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A Brief Review of FDA's Novel Tools for Ensuring Pharmaceutical Quality in the Human Drug Supply Chain

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Abstract

Purpose: Pharmaceutical manufacturers execute quality control operations and Good Manufacturing Practices (GMP) to provide safe drugs. The Federal Drug and Food Administration (FDA) is tasked with ensuring manufacturers are performing such procedures. Faced with limited resources the FDA has developed novel tools to aid supply chain oversight. This paper briefly reviews these tools.

Methods: Current inspection approaches employed by the FDA are identified by searching the FDA's guidelines, the Code of Federal Regulations, public reports and other online resources.

Outcomes:

Industry: A risk-based site selection model (SSM) is used to prioritize on-site inspections for FDA investigators. Theoretically, the SSM allows FDA investigators to focus on firms that are at high risk of failing to meet quality standards. Analytical testing of drugs is performed by FDA laboratories as well as manufacturers' laboratories. Despite this, two of the highest profile recalls in the last several years (Valsartan and Ranitidine) were not initially identified by the FDA. Instead, Valisure, an online pharmacy that tests each batch of inventory, detected the issues.

Physicians and Consumers: The FDA has provided easy-to-use online tools for patient and physician reporting of drug quality problems. The FDA has also created consumer education campaigns to aid in protecting patients from fraud and counterfeiting.

Conclusion: The FDA has developed novel methods of redistributing their workforce to maximize product quality and consumer safety with limited resources. The methods include a risk-based SSM for prioritizing on-site inspections, providing education tools, and online reporting of quality problems. FDA laboratories also provide analytical testing to ensure purity standards are met. The recent publicized discoveries of Valisure are leading other pharmacies such as the University of Kentucky Central Pharmacy to begin testing incoming drugs. It is critical for these pharmacies and the FDA to cooperate to protect the pharmaceutical supply chain moving forward.

Keywords: pharmaceutical manufacturing, FDA, CDER, FDA site selection tool, risk-based modeling, risk reduction, GxP, cGMP, human drug manufacturing, drug surveillance, pharmaceutical supply chain, pharmacy-level investigators.

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Introduction

Visually detecting adulterated, defective, or contaminated pharmaceuticals is nearly impossible (beyond cosmetic defects like a cracked vial). Instead, specialized and often destructive analytical techniques such as liquid chromatography and mass spectrometry must be used to identify adulterated products (Nikolin et al., 2004). For this reason, pharmacists can unintentionally dispense counterfeit, adulterated, or misbranded medicine to patients. Simply put, bad drugs can lead to bad outcomes. Patients may experience loss of therapeutic benefits, become ill, and, in extreme cases, death. To ensure drug quality, pharmaceutical manufacturers execute quality control and other current good manufacturing practices (cGMP). cGMP is among the GxPs, or Good "x" family of guidelines, where x is manufacturing, laboratory, research, engineering, documentation, etc. These guidelines are created collaboratively by agencies such as the US Food and Drug Administration (FDA) and the Global International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). GxP guidelines are intended to provide accountability and traceability to the "x" activity. cGMP itself generally refers to the requirements outlined in the Federal Food, Drug, and Cosmetic Act of 1998 (FD&C Act), Section 501(a)(2)(B). It is generally accepted that by following cGMPs, undesirable events will be mitigated. However, following cGMP does not provide a guarantee against adulterated or defective drugs. Further, many manufacturers fail to meet cGMP standards at all (Campbell and Lodder, 2021).

The FD&C Act requirement for drug manufacturers to follow cGMP is enforceable by the FDA (FDA, 2016; "Federal Food, Drug, and Cosmetic Act ß501(a)(2)(B), 21 U.S.C. ß351," 1998). Despite this, many manufacturers still fail to meet cGMP standards. Lack of compliance is often unintentional; however, sometimes deliberate fraud occurs (Campbell and Lodder, 2021; Eban, 2019; Evana et al., 2019; Mu and Carroll, 2016; Okoye and Nwoka, 2019). Regardless of the intent, manufacturers failing to meet cGMP standards have occupied FDA inspectors for decades. Indeed, the FDA now conducts quality testing of products and perform on-site inspections of drug manufacturing firms. However, with limited resources, the FDA has struggled to keep up with the demands. By the end of the fiscal year (FY) of 2019, the number of drug manufacturing sites worldwide totaled 4,273, down 8.6% from the previous year (FDA, 2020a). Yet only 1,258 drug quality surveillance inspections were conducted of these firms. For data regarding the number of on-site inspections conducted, the FDA provides a database that may be reviewed at https://www.accessdata.fda.gov/scripts/fdatrack/view/track.cfm?program=oip&status=public&id=OIP-Number-of-inspections-completed-in-country-by commodity&fy=2020.

Further, the FDA relied on European Union (EU) regulators under the Mutual Recognition Agreement to conduct 109 drug quality inspections in the EU region (FDA, 2020a; FDA and EU, 2017). Despite the decrease in total manufacturing sites and reliance on EU regulators, the FDA reported a decrease of more than 4% in annual domestic on-site inspections performed over two years (FY17-19) (FDA, 2020a). On the other hand, more than a 6% increase in on-site inspections in India was reported. However, the total percentage of foreign manufacturers decreased from

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61% to 58% from FY2018 to FY2019. Therefore, it seems the FDA may lack the necessary resources to frequently inspect domestic and foreign drug manufacturing sites (FDA, 2019, 2020a).

The reasoning behind FDA's reduced inspections was briefly alluded to by the organization in response to the United States Government Accountability Office (GAO) preliminary findings of the FDA's performance (Denigan-Macauley, 2019). In a report released by GAO (GAO-20-262T), a testimony before the Subcommittee on Oversight and Investigations, the Committee on Energy and Commerce, and the US House of Representatives, the GAO outlined that between the FYs of 2016 and 2018, both foreign and domestic inspections decreased by approximately 10% and 13% respectively. In response, the FDA attributed the decrease to job vacancies, claiming that in June of 2018, the FDA employed 190 investigators capable of conducting foreign inspections, but by November, the FDA had 58 vacancies(Denigan-Macauley, 2019).

Facing shrinking resources and persistent demand, the FDA relies now more than ever on state-of-the-art tools to effectively redistribute the available workforce. Applying today's technology to computable tasks allows human workers to focus on and more adequately tackle the complex intricacies of the pharmaceutical supply chain (PSC). Proper redistribution of the FDA's workforce could help increase the identification and elimination of potential threats to the PSC.

This paper provides a brief review of the FDA's current methods. The section "Risk-Based Site Selection" focuses on the FDA's site-selection model (SSM) for on-site inspections. The section "Analytical Testing" provides a brief description of the FDA's role in drug quality testing. Finally, a brief description of tools and campaigns developed to educate both consumers and supply chain personnel regarding risk in distributing and purchasing drugs is discussed.

Risk-Based Site Selection

On-site inspections are intended to verify a manufacturing firm's compliance with cGMP. The basis for cGMP can be found in the Code of Federal Regulations - (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=211). As outlined in the FD&C Act, domestic drug manufacturing firms must be inspected at least once every two years. However, fulfilling this requirement has proven difficult since the establishment of the FD&C Act in 1998. This may be partially due to the globalization and increased complexities of the PSC (Singh, 2016). Indeed, most drug manufacturing firms are now located overseas (Baldwin, 2012; FDA, 2017a, 2019; Woodcock, 2019). Lacking the necessary resources, the FDA was unable to keep the FD&C Act requirement. Failing to conduct biennial inspections of domestic drug firms, the FDA responded by introducing a risk-based site-selection model in the FY2005 (CDER, 2018). The model is an outcome of the FDA's pharmaceutical cGMPs for the 21st-century initiative that was first announced in 2002 (FDA, 2004b). The initiative aimed to ensure FDA policies and actions were risk-based and scientifically backed. Developed through expert opinion, recall history, and other FDA records, the risk-based SSM ranks manufacturing sites for inspection.

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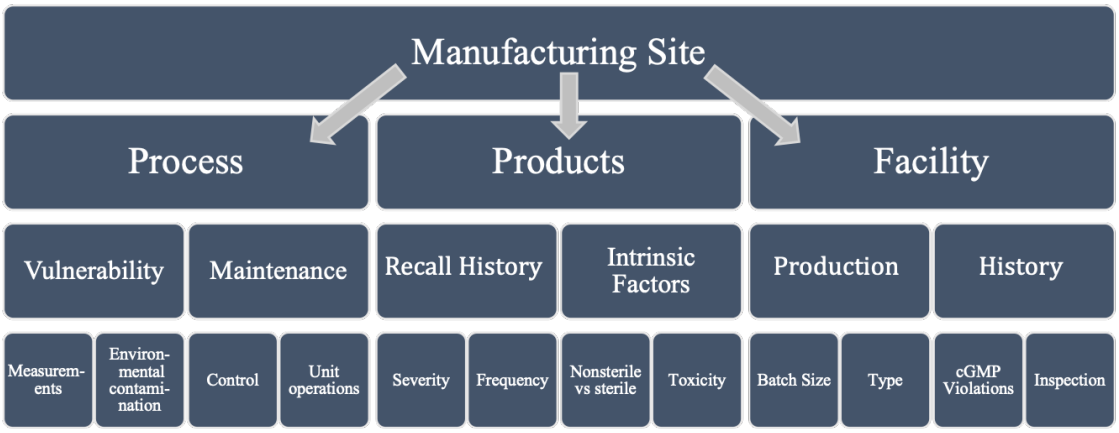

Figure 1: Representative conceptual layout of FDA's risk-based site-selection model (SSM). Where the model theoretically inputs a manufacturing site to be analyzed in terms of risk factors. Beginning by dividing the site into three general groups: Process, Products, and Facility. Further division of these general groups then takes place. Breaking each group into categories of risk, such as product recall history. Once a site's relevant characteristics are deconstructed into risk categories, risk-factors are then itemized. Such risk factors include a facility's production type (e.g., packing facility, API production, labeling facility) and process hazards such as environmental contaminants (e.g., the process using significant amounts of hazardous material). Each risk factor contributes to a weighted risk potential for each general group (FDA, 2004a).The estimated combined risk potential for the site is then calculated through a linear combination of these groups (FDA, 2004a). Hierarchical map modified from (FDA, 2004a).

The SSM was developed through what the FDA describes as a "multi-step analytical process," which consists of (1) hazard identification, (2) conceptual modeling, (3) risk estimation, and (4) risk filtering (FDA, 2004a). Hazard identification was conducted by gathering qualitative data from experts in fields such as investigative inspection. These experts were then asked to answer questions such as “In your experience, what are the principal factors important in predicting adverse impacts to drug quality?” and then asked follow-up questions such as “What variables are associated with, or predictive of, those hazards?” (FDA, 2004a). This step was intended to be an initial brainstorming stage and identified 70 potential risk factors (FDA, 2004a). Next, the potential risk factors were filtered, eliminating duplicates and those difficult to quantify. With the remaining risk factors, a conceptual model was constructed. Organized by FDA personnel, risk factors were connected based on generality and relationship. The resulting conceptual framework is summarized in Figure 1.

Examining Figure 1, the SSM analyzes a manufacturing site in terms of risk factors. The model first divides a manufacturing site into three general groups: Process, Products, and Facility. Further division of these groups then takes place. Breaking each group into categories of risk, such as product recall history. Once a site's relevant characteristics are deconstructed into risk categories, risk factors are then listed out. Risk factors include a facility's production type (e.g., packing facility, API production, labeling facility) and process hazards (e.g., the process using

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significant amounts of hazardous material). Each risk factor can be thought to contribute to a weighted risk potential for each of the general groups (Process, Products, and Facility) (FDA, 2004a). That is the risk potential for each general group is a combination of the weighted risk factors. The estimated combined risk potential for the site is calculated through a linear combination of these groups (FDA, 2004a). Although the pilot SSM's exact algorithm has not been released, it may be assumed from documents provided by the FDA that the linear combination takes on a form similar to that illustrated through Equations 1and 2. . By allowing the column vector $\vec{v}_{i,j}$ to represent risk factor i belonging to group j (e.g., Process, Products, or Facility) for site k a and by assuming that the assignment of the $w_{i,j}th$ weight factor corresponds to the $v_{i,j}th$ risk factor, then the combined weighted risk factors for group j can be thought to take the form of Equation 1.

$$\vec{w}_{i,j} * \vec{v}_{i,j} = R_j \text{ Equation 1}$$

Where, $\vec{w}_{i,j}$ is the row vector representation of weight factors, corresponding to risk factors with the column vector $\vec{v}_{i,j}$. Then $R_j$represents the mathematical combination of weighted risk factors belonging to group j (Process, Products, or Facility). It should be noted that the weighted risk factors are numerically discrete values and the weight factor assigned to select risk factors are determined by expert opinion, empirical evidence or a mixture of both (FDA, 2004a).

Lastly, the potential risk of site k is given by linearly combining R_j for each group and can be thought of as taking the form of Equation 2.

$$aR_1 + bR_2 + cR_3 = R_{S_k} \text{Equation 2.}$$

Where a, b, c are scalar constants and $R_{1,2,3}$ is R_j with $j = 1,2,3$ representing the Process, Products and Facility group respectively. Then the output of this model is a numerical value R_{S_k} representing a site S_k risk potential based upon the linear combination of groups R_j. A simple python script is provided to illustrate the model (an Octave script can be provided upon request). Type in some test numbers and see how these equations act.
https://colab.research.google.com/drive/1A1DZ1ExxhsJjG2Wbj6zbW74pNg7yhcsl?usp=sharing

In essence, the SSM model attempts to represent a manufacturer's potential failure through mathematically combining weighted risk factors into one numerical value (e.g., S_k). This score is then thought to be used to prioritize on-site inspections. That is given a scenario where manufacturer A is more likely to produce suboptimal drug products than manufacturer B according to the respective S_k scores. Then manufacturer A will be prioritized for on-site inspection by the FDA over manufacturer B. Therefore, the SSM allows FDA investigators to focus their efforts on high-risk sites.

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Analytical Testing

Pharmaceutical manufacturing requires among the highest quality standards of any industry. However, batch to batch and sometimes item to item variation is an inescapable element of process manufacturing (Xie and Schenkendorf, 2019). To mitigate the risk to product quality introduced by these inconsistencies, drug manufacturers are tasked with validation activities such as testing batches to ensure high-quality production is maintained (e.g., a product free from contaminants and reproducibly delivers the therapeutic benefit described on the label Woodcock, 2004). Despite this requirement, impurities are not always identified before distribution. Such events occur in other types of manufacturing, such as food, where a defective fruit, for example, may slip into distribution. However, this is typically less of an issue, given that a defective orange can be inspected at the consumer level for quality. This is not the case for drug products where visual detection of counterfeit, adulterated or misbranded medicine is nearly impossible. Instead, specialized equipment must be used that the everyday patient does not have access to, such as infrared spectrometry (Galante et al., 1990). Hence, the FDA must conduct quality testing for patients. In FY2019 FDA, laboratories analyzed nearly 734 drug samples (FDA, 2020a). Included in the drugs tested was Valsartan, a common blood pressure medication. After receiving notice that Valsartan was potentially contaminated with N-nitrosodimethylamine (NDMA), an impurity with potential carcinogenic properties (Mahase, 2019; Pottegård et al., 2018) The FDA responded by developing a method to detect and quantify NDMA and other nitrosamine impurities in angiotensin II receptor blockers (ARB's) (FDA, 2020a). Valsartan was then tested for NDMA in FDA laboratories, where the initial claims were confirmed. These results prompted a recall of many ARB's in the US, including Valsartan, Losartan, Irbesartan, and Olmesartan (Farrukh et al., 2019). Following this recall, in June 2019, NDMA was found in Ranitidine by Valisure, an online pharmacy that tests each batch of products before disturbing to customers (Valisure, 2019). In response, the FDA again developed a method to detect and quantify NDMA in Ranitidine. In total, the FDA for the FY2019 would develop methods to detect and quantify eight different types of nitrosamines for ten different drugs (FDA, 2020a). Following the FDA's initial notification, Valisure then submitted a citizens' petition in September 2019 to have Ranitidine removed from shelves for public safety. The petition may be reviewed here: https://www.valisure.com/wp-content/uploads/Valisure-Ranitidine-FDA-Citizen-Petition-v4.12.pdf.

In response to the seemingly sudden uptake in nitrosamine impurities, the FDA sent out 23 investigators globally to investigate sites related to the recalls, of which 61% of whom received a report of OAI or official action indicated—suggesting that many of the sites affected by the recalls were not in full compliance with cGMP (FDA, 2020a). However, there are indicators that using the solvent dimethylformamide (DMF) in synthesizing the API in Valsartan's case is to blame (Parr and Joseph, 2019). Further, DMF is classified as a Group 2A probable human carcinogen by the World Health Organization (WHO) and the International Association for Research of Cancer (IARC) (Society, 2019). Despite this, the FDA deemed 8,800,000 nanograms safe for daily intake

limits; this prompted Valisure in June 2019 to issue another citizen's petition to the FDA, requesting lower daily intake limits of DMF and a recall of all Valsartan processed with this solvent. The citizen petition submitted by Valisure can be reviewed here: https://www.regulations.gov/document?D=FDA-2019-P-2869-0001. Given that arguably the two most extensive recalls in the past couple of years have been initiated by Valisure and not the FDA, it seems the FDA may benefit from aid in this area of surveying the PSC. Luckily, Valisure has inspired other quality testing pharmacies to emerge, such as the University of Kentucky (UK) Central Pharmacy. Here, the injectable medication used within the UK hospital is undergoing quality testing. Similar quality testing sites will likely begin to appear as more recalls and safety alerts result from such work. Collaboration between the FDA and these "second check" pharmacies will be critical for optimized drug quality testing. Another tactic to catch faulty batches of drugs is to use patient and physician reports. This topic will be touched on in the next section.

Consumer Tools

In addition to providing guidelines, on-site inspections, and quality analysis testing, the FDA also provides tools for patients and physicians to participate in drug surveillance. *MedWatch* is an online tool that allows patients, doctors, and consumers to voluntarily report potential risks to the FDA (FDA, 2020b). *MedWatch* accepts reports regarding prescription and over-the-counter (OTC) medicines, biologics, medical devices, combination products (e.g., nasal spray), cosmetics, and foods. *MedWatch* volunteers are prompted to fill out either a 3500 or 3500B form depending on the individual's role as a health professional or consumer/patient. Once the appropriate form is selected, the system generates a report ID. The system records the report date, demographic information, and description of the potential risk before allowing the reporter to submit the form to the FDA electronically. Using this information, the FDA can quickly identify threats and, when needed, issue safety alerts informed from this tool. *MedWatch* can be easily accessed at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home. Supplementary to encouraging patient participation, the FDA also provides educational tools to lower consumer risk.

The FDA provides several educational campaigns to lower consumer risk. For example, the BeSafeRx campaign raises awareness about the dangers of buying prescription medicines from fake online pharmacies (FDA, 2015). BeSafeRx provides tips on identifying safe online pharmacies, such as ensuring the pharmacy is licensed within the patient's state's board of pharmacy. To supplement this, the FDA provides a database in which such information can be received quickly. This database can be explored at: https://www.fda.gov/drugs/besaferx-know-your-online-pharmacy/know-your-online-pharmacy.

The FDA does not limit developing educational campaigns and tools to consumers. Manufacturers and other supply chain personnel can also find aid through tools such as the supply chain security tool kit. Developed through a collaboration with the Asia Pacific Economic

Cooperation, the FDA created the supply chain security tool kit focusing on medical products (FDA, 2017b). Constructed to improve supply chain security, the tool kit addresses vulnerabilities in the medical product supply chain. It provides recommendations on best practices to prevent and detect substandard medical products before reaching consumers (FDA, 2017b). The educational tool kit was developed to provide training material to educate its readers on the supply chain by covering ten categories:

- good manufacturing practices
- good distribution practices
- good import/export practices
- clinical/retail pharmacy practices
- product security
- detection technology
- internet sales
- track and trace systems
- surveillance and monitoring
- single points of contact

The full tool kit can be accessed at:
http://www.nifds.go.kr/apec/SupplyChain/APEC_SupplyChainToolkit_170317.pdf.

Conclusion

Pharmaceutical manufacturers execute quality control and other GMP to provide safe high-quality drugs. The FDA is tasked with ensuring manufacturers are performing such procedures. Faced with limited resources, the FDA has developed novel tools to aid supply chain oversight, including a risk-based approach to prioritizing on-site inspections and analytical testing of drugs in FDA laboratories. However, arguably two of the largest recalls in recent years were initiated by Valisure, not the FDA. The success of Valisure has since inspired other quality testing pharmacies such as the UK Central Pharmacy to emerge. Lastly, the FDA provides tools to encourage participation and education of quality manufacturing for both patients and supply chain personnel.

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