical misbranding,\textsuperscript{143} in violation of 21 U.S.C. § 331(a), which prohibits “[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.”\textsuperscript{144} The defendant argued a basic corporate law principle, that corporate directors cannot be held personally liable for corporate wrongs unless the prosecution could prove that the corporation was merely the “counterfeit . . . serving as a screen” for the defendant.\textsuperscript{145}

The Court concluded that the typical alter ego theories of corporate law, which would allow for a piercing of the corporate veil, were not applicable under the circumstances of this case because: (1) "the only way in which [the] corporation can act is through the individuals who act on its behalf,"\textsuperscript{146} (2) the intent of the legislature was to subject corporate officers to criminal liability under the FDCA,\textsuperscript{147} and (3) the FDCA is unique in the fact that it “touch[es]
phases of the lives and health of [the] people which, in the circumstances of modern industrialism, are largely beyond self-protection.” 148 The Court held that the combination of these three unique factors allowed the legislature to dispense with the mens rea element typically required for criminal conviction (i.e., awareness of wrongdoing), and hold corporate managers criminally liable for adulterated products that are dispensed from their facilities whether or not they knew of the violation, utilizing an alternative avenue to hold corporate officers criminally liable without piercing the corporate veil. 149

The Supreme Court in Dotterweich did recognize that this holding could potentially open the door to a floodgate of prosecutions against corporate officers, even those far removed from the alleged violations of the FDCA, so they limited their holding to encompass only those persons “standing in responsible relation to a public danger.” 150 After the holding in Dotterweich, lower courts struggled to interpret the scope of this “responsible relation.” 151 In order to provide better guidance to lower courts applying the Dotterweich reasonable relation standard, the Supreme Court granted certiorari to a case from Maryland, United States v. Park. 152

Park, the defendant, was the Chief Executive Officer of Acme Markets, Inc., a food chain with over thirty five thousand employees and sixteen warehouses throughout the United States. 153 Park was charged with five counts of violating 21 U.S.C. § 331(k) 154 after the

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148 Id. at 280.
149 Id. at 280–81. The resulting liability for corporate officers under the responsible corporate officer doctrine is similar to the type of corporate liability in Caremark claims: oversight liability. See In Re Caremark Int’l Inc. Derivative Litig., 698 A.2d 959, 970 (Del. Ch. 1996) (“[A] director’s obligation includes a duty to attempt in good faith to assure that a corporate information and reporting system, which the board concludes is adequate, exists, and that failure to do so under some circumstances may . . . render a director liable for losses caused by non-compliance with applicable legal standards.”). Similarly here, when corporate officers of pharmaceutical companies do not ensure that their companies are in compliance with the sterility manufacturing processes outlined in their drug approval documents submitted to the FDA, they can be cited as violating those standards and face subsequent criminal prosecution.
150 Dotterweich, 320 U.S. at 281.
151 Carol Benjamin & Betsy J. Floman, Federal Food and Drug Act Violations, 31 AM. CRIM. L. REV. 629, 631 (1994); see Dotterweich, 320 U.S. at 285 (“It would be too treacherous to define or even to indicate by way of illustration the class of employees which stands in such a responsible relation. . . . In such matters the good sense of prosecutors, the wise guidance of trial judges, and the ultimate judgment of juries must be trusted.”).
153 Id. at 660. Park’s office was at Acme’s headquarters, located in Philadelphia, Pennsylvania. Id.
154 Id. 21 U.S.C. § 331(k) states:
FDA discovered that Acme food products that were being stored in its Baltimore warehouse were “accessible to rodents” and stored under other unsanitary conditions. The government maintained that the defendant was personally presented with a letter laying out the conditions of the Baltimore warehouse after the FDA’s first inspection during the later months of 1971, and that the FDA was assured by management officials at Acme that actions were being taken to resolve the unsanitary conditions at the facility. The FDA performed a follow-up inspection in March of 1972 and although the inspector found marked improvement, “there was still evidence of rodent activity in the building and in the warehouses,” contaminating food items.

After the government rested their case-in-chief, the defendant moved for summary judgment on grounds similar to those asserted by the defendant in Dotterweich; Park’s counsel argued that Park was not personally responsible for the FDCA violation because as the CEO of the company, he delegated the duty of warehouse sanitation to lower level managerial staff members. The motion was denied, and therefore the defendant proceeded to testify that he had followed up with his legal personnel after receiving the FDA letters and did not “believe there was anything [he] could have done more constructively than what [he] found was being done” to remedy the problems identified.

The jury found that Park was within the scope of responsible relationship established in Dotterweich and held him personally

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The alteration, mutilation, destruction, obliteration, or removal of the whole or any part of the labeling of, or the doing of any other act with respect to, a food, drug, device, tobacco product, or cosmetic, if such act is done while such article is held for sale (whether or not the first sale) after shipment in interstate commerce and results in such article being adulterated or misbranded.


155 Park, 421 U.S. at 660. One of the witnesses for the FDA was a consumer safety officer who testified that,

We found extensive evidence of rodent infestation in the form of rat and mouse pellets throughout the entire perimeter area and along the wall.

We also found that the doors leading to the basement area from the rail siding had openings at the bottom or openings beneath part of the door that came down at the bottom large enough to admit rodent entry. There were also rodent pellets found on a number of different packages of boxes of various items stored in the basement, and looking at this document, I see there were also broken windows along the rail siding.

Id. at 661 & n.4.

156 Id. at 662.

157 Id.

158 Id. at 663–64.

159 Id. (alterations in original).
liable for the sanitation violations that occurred at Acme under his supervision, although he did not personally create the unsanitary conditions that resulted in the improper practices upon which the charge was predicated.\textsuperscript{160} Park appealed his convictions to the Fourth Circuit, which reversed his conviction and held that the lower court should have instructed the jury that it needed to find an actus reus element—that the defendant committed some act or omission that contributed to the crime—because the \textit{Dotterweich} precedent only removed the mens rea element.\textsuperscript{161} The Supreme Court granted certiorari to determine whether a wrongful act or omission needed to be established in order to prosecute a corporate officer under the FDCA for violating section 331 of that act.\textsuperscript{162}

The Supreme Court reinstated the defendant’s convictions\textsuperscript{163} and addressed the Fourth Circuit’s concerns by stating that no specific actus reus needed to be found by the jury in order to convict a corporate officer of violating the FDCA because “by virtue of the relationship [a corporate officer bears] to the corporation, the [officer has] the power to prevent the act complained of.”\textsuperscript{164} The Court affirmed the ruling in \textit{Dotterweich} by holding that corporate officers in the food and drug industry have a duty not only to seek out and remedy potential violations of the FDCA occurring within their companies, but also to promulgate procedures that will prevent such violations from occurring in the first place, and that a failure to satisfy either of those duties will lead to personal criminal liability of the corporate officer, whether or not the officer had any direct involvement in the violations.\textsuperscript{165}

\textsuperscript{160} Id. at 665–66.
\textsuperscript{161} See id. at 666–67.
\textsuperscript{162} See id. at 667.
\textsuperscript{163} Id.
\textsuperscript{164} Id. at 671.
\textsuperscript{165} Id. at 672. The Court again relied upon the unique aspects of the food and drug industry that require the utmost concern for safety as well as the intent of Congress, which promulgated the FDCA. See id. The Court in \textit{Park} declined to develop a rigid definition of an officer deemed to be within a “responsible relationship” to potential violations, but it did offer an affirmative defense for corporate officers: that if the officer charged was “powerless” to prevent and/or correct the violation, the officer can use that as an affirmative defense to the charges brought against them. See id. at 673. Additionally, once again, the Court declined to impose on the government a duty to prove that the defendant had any conscious involvement in the harm charged. See id. at 670–71.
C. The Revival of the Responsible Corporate Officer Doctrine

After the Park case was decided, the responsible corporate officer doctrine was seen in court frequently. The FDA was seeking out corporate officers who were allowing FDCA prohibited acts to continue within their facilities and prosecuting them under the responsible corporate officer doctrine.\textsuperscript{166} However, by the late 1980s, the DOJ often declined to bring Park cases due to staffing limitations, lack of resources, and the low penalties that could be enforced against the defendants under the statute.\textsuperscript{167} Then, in 2009 the responsible corporate officer doctrine suddenly reappeared after years of lying dormant, and has since resulted in six executives of food and drug companies pleading guilty to criminal violations of the FDCA under the Park doctrine.\textsuperscript{168}

Additionally, in early March of 2010, FDA Commissioner Hamburg wrote a letter to Senator Charles Grassley in which she called for an increased prosecution of “responsible corporate officials” under the FDCA for misdemeanor prosecutions.\textsuperscript{169} The letter was followed by a deluge of different high-ranking FDA officials confirming to the public and to manufacturing companies that the Park doctrine in fact has been resurrected, indicating that the doctrine will now be applied with more vigor than ever before.\textsuperscript{170}

\textsuperscript{166} See, e.g., United States v. Y. Hata & Co., 535 F.2d 508, 509 (9th Cir. 1976); United States v. Starr, 535 F.2d 512, 514 (9th Cir. 1976). Most cases were brought under the misdemeanor provision of 21 U.S.C. § 333(a) and for the most part the corporate officers pled guilty and were subject to fines under the Act. See John R. Fleder et al., Webinar presented by Hyman, Phelps & McNamara, P.C.: FDA and the Park Doctrine 23 (Oct. 8, 2010), http://www.fdalawblog.net/files/fda-and-the-park-doctrine.pdf.

\textsuperscript{167} See Fleder et al., supra note 166, at 30. Additionally, the OCI department, discussed supra at Section V.A, was established in 1992, and its attention was heavily focused on fraud investigations instead of Park cases. See id. at 34. However, in 1988 Niels L. Hoyvald, former president and CEO of Beech-Nut Nutrition Corporation, and the company’s former Vice-President, John F. Lavery, were prosecuted under the Park doctrine and convicted of 359 and 429 felony counts under the FDCA, respectively, for the manufacturing and sale of adulterated apple juice. See Benjamin & Floman, supra note 151, at 643. They were each fined $100,000 and one year and one day each in jail (although ultimately the convictions were reversed on improper venue grounds). Id. at 644.

\textsuperscript{168} See generally Fleder et al., supra note 166, at 35–36 (discussing the cases of Chemnutra Inc., and Synthes, Inc.).


\textsuperscript{170} The Director of the Office of Compliance testified before Congress on May 27, 2010 that
The criminal penalties available under 18 U.S.C. § 3571 for Park doctrine prosecutions have also been elevated since the doctrine was being enforced twenty years ago. Eighteen U.S.C. § 3571 now allows for fines of up to $100,000 per FDCA violation ($250,000 if the violation results in a death), coupled with the threat of exclusion from participation in federal health care programs, FDA debarment, and disqualification.

Since the revival of the Park doctrine, some notable court decisions have been handed down. In March 2011, the former CEO of KV Pharmaceutical Company was sentenced to one month in jail, ordered to pay $1 million in fines, and ordered to forfeit $900,000 after pleading guilty to two misdemeanor violations of the FDCA. The former CEO also was excluded from participating in federal healthcare programs for the next twenty years. After Forest Pharmaceuticals Inc. pled guilty to multiple criminal charges, including violating provisions of the FDCA, the Office of the Inspector General within the Federal Department of Health and Human Services Department of the federal government contacted Howard Solomon, Forest’s CEO, and informed him that they intended to exclude him from doing business with federal healthcare programs even though he was not criminally charged in

the CDER “is working to increase [their] enforcement on the criminal side and to connect carefully what [they] do on the criminal side with what [they] do on the civil side.” Steven M. Kowal, FDA to Prosecute More Aggressively With More Potent Weapons, K&L GATES (Nov. 2, 2010), http://www.klgates.com/fda-to-prosecute-more-aggressively-with-more-potent-weapons-11-01-2010/?nomobile=perm. FDA Deputy Chief Counsel for Litigation, Eric Blumberg, stated that “[v]ery soon, and I have no one particular in mind, some corporate executive is going to be the first in a long line.” Lea Yu, FDA Eyes Criminal Charges Against Executives, FAIRWARNING.ORG (Aug. 26, 2010), http://www.fairwarning.org/2010/08/fda-eyes-prosecutions-to-toughen-enforcement/. Deputy Assistant United States Attorney General Ann Ravel stated at the Food and Drug Law Institute Conference on September 21, 2010, that “[t]he Department is intent on identifying and, where appropriate, prosecuting the individuals who are responsible for illegal off-label marketing.” Fleder et al., supra note 166, at 41.

172 Fleder et al., supra note 166, at 45.
174 See id.
the Forest matter. This was a significant event because it demonstrates that corporate officers, even those not criminally charged, could be facing career-ending sanctions if their companies are found guilty of FDCA violations.

The revival of Park prosecutions is an important tool that the FDA is using to ensure strict compliance with regulations governing the pharmaceutical industry. When corporations are faced with warning letters and potential facility closures, the officers of these corporations may well fear that they personally may face criminal prosecution. As is apparent from these case studies, as well as the FDA’s public statement that it will pursue Park prosecutions against officers of food and drug companies, corporate managers need to be extra vigilant and cautious regarding their company’s operations.

VI. CONCLUSION

There is no question that the FDA is an important agency, established to ensure that the public has access to safe and effective drug products. However, the FDA must weigh the costs and benefits of the potential life-saving drug with the corresponding harm that the same drug can have on the American people. Although the market for sterile injectable drugs is not impacted solely by the FDA, the FDA in its power must recognize that an adequate supply of sterile injectable drugs is essential. Even the slightest disruption in the supply of sterile injectable drugs can, and typically does, result in a shortage, which can result in the loss of human life or prolonged suffering.

The FDA’s current iron-fist hold over companies that manufacture sterile injectable drugs must be reevaluated. Although the reinvigoration of the Park doctrine and an increase in the number of warning letters help to ensure companies are operating in compliance with safety regulations, the FDA must also help ensure that the public has access to these life-saving drugs. It does not follow that because these tools, on their face, achieve the intended result of compliance, that they are being utilized effectively. Rather, the simultaneous regulatory enforcement proceedings on many major sterile injectable producers are

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significant and extremely risky decisions that run the now-recognized risk of production delays or plant closures. In the future, it is suggested that the FDA consider, with more weight, the effect that major, across-the-board supply disruptions will have on the drug market as a whole, in an effort to ensure that life-saving injectable drugs remain available to patients throughout the country.
APPENDIX

Figure 1:
Number of New Drugs on Shortage Per Year

Source: Drug Information Service, University of Utah (2013)
Figure 2:
Number of Active Drugs on Shortage by Quarter

Source: Drug Information Service, University of Utah (2013)
Figure 3: Shortages by Drug Class

Source: FDA, Center for Drug Evaluation and Research (2010–2011)
Source: FDA, Center for Drug Evaluation and Research (2010–2011)
Figure 5:
Brand v. Generic Drugs on Shortage

- Generic 83%
- Other-Branded Generic 2%
- Branded Generic 4%
- Brand 11%

Source: FDA, Center for Drug Evaluation and Research (2011)
Figure 6:
Number of Form 483s issued by the FDA

Source: FDA