

American University Washington College of Law

Digital Commons @ American University Washington College of Law

Upper Level Writing Requirement Research Papers

Student Works

2020

Revisiting Cook v. Food and Drug Administration: A lens for analyzing the current state of FDA enforcement and assurance of product quality – increased oversight or not enough?

Catherine Gould

Follow this and additional works at: https://digitalcommons.wcl.american.edu/stu_upperlevel_papers



Part of the [Food and Drug Law Commons](#), and the [Supreme Court of the United States Commons](#)

Revisiting *Cook v. Food and Drug Administration*: A lens for analyzing the current state of FDA enforcement and assurance of product quality – increased oversight or not enough?

Consider the following tragic story. After work, Johnny Smith's mother visited her local drug store to buy him over the counter (OTC) medications for what she hoped was just a common cold. Johnny has leukemia and his parents were trying to ensure he would be well in time for his next chemotherapy treatment in two weeks. After selecting a cherry children's cold and flu product and some cherry throat lozenges, remembering it helped his congestion last time, she picked up a bottle of nasal spray. That evening, elated that his mother got his favorite flavor, Johnny took the OTC medications, used the nasal spray, and to his parent's delight, slept soundly. Initially, Johnny seemed to be improving, so his parents continued the OTC medications. The Smiths were happy with the progress and beginning to gain confidence he would be fully recovered for his chemotherapy treatment, when Johnny's oncologist called. Due to a shortage of his chemotherapy medication, she was not sure that Johnny would be able to get his treatment in two weeks as planned. More concerning, she could not give the Smiths an estimate of when the chemotherapy medication would be available. A couple days later, Johnny complained his neck was stiff. His parents supposed he slept in an odd position and did not think much of it. Then he began complaining about the smell and taste of the medicine that he liked just days before and soon after was nauseous and vomiting. Johnny's temperature spiked. His parents found him generally lethargic, off balance, and not with it, so they called his doctor. While on the phone with his pediatrician, Johnny started convulsing, and the doctor directed his parents to call 911 and get him to an emergency room.

Over the next three days Johnny's situation went from bad to worse. The doctors were unable to identify what was wrong with him. The hospital transferred him to the pediatric intensive care unit (PICU) and he slipped into a coma. Later that day, the PICU physician told Johnny's parents he had primary amebic meningoencephalitis (PAM), a life-threatening parasitic brain infection. The PICU physician asked Johnny's parents if he had by chance been swimming in any warm freshwater where he could have taken in water through his nose. His parents replied no, but then his mother mentioned the nasal spray. The PICU physician requested his parents bring in the nasal spray for testing. The hospital sent the nasal spray for testing and laboratory analysis confirmed the presence of *Naegleria fowleri*, the organism responsible for Johnny's infection. Wrought with guilt and anguish Johnny's parents were stunned, discouraged, and angry. How could this happen? A common OTC medication intended to help their son instead put his life at risk. And if he survived, his life-saving chemotherapy medication may not be available.

Though fortunately fictitious, the above scenario is possible with the current state of the U.S. Food and Drug Administration (FDA) regulations and enforcement. This paper will first discuss past cases on the extent of agency deference and enforcement discretion, namely *Chevron U.S.A. Inc. v. Natural Resources Defense Council Inc.*, *Heckler v. Chaney* and *Cook v. Food and Drug Administration*. Second the paper will discuss the registration requirement emphasized in *Cook*. Third, the paper will discuss the current state of FDA regulatory actions and enforcement. Fourth, the paper will discuss potential implications of the *Cook* decision. Lastly, the paper will propose legislative modifications to the Food Drug and Cosmetic Act (FDCA). Note that while the discussion in this paper may be applicable to other FDA regulated commodities, this paper will focus on FDA commodities that the Center for Drug Evaluation and Research (CDER) regulates.

Selected case law on agency deference and enforcement discretion

While the facts giving rise to *Heckler v. Chaney* and *Cook v. FDA* below involved lethal injection drugs and inmates on death row, the holdings apply to a much broader scope of products. This paper's scope is broader than lethal injection drugs or enforcement discretion involving such drugs.

I. *Chevron U.S.A. Inc., v. Natural Resources Defense Council Inc.*

Clean Air Act amendments passed in 1977 required polluters to get permits from the State before building new or modified stationary sources of pollution. The Environmental Protection Agency (EPA) interpreted the term “stationary source” and promulgated regulations in 1981. The regulations allowed States to adopt a definition of the term “stationary source” that included the whole plant instead of individual pollution-emitting equipment. The National Resources Defense Council (NRDC) challenged the EPA’s interpretation and Chevron stepped in to defend it. The Court of Appeals vacated the regulations, holding that because the purpose of the statutes was to improve air quality, not maintain it, the EPA’s plantwide definition was not appropriate.¹ Chevron appealed and the Supreme Court of the United States granted certiorari.

In *Chevron U.S.A. Inc., v. Natural Resources Defense Council Inc.*, the Supreme Court decided whether EPA’s definition and regulations were based on a reasonable construction of the Clean Air Act statute’s term “stationary source.” The Supreme Court first established that if Congress’ intent is clear then both the courts and the agency must yield to the unambiguous express Congressional intent.² If the court determines that the statute is silent or ambiguous on an issue, then it must determine whether the agency’s action was based on a permissible construction of the statute.³ The Supreme Court interpreted Congress leaving a gap as express delegation to the agency to interpret a specific provision.⁴ Courts should give the resulting agency regulations deference unless they are arbitrary, capricious, or manifestly contrary to the statute.⁵

II. *Heckler v. Chaney*

Chaney along with other inmates on death row in Oklahoma and Texas petitioned FDA to take enforcement action against drugs used in lethal injection because they were in violation of the FDCA. Specifically, the drugs were not approved for lethal injection, allegedly rendering them misbranded. When the FDA declined to take enforcement action, Chaney brought an action in Federal District Court against the Secretary of Health and Human Services, Heckler. The District Court granted summary judgment for Heckler, but the Court of Appeals for the District of Columbia circuit reversed the decision, holding that FDA’s failure to take enforcement action was reviewable and an abuse of discretion. The Supreme Court granted certiorari.

In *Heckler v. Chaney*⁶, the Supreme Court decided the extent to which FDA declining to take enforcement action is subject to judicial review.⁷ The Supreme Court held that an agency’s decision not to take enforcement action is presumed immune from judicial review under the Administrative Procedures Act (APA) 5 U.S.C. § 701(a)(2).⁸ The Supreme Court noted that under the FDCA, FDA is authorized to conduct examination and investigations, and bring seizure, injunction, and criminal sanction actions to enforce the FDCA. But the statute does not detail when FDA should pursue such actions.⁹ Therefore, the FDA declining to take enforcement action was not subject to judicial review. However, the Supreme Court also made it clear that judicial review is appropriate where the statute clearly provides guidelines for the agency to follow when exercising enforcement powers.¹⁰

III. *Cook v. Food and Drug Administration*

¹ *Chevron U.S.A. Inc., v. Natural Resources Defense Council Inc.*, 467 U.S. 837, 837 (1984)

² *Id.* at 842-43

³ *Id.* at 843

⁴ *Id.* at 844

⁵ *Id.*

⁶ *Heckler v. Chaney*, 470 U.S. 821 (1985)

⁷ *Id.* at 828

⁸ *Id.* at 832

⁹ *Id.* at 835

¹⁰ *Id.* at 833

Cook and other inmates on death row in Arizona, California, and Tennessee brought an action against the FDA. The plaintiffs alleged that FDA permitting importation of unapproved and misbranded sodium thiopental, a drug used in lethal injection, violated the FDCA and APA. The United States District Court for the District of Columbia ruled in favor of Cook, permanently enjoined FDA from allowing further importation, and required FDA to notify the correctional facilities the product was unlawful and should be sent to FDA.

In *Cook v. FDA*, the United States Court of Appeals, District of Columbia (D.C.) Circuit held that 21 U.S.C. § 381(a) is “plain and unambiguous”, therefore requires FDA to (1) sample drugs from unregistered establishments, (2) examine the samples to determine if there is the appearance of a violation of the FDCA, and (3) refuse admission where there is an apparent violation.¹¹ The D.C. Circuit also vacated the order for the FDA to notify the correctional facilities and retrieve the product, but discussion of that holding is omitted from this paper as it is not relevant to the subject matter herein.

The D.C. Circuit rejected FDA’s argument that 21 U.S.C. § 381(a) gives FDA unreviewable enforcement discretion and FDA interpretation should be given deference in accordance with *Chevron*.¹² Though *Chevron* held that where a statute is silent or ambiguous with respect to a specific issue, courts should defer to the interpretation of the agency administering the statute, the D.C. Circuit noted that *Chevron* is not applicable when the statute is clear and unambiguous.¹³ Additionally, the D.C. Circuit distinguished *Cook* from *Chaney* on similar grounds. Whereas, in *Chaney* the statute in question did not specify when FDA must pursue enforcement action, 21 U.S.C. § 381(a) “sets forth precisely” what FDA must do.¹⁴

The FDA offered several arguments for its interpretation of 21 U.S.C. § 381(a). FDA argued that 21 U.S.C. § 381(a) should not be construed to require enforcement because FDA was in a better position to know how to best allocate limited resources. The D.C. Circuit rejected this argument stating that 21 U.S.C. § 381(a) does not require FDA to sample and examine all entries, only those from unregistered establishments.¹⁵ Additionally, the FDA argued that it needs enforcement discretion to allow entry of otherwise violative product to address drug shortages. The D.C. Circuit rejected the argument noting that importation of unapproved products was a tool FDA uses in a minority of situations and it could be addressed using the investigational new drug process (IND).¹⁶ Lastly, the FDA argued that it needed enforcement discretion under 21 U.S.C. § 381(a) to allow importation of drugs for personal use per 21 U.S.C. § 384(j)(1)(B). However, the D.C. Circuit noted that 21 U.S.C. § 384(j)(2) already provides a mechanism for FDA to provide a waiver for this purpose.¹⁷

The D.C. Circuit opinion contains a degree of ambiguity in its “Textual Analysis” section where it discusses areas of potential enforcement discretion.¹⁸ It acknowledges that per 21 U.S.C. § 381(a) FDA has discretion to sample or examine products in addition to those from unregistered facilities and that it may detect violations of the FDCA through means other than sampling and examination. After reiterating that it is only saying that FDA must sample and examine drugs from an unregistered facility, the D.C. Circuit states that it is not saying “the FDA must find any type of drug ‘appears’ to violate a substantive portion of the FDCA” but if it finds a drug that apparently violates the FDCA, it

¹¹ *Cook v. Food and Drug Administration*, 733 F.3d 1, 10 (2013)

¹² *Chevron U.S.A. Inc., v. Natural Resources Defense Council Inc.*, 467 U.S. 837 (1984)

¹³ *Cook v. Food and Drug Administration*, 733 F.3d 1, 5 (2013)

¹⁴ *Id.* at 7

¹⁵ *Id.* at 9

¹⁶ *Id.* at 10

¹⁷ *Id.*

¹⁸ *Id.* at 8-9

must refuse it.¹⁹ Which begs the question – is the D.C. Circuit indicating that if FDA through electronic screening, sampling, or otherwise, identifies a product offered for import from a *registered* facility is in violation of the FDCA, it must refuse admission of that product? If so, the implications of *Cook* are broader than the narrow holding pertaining to unregistered facilities.

In its conclusion, the D.C. Circuit presents its holding specifically in terms of what the FDA is required to do with drugs from an unregistered facility – sample, examine for appearance of violation, and refuse admission if there is an apparent violation of the FDCA. But whether 21 U.S.C. § 381(a) is clear and unambiguous with respect to whether FDA must refuse products that violate the FDCA from a *registered* facility appears to be an open question.

Registration

The *Cook* decision focused on the fact that the company supplying the sodium thiopental to the United States was not registered with the FDA. Statutory registration and listing requirements are set forth in 21 U.S.C. § 360, requiring firms that manufacture, prepare, propagate, compound, or process drugs in the United States or that are offered for import into the United States to register with the FDA annually. Registration and listing requirements are further codified in 21 CFR § 207. Both domestic and foreign companies must also list all drugs manufactured, prepared, propagated, compounded, or processed for commercial distribution in the United States at the time of registration. The purpose of registration and listing as outlined in 21 CFR § 207.5 is to identify which entities are manufacturing, repackaging, relabeling, and salvaging drug products and where they perform these functions. Per the regulation, the information is used to facilitate implementation and enforcement of the FDCA.²⁰ Exactly how the FDA uses the registration and listing information as provided in the regulation is somewhat nebulous. However, the FDA’s website on Guidance, Compliance, and Regulatory information provides some additional clarity. FDA uses the information for post-marketing surveillance programs, user fee assessments, monitoring availability of drugs and shortages, and identifying unapproved drugs.²¹ Post-marketing surveillance programs include post-marketing inspections of registered facilities. CDER’s risk-based site selection model for scheduling CGMP surveillance inspections pulls information from CDER’s electronic Drug Registration and Listing System (eDRLS).²² If a facility is not registered, it will not be in FDA’s queue of facilities to inspect. From a product quality assurance perspective, ensuring the FDA has complete and accurate facility information of facilities supplying products to the U.S. market is critical so that those facilities can be incorporated into CDER’s risk-based site selection model for scheduling inspections.

There are three submissions required to register a facility and list products with the FDA. The first, establishment registration, requires a company to provide the name and Dun and Bradstreet (DUNS) number of the facility, contact information of someone that will receive FDA communications for the establishment, and the business operations the facility performs. Additionally, if it is a foreign establishment, the company must provide all importers and the name and DUNS number of a U.S. agent. The second submission is a labeler code request form, which will obtain a National Drug Code (NDC) for listed products. The third submission is the listing information. Registered facilities must list all products produced under their labeler code.²³ The process for registration and listing is quick and completed electronically. Currently, there is no fee to

¹⁹ *Id.* at 9

²⁰ 21 CFR § 207.5

²¹ Guidance, Compliance & Regulatory Information, <https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-registration-and-listing-system-drls-and-edrls>

²² CDER Manual of Policies and Procedures, MAPP 5014.1, Office of Pharmaceutical Quality Understanding CDER’s Risk-Based Site Selection Model, <https://www.fda.gov/media/116004/download>

²³ CDER Electronic Drug Registration and Listing Instructions, <https://www.fda.gov/drugs/drug-registration-and-listing-system-drls-and-edrls/electronic-drug-registration-and-listing-instructions>

register a facility, though there are entities that will undertake the task of registering and listing for drug companies who charge a fee for doing so.

However, registration itself does not provide any assurance of the product quality. It merely satisfies the registration and listing requirements and puts the company on FDA's radar. While FDA will use the data to schedule inspection of the registered facility, for non-application products there is no regulation or reason a company cannot distribute products within the United States without an FDA inspection. This is true for both domestic and foreign facilities manufacturing non-application products. In addition to application review, CDER regulated products subject to a new drug application (NDA), abbreviated new drug application (ANDA), or biologic license application (BLA) generally require a pre-approval inspection of the manufacturing facility or facilities before companies can market the products. That is not the case for non-application products such as unapproved drug or OTC products marketed under an OTC monograph. Therefore, a company manufacturing an unapproved drug, as was the case in *Cook*, or an OTC product, such as the nasal spray in the unfortunate story of the Smiths, whether located domestically or internationally, could market the product in the United States without any oversight of manufacturing processes that can have a critical impact on product quality, safety, or efficacy.

In the Smith tragedy, the manufacturer of that OTC nasal spray could be located domestically or internationally and in compliance with all registration and listing requirements. Furthermore, in the case of the Smiths, if the product was from a foreign company, FDA may not be deviating from the *Cook* holding – the facility was registered and FDA had no reason to suspect that the product coming in was in violation of FDCA. Our current SARS-CoV-2 outbreak is ripe for such a tragedy. Entities, though perhaps not with mal intent, see a market opportunity, a way to “help,” or both, and begin manufacturing products without adequate controls. Compounding the problem, FDA inspections are quite limited during this current outbreak, meaning the delay between a company registering and listing, and the time of an FDA inspection would be far greater than general. Consequently, it is likely that people, like Johnny Smith, would suffer adverse health consequences before the FDA had an opportunity to identify the problems. Even in times when FDA inspections are not encumbered due to an outbreak, there could be a delay between distribution of non-application products and an FDA inspection. Therefore, in the current state of FDA regulation, assurance of product quality of non-application products prior to marketing is lacking.

FDA Regulatory Actions

When FDA identifies violations of the FDCA, it can take various regulatory actions to enforce law, such as holding a regulatory meeting, advisory actions, administrative actions, judicial actions, or in the case of international facilities, stopping products from entering the U.S. supply chain. Ultimately, the goal is to achieve voluntary compliance with the FDCA before heavy handed enforcement actions are necessary. Therefore, FDA will generally proceed with escalating strategies unless doing so would be contrary to public protection.²⁴

The purpose of a regulatory meeting is to obtain prompt voluntary compliance in a setting that allows for dialogue. The outcome of a regulatory meeting is often a company's commitment to take action to correct the conditions or practices at issue.²⁵ The significance of a regulatory meeting may vary. For example, a meeting with a large company's CEO and the FDA Center Director is likely of greater significance than a regulatory meeting held between an individual in charge of one facility in a corporate structure, and CDER Office of Compliance sub-office or local Office of Regulatory Affairs (ORA)

²⁴ FDA Regulatory Procedures Manual, Chapter 4, Advisory Actions <https://www.fda.gov/media/71878/download>

²⁵ FDA Regulatory Procedures Manual, Chapter 10, section 10-3 Regulatory Meetings
<https://www.fda.gov/media/71765>

personnel. Generally, if individuals at the top of the hierarchy are meeting, it would suggest that there are issues that have not been adequately corrected or need to be comprehensively corrected across an organization.

Advisory actions include untitled letters and warning letters. This paper will not cover untitled letters because they are less common, do not carry the significance of a warning letter, and do not necessarily have the component of a warning letter that identifies products as either adulterated, misbranded, or both. In some cases, FDA issues warning letters due to objectionable findings during an FDA inspection, such as inspections to verify compliance with current good manufacturing practices (CGMP). However, FDA can issue warning letters without conducting an inspection. A recent example of such warning letters would be those FDA issued to companies for marketing unapproved and misbranded products associated with SARS-CoV2 and COVID-19 claims.²⁶ Since March 2020, FDA has issued over forty warning letters to companies marketing products claiming to mitigate, prevent, treat, diagnose, or cure COVID-19 based on a review of marketing material on the companies' websites.

FDA issues warning letters in cases where it identified violations of regulatory significance.²⁷ However, issuance of a warning letter does not commit FDA to pursuing further enforcement action. In addition to serving the purposes identified in the Regulatory Procedures Manual of achieving voluntary compliance and establishing prior notice to companies, warning letters also serve a broader purpose. After issuance, FDA publishes redacted warning letters.²⁸ Doing so provides a degree of transparency to the industry, enabling it to learn from other companies' missteps. Companies can view the redacted warning letters and assess whether they may have similar issues. If so, they can begin implementing corrective and preventive actions. In that way, warning letters may serve as a catalyst for continuous improvement of facility operations across the industry.

With the passage of the Food and Drug Administration Safety Innovation Act (FDASIA) in 2012, FDA gained the authority for administrative detention of drugs. The purpose of executing an administrative detention order is to prevent the movement, distribution, and use of products the FDA believes are adulterated or misbranded until FDA pursues additional regulatory action.²⁹ Essentially, it protects the public while buying FDA time, up to twenty days, to execute an appropriate action. Administrative detention orders are rare. Since the FDA gained the authority to administratively detain drugs in 2012, the first administrative detention order that included drug products was executed in October 2018, followed by a seizure in November.³⁰

Judicial actions include seizures and injunctions. FDA's authority to pursue seizures of violative products through the courts comes from 21 U.S.C. § 334. FDA must also pursue injunction through the courts as specified in 21 U.S.C. § 332. In some respects, the goal of seizures and injunctions are the same. FDA initiates a seizure so that a company will make a claim on the goods and enter into a consent decree. In general, FDA does not generally pursue seizures or injunctions unless there are egregious violations or a recidivist history of non-compliance. Seizures and injunctions are far less frequent than warning letters. For instance, in fiscal year 2017, there were no seizures and six injunctions for CDER regulated products.

²⁶ FDA Warning Letters, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>

²⁷ *Id.*

²⁸ FDA Warning Letters, <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters>

²⁹ FDA Regulatory Procedures Manual, Chapter 5, <https://www.fda.gov/media/77026/download>

³⁰ FDA Press Release, FDA seizes food and medical products held under insanitary conditions at an Arkansas grocery warehouse, <https://www.fda.gov/news-events/press-announcements/fda-seizes-food-and-medical-products-held-under-insanitary-conditions-arkansas-grocery-warehouse>

In contrast, in the same timeframe, FDA issued one hundred sixty-one warning letters for CDER regulated products.³¹

For products coming to the United States from foreign facilities, if FDA identifies egregious violations or issues that pose a significant risk to the public, it can prevent products from entering the United States through the import alert process. FDA has various import alerts that are assigned numbers.³² For example, import alert 66-40 is for companies that have not met drug CGMP requirements.³³ If a facility is on an import alert for drug products, then drug products from that facility will be detained without physical examination and refused entry. Depending on the violation, import alerts may be specific to a product or apply to the entire facility.

While FDA may use warning letters and regulatory meetings regardless of the facility location, administrative detention, seizures, and injunctions are only viable options for domestic facilities. Whereas, import alerts are only for international facilities. In addition to whether the facility is in the United States, FDA considers other factors when determining the most appropriate regulatory action such as compliance history, impact of violations on product quality or the risk that products pose to the public, previous regulatory actions, and the company's follow up actions.

Implications of *Cook* decision

A broad interpretation of *Cook* incorporating the idea that if FDA identifies any violation of a drug product, be it from a registered or unregistered foreign facility, FDA must refuse admission for those articles, binds FDA to taking action against violative products from international facilities. The result of a broad interpretation of *Cook* is a scenario where FDA has greater discretion for domestic facilities, creating an unlevel playing field between domestic and international facilities. Additionally, this interpretation of *Cook* could easily lead to or exacerbate a shortage situation, like the one in the story of the Smiths, which appears to be the basis for one of the FDA arguments in the *Cook* case.

When FDA issues certain warning letters, the introductory language identifies the section of the FDCA the products violate. For example, warning letters identifying non-compliance with CGMP generally apply to all products manufactured at the facility and contain the following language.

*Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drugs are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).*³⁴

Whereas, for misbranding and unapproved drug charges, the language may be limited to certain products. For example,

*[Y]our products 'Puriton Eye Relief Drops' and 'Puriton Intimate Disinfection Spray' are misbranded drugs in violation of section 503(b)(4) of the FD&C Act, 21 U.S.C. 353(b)(4), in that their labels fail to bear the symbol, 'Rx only.' In addition, your 'Puriton Natural Mineral Cleansing Bar Soap' is an unapproved new drug sold in violation of sections 505(a) and 301(d) of the FD&C Act, 21 U.S.C. 355(a) and 331(d).*³⁵

Why is warning letter language relevant to this discussion? Because, if FDA has issued a warning letter to a domestic facility, even though the warning letter states that the products are adulterated, misbranded, or both, the company can continue to distribute its products in the United States. The FDA

³¹ FDA Enforcement Statistics Summary Fiscal Year 2017 <https://www.fda.gov/media/110196/download>

³² FDA Import Alerts by Number https://www.accessdata.fda.gov/cms_ia/ialist.html

³³ FDA Import Alert 66-40, https://www.accessdata.fda.gov/cms_ia/importalert_189.html

³⁴ FDA warning letter to Kadesh International, May 2, 2019: <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/kadesh-international-570947-05022019>

³⁵ Id.

having identified the products as in violation of the FDCA is not compelled to pursue further action, such as administrative detention, seizure, or injunction. Contrast that with what would happen under a broad interpretation of *Cook*. If FDA issued a warning letter to a foreign facility that identified products were in violation of the FDCA, then those products must be refused. In essence, for CGMP violations, every facility that received a warning letter would in effect be on import alert and essentially prohibited from distributing its products in the United States.

The broad interpretation of *Cook* also would have significant impact on drug shortages. Pursuant to 21 U.S.C. § 356d(b), prior to issuing a warning letter or taking an enforcement action, CDER Office of Compliance consults with CDER's Drug Shortage Staff. If a facility manufactures products without which there would be a drug shortage concern, there are measures CDER Office of Compliance takes to avoid a shortage. When managing drug shortages CDER considers the risk of not having the product available against the risk associated with the violation or product defect.³⁶ Though warning letters are advisory actions and are not intended or expected to stop drug production or distribution, FDA will add standard shortage language to the warning letter, notifying the company that prior to making any decisions that could impact supply, it should notify CDER's Drug Shortage Staff.³⁷ If CDER's Drug Shortage Staff identifies a shortage concern for products manufactured at a facility proposed for addition to an import alert, then CDER Office of Compliance may exclude certain products from the import alert to avoid or mitigate a shortage. However, as previously explained, under the broad interpretation of *Cook* issuing a warning letter to an international facility would have the same effect as an import alert and FDA would not be able to exclude any products from import alert if the warning letter had designated them as adulterated or misbranded. This would leave FDA with an extremely undesirable choice – to avoid a shortage, do not take regulatory action or take the action and cause a shortage. Neither choice is in the best interest of public health. Furthermore, it would make it difficult to alleviate a shortage through temporary importation of unapproved products from foreign facilities. As the D.C. Circuit alluded to in *Cook*, the company wanting to temporarily distribute its product would have to go through the emergency use IND process.

According to a narrow interpretation of *Cook*, provisions in 21 U.S.C. § 381(a) indicating FDA shall refuse entry to any products that violate the FDCA are limited to those products from facilities that are not registered. In other words, had the facility supplying thiopental to the United States in *Cook* been registered with the FDA, the fact that the product was unapproved, misbranded, adulterated or otherwise in violation of FDCA, would be insufficient to compel FDA to refuse entry. Therefore, so long as a facility is registered with FDA, FDA would appear to have the enforcement discretion for which it argued in *Cook*. Applying the narrow holding in *Cook*, the D.C. Circuit decision did not increase FDA's enforcement obligations or significantly limit its discretion.

The D.C. Circuit decided *Cook* in 2013, so the varying interpretations discussed above raise the question – how has FDA operated since the *Cook* decision? FDA appears to be operating under the narrow interpretation of *Cook*, as evidenced by the fact that FDA has continued to exercise enforcement discretion for drug shortages to allow temporary distribution of unapproved drugs in United States. Take the following example. FDA maintains an online list of current shortages.³⁸ One of the drugs currently on the shortage list is bupivacaine hydrochloride injection³⁹, a drug used for local anesthesia and epidurals.

³⁶ CDER Manual of Policies and Procedures, Drug Shortage Management, MAPP 4190.1 Rev.3, <https://www.fda.gov/media/72447/download>

³⁷ FDA Regulatory Procedures Manual, Chapter 4, p. 20 <https://www.fda.gov/media/71878/download>

³⁸ FDA Drug Shortages, <https://www.accessdata.fda.gov/scripts/drugshortages/>

³⁹ FDA Drug Shortages, bupivacaine hydrochloride injection https://www.accessdata.fda.gov/scripts/drugshortages/dsp_ActiveIngredientDetails.cfm?AI=Bupivacaine%20Hydrochloride%20Injection,%20USP&st=c&tab=tabs-1#

Looking at the details of the shortage, you can see that one company, Areva Pharmaceuticals, is temporarily importing the product from Fisiopharma, located in Italy, to address the drug shortage. The shortage information also contains a link to a Dear Health Care Provider letter that Areva Pharmaceuticals issued in conjunction with the temporary importation. Though the Dear Health Care Provider letter, notifying providers of the temporary solution to the shortage, does not specifically state that the facility is registered with FDA, one can easily cross reference with another online resource to confirm. DailyMed⁴⁰ is a resource from the U.S. National Library of Medicine that pulls information from eDRLS. Sure enough, if you search for the drug name in DailyMed, you will find an entry for bupivacaine hydrochloride injection associated with Areva Pharmaceuticals.⁴¹ Notably, the marketing category is “unapproved drug for use in drug shortage,” and where the package insert information would normally appear for FDA approved drugs, the Dear Health Care Provider letter is in its place. Additionally, the manufacturing facility is provided at the bottom of the “ingredients and appearance” section under the “establishment” heading. It is also possible to verify registration status using FDA’s Drug Establishments Current Registration Site,⁴² but doing so requires knowledge of the manufacturing facility and it does not provide as much detail as DailyMed searches.

Additionally, it does not appear that facilities are included on an import alert for every warning letter the FDA issued to a foreign facility, identifying its products as adulterated. For example, in April 2020, FDA issued a warning letter to Shriram Institute for Industrial Research (Shriram) for failure to comply with 21 U.S.C. § 351(a)(2)(B) of the FDCA. The warning letter clearly states that drugs from Shriram are adulterated.⁴³ However, if you look at import alert 66-40 for facilities that have not met drug CGMP, Shriram does not appear on the import alert.⁴⁴ If FDA was abiding by a broad interpretation of *Cook*, the expectation would be that if a warning letter stated that all products from the facility were adulterated, then all of those products should be refused (i.e., on import alert). Moreover, for facilities that FDA placed on import alert and issued a warning letter identifying all products from the facility as adulterated, there are instances where FDA excluded certain products from the import alert. For example, looking at the import alert 66-40 list,⁴⁵ there are at least ten drug products that are excluded from the import alert. Under a broad interpretation of *Cook* FDA would not have the discretion to allow entry of certain products because it had already determined that all products from the facility were adulterated.

Not having FDA’s enforcement discretion curtailed is a positive outcome from an enforcement strategy and drug shortage perspective. But the term enforcement discretion itself implies that FDA is aware of a situation and has made a calculated determination it will not take action at the time. The concern is in situations when FDA does not have knowledge or information to make that determination. If FDA does not have a regulatory framework that ensures some oversight of products before marketing, as is the case with non-application products, that is not enforcement discretion, but rather a gaping hole in FDA oversight that can lead to patient harm as in the Smith tragedy. Under existing FDCA statute and FDA regulations, there is insufficient regulation for marketing non-application products.

Legislative proposals

⁴⁰ DailyMed, U.S. National Library of Medicine, <https://dailymed.nlm.nih.gov/dailymed/>

⁴¹ DailyMed, U.S. National Library of Medicine, bupivacaine hydrochloride, Areva Pharmaceuticals <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=8c168503-9120-20ea-e053-2a95a90a8bf2>

⁴² FDA Drug Establishments Current Registration Site, <https://www.accessdata.fda.gov/scripts/cder/drls/getdrls.cfm>

⁴³ FDA Warning Letter, Shriram Institute for Industrial Research, April 15, 2020 <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/shriram-institute-industrial-research-597629-04152020>

⁴⁴ FDA Import Alert 66-40, https://www.accessdata.fda.gov/cms_ia/importalert_189.html

⁴⁵ Id.

I. Changes to 21 U.S.C. § 381

Currently, 21 U.S.C. § 381 opens with stating that the Secretary of the Treasury (Customs and Border Patrol) must provide samples of products offered for entry upon the Secretary of Health and Human Service's (FDA) request. It then goes on to specify what FDA must do for products from unregistered facilities. To resolve ambiguities discussed above, 21 U.S.C. § 381 should first clearly dispense with what the FDA must do with respect to unregistered facilities. Additionally, the sampling requirements in 21 U.S.C. § 381(a) should be eliminated for drug products. Currently, the direction appears circular. Not being registered with the FDA, by definition, renders a product misbranded within the meaning of 21 U.S.C. § 352(o). What is the sense in requiring FDA to obtain samples from Customs and Border Patrol (CBP) and examine them when violation of any part of the FDCA will result in refusal? For example, 21 U.S.C. § 381 could be modified to indicate that if any drugs are "manufactured, prepared, propagated, compounded or processed" in an unregistered establishment are offered for import into the United States, such article shall be refused admission except pursuant to 21 U.S.C. § 384(j).

After stating exactly what must be done with products from an unregistered facility, the section should move on to registered facilities. For registered establishments 21 U.S.C. § 381 should indicate that CBP must provide samples to the FDA upon FDA's request. If FDA identifies any violations from examination of samples or otherwise (e.g., electronic screening or other FDA data), then it *may* refuse admission of those articles.

Proposed rewrite: Regarding products from registered establishments, the Secretary of the Treasury shall deliver to the Secretary of Health and Human Services upon his request . . . giving notice thereof to the owner or consignee, who may appear before the Secretary of HHS and have the right to introduce testimony. If it appears from the examination of such products or otherwise that (1) such article has been manufactured, processed, or pack under insanitary . . . (2) such article is forbidden or restricted in sale . . . (3) such article is adulterated, misbranded, or in violation . . . (4) the record keeping requirements . . . or (5) such article is being importer or offered for import in violation of section 331(cc) . . . then such articles may be refused admission.

The proposed modifications to 21 U.S.C. § 381 are necessary to resolve the ambiguities and varying interpretations of the statute. With respect to unregistered facility, it is unlikely that FDA needs wide enforcement discretion. The registration process is not onerous making it easy for facilities to abide by registration and listing requirements. Therefore, if there was an unregistered facility that could help alleviate a shortage, FDA would simply inform the company that it needs to register the facility and list the product in question. As discussed above, FDA is already using this approach. However, with respect to registered facilities, maintaining FDA's enforcement discretion is warranted. Otherwise, not only would it create unequal enforcement between domestic and foreign facilities, but it would make it difficult for FDA to employ its strategies to mitigate or prevent drug shortages.

II. Adulteration provision for facilities FDA has not inspected

Registration of a facility alone is insufficient to provide assurance of a product's quality and safety. The nasal spray in the Smith tragedy could have been from a registered facility, but not FDA inspected. An initial FDA inspection would have covered the following systems at the facility: quality system, facilities and equipment system, materials system, production system, packaging and labeling system, and

laboratory control system.⁴⁶ Within the materials system, FDA investigators look into the components that go into the finished product, including water. In the Smith tragedy, the parasite in the nasal spray is commonly found in warm freshwater, such as lakes or rivers. It is likely an FDA investigator could have identified the manufacturing facility's lack of control over the water source used, so that the FDA could take appropriate and timely action to protect the public from the product. However, because there is no requirement that a facility be inspected prior to marketing a product, the public is at increased risk of exposure to products with questionable quality and safety.

Requiring all products to have an approved application prior to marketing would be widely unpopular with industry and impractical for the FDA. It is unlikely the FDA would be able to keep up with review of the applications and enforcing non-compliance with such a requirement. However, requiring that products must be from a facility that FDA has inspected may be viable and would provide increased quality assurance. Congress could modify 21 U.S.C. § 351 to include an adulteration provision for drug products from a facility that FDA has not inspected. For example, add 21 U.S.C. § 351(k) that provides "if it is a drug and it has been manufactured in any factory or establishment that FDA has not inspected." Because products from facilities FDA has not inspected are by definition adulterated, then it would become a prohibited act under 21 U.S.C. § 331(a) to introduce or deliver for introduction such products into interstate commerce. There is already an adulteration provision, 21 U.S.C. § 351(j), rendering products from a facility that delays, denies, limits, or refuses an FDA inspection adulterated. From the standpoint of protecting the public from harmful products, whether problems cannot be identified because the company did not permit it or because FDA could not inspect the manufacturing facility before the company began marketing its products, the result is the same. In both scenarios there is the potential for unidentified problems to adversely affect product quality and safety, which poses an increased risk to the public.

Adding the new adulteration provision will probably have little impact on the majority of the industry. Companies marketing application products will not experience any additional burden or changes because FDA would not approve its application if the manufacturing facility had never been inspected. It is also probable that FDA inspected facilities that have manufactured unapproved drugs for some time. CDER's enforcement priorities for marketed unapproved drugs include other violations of the FDCA, for example CGMP violations.⁴⁷ Thus the proposed adulteration provision would not even affect all unapproved drug manufacturers. Similarly, it is likely that large OTC manufacturers that have marketed products for some time would not be affected because it is likely they have had an FDA inspection. The proposed adulteration provision would impact new facilities manufacturing non-application products and for good reason. From the manufacturing facility's perspective, it is beneficial to ensure that it is complying with the FDCA statute and FDA regulations early on. In many cases it is far more expensive to fix problems the longer they have persisted. From the public health perspective, inspecting these new facilities prior to the company marketing the products decreases the risk to the public.

Enforcing the proposed adulteration provision for foreign facilities would be relatively straightforward. During import entry review, FDA could simply refuse admission for drug products if FDA had not inspected the manufacturing facility. If the entry review system and inspection database systems were integrated, this could even be done via automation. Additionally, as long as the above proposed changes to 21 U.S.C. § 381 were adopted, the additional adulteration provision should not result in increased shortages or impede FDA's ability to respond to shortages. If FDA had not inspected a

⁴⁶ FDA Compliance Program 7356.002, Chapter 56: Drug Quality Assurance
<https://www.fda.gov/media/75167/download>

⁴⁷ Guidance for FDA Staff and Industry, Marketed Unapproved Drugs – Compliance Policy Guide,
<https://www.fda.gov/media/71004/download>

facility wanting to temporarily distribute unapproved products in the United States to alleviate a shortage, like any other adulteration or misbranding violation, FDA could make a risk-based decision to exercise enforcement discretion.

Enforcing the proposed adulteration provision for domestic facilities could be more challenging. While many companies will not knowingly violate the FDCA, there are may be those, generally smaller, companies that are unaware and unfamiliar with FDCA statutes and regulations. To combat the lack of knowledge, FDA could send an automatic notice to registrants upon registration of a facility that introducing products into interstate commerce if FDA has not inspected the facility is a violation of the FDCA and that they should not market products until FDA has inspected their facilities. Again, if the FDA's registration system and inspection database system were integrated, it could be an automated process where FDA could target this notice to only those facilities that FDA had not inspected. It may be challenging to identify domestic facilities that shipped products manufactured in a facility that FDA has not inspected. However, because through the registration and listing process, FDA would know the NDCs, FDA could take the NDCs of products from facilities without an FDA inspection and use sales data from the IQVIA National Sales Perspectives (NSP) database to determine whether those products have been marketed. Because IQVIA NSP is not a system internal to FDA, FDA may not be able to automate the process.

Concededly, FDA inspections are a snap shot of what occurs in facilities and will not identify all problems at a facility one hundred percent of the time. But there is no doubt an FDA inspection of a facility, previously not FDA inspected, substantially increases the likelihood that FDA will be able to identify major problems with the potential to result in serious adverse health consequences to product users before they reach the public.

Conclusion

The *Cook* decision made it clear that FDA does not have enforcement discretion with respect to unregistered facilities. However, it did not clearly answer the question of whether FDA has enforcement discretion with respect to registered facilities. This paper highlighted why it is important to maintain FDA's enforcement discretion for registered facilities. Failure to do so would lead to unequal enforcement between domestic and foreign facilities and have a detrimental impact on drug shortages. Additionally, the registration which was a focal point in the *Cook* decision does not directly have any bearing on the products' quality, safety, or efficacy. There could be products of substandard quality from an unregistered facility or a registered facility. The focus on the registration requirement does not represent a shortcoming of or error in the D.C. Circuit court's decision as the judiciary's role is to interpret the law. But understanding the purpose of registration requirements highlights that alone, registration does not significantly further the FDA's mission in protecting the public health from poor quality drug products because it does not ensure that FDA had the opportunity to evaluate practices at the manufacturing facility with the potential to have a significant impact on product quality. Assurance of product quality and safety requires FDA to have sufficient knowledge of the practices at the facility. While the application process provides the FDA with sufficient information so that the FDA can approve safe and efficacious products with acceptable quality, the non-application products present a gap in FDA oversight. The proposed legislative solutions seek to remove ambiguity and provide FDA with the decision making and oversight power necessary to adequately protect the public and ensure access to products that meet appropriate quality standards.