# 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 pharmaceutical manufacturing oversight. This paper briefly reviews these tools.

### Methods

Current inspection approaches employed by the FDA are identified by searching the FDA's guidances, 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, use of this SSM allows FDA investigators to focus on critical 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 couple 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.

**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 drug supply.

*Keywords: pharmaceutical manufacturing, FDA, CDER, FDA site selection tool, risk-based modeling, risk reduction, GxP, cGMP, human drug manufacturing, drug surveillance.*

## Introduction

Pharmaceutical products often lack visible signs of adulteration. Detecting adulterated, defective, or contaminated drugs visually is nearly impossible (beyond cosmetic defects like a cracked vial). Instead, specialized destructive analytical techniques such as liquid chromatography and mass spectrometry must be used to identify adulterated products. For this reason, pharmacists can unintentionally dispense adulterated products, and patients are also vulnerable to consuming adulterated drugs unknowingly. 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 (GMP). cGMP is among the cGxPs, or Good "x" Practices family of guidelines, where x is Manufacturing, Laboratory, Research, Engineering, Documentation, or many other words. These guidelines are created collaboratively in pharma by agencies such as the US Food and Drug Administration (FDA) and the Global International Council for Harmonisation 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 reduced or mitigated. However, following cGMP does not provide a guarantee against adulterated or defective drugs.

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 USC ß351," 1998). Despite this, many manufacturers still fail to follow cGMP. Lack of compliance is often unintentional; however, sometimes deliberate fraud occurs (Eban, 2019; Evana et al., 2019; Mu and Carroll, 2016; Okoye and Nwoka, 2019). Regardless of the reasons, manufacturers failing to

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follow cGMP guidelines have occupied FDA inspectors for decades. FDA conducts quality testing of products and performs on-site inspections of drug manufacturing firms. However, with limited resources, the FDA has struggled to keep up with manufacturers.  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, 2020). 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, which 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.  The FDA relied on European Union (EU) regulators under the Mutual Recognition Agreement to conduct 109 drug quality inspections in the EU (FDA, 2020; 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, 2020). On the other hand, more than a 6% increase in on-site inspections in India were reported, as well as a greater than 2% increase in the rest of the world's on-site inspections. Given that the percentage of foreign manufacturers has decreased from 61% to 58% since FY2018 to FY2019, it seems the FDA lacks the necessary resources to frequently inspect domestic and foreign drug manufacturing sites (FDA, 2019a, 2020).

The issue of reduced inspections was briefly alluded to by the FDA in response to the United States Government Accountability Office (GAO) regarding GAO's preliminary findings on the FDA's foreign inspections (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 preliminary analysis that found between the FYs of 2016 and 2018, both foreign and domestic inspections decreased by approximately 10% and 13% respectively. In its 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 an additional 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 redistribute the available workforce effectively. Applying today's technology to computable tasks allows human workers to focus on and more adequately tackle the complex intricacies of the drug supply chain. Proper redistribution of the FDA's workforce could help increase the identification and elimination of potential risks to the drug supply. This paper is a brief review of the FDA's current methods. The section "Risk-Based Site Selection" focuses on the FDA's site selection model 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 the FDA has developed to educate both consumers and supply chain personnel regarding risk in the distribution and purchasing of drugs is discussed.

## Risk-Based Site Selection

One method used by the FDA to safeguard the US drug supply is on-site inspections. These inspections are intended to verify a manufacturing firm is complying 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 are to be inspected at least once every two years. However, fulfilling this requirement has been difficult since the
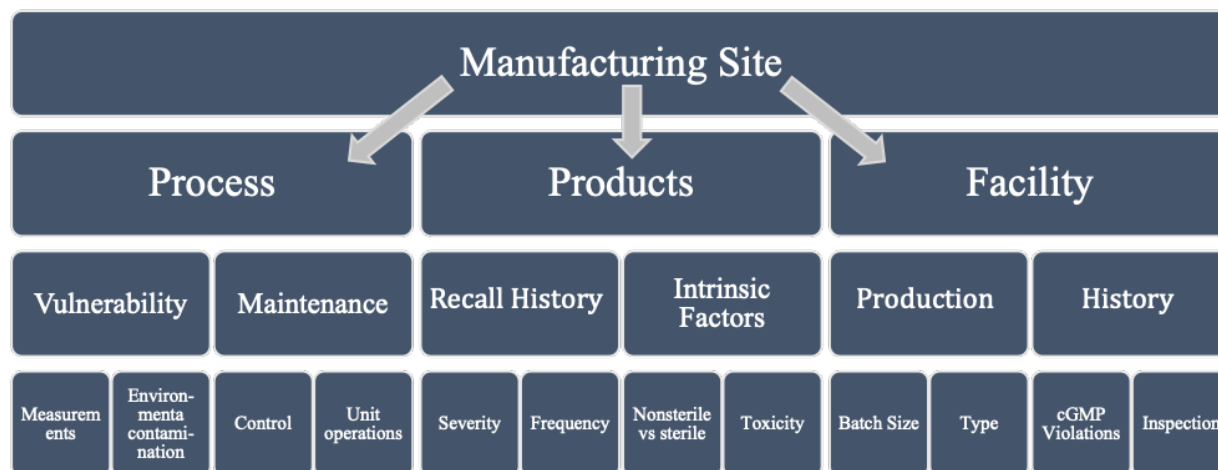


**Figure 1:** Representative conceptual layout of the FDA's risk-based site selection model (SSM). Where the model theoretically inputs a manufacturing site to be analyzed in terms of risk factors. The model divides the site into three general groups: Process, Products and Facility. Further division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

establishment of the FD&C Act in 1998. This may be partially due to the globalization and increased complexities of the drug supply chain that have contributed to the majority of drug manufacturing firms being located outside the United States (Baldwin, 2012; FDA, 2019b, 2017a; Woodcock, 2019). Lacking the necessary resources, the FDA was unable to keep the requirement of the FD&C Act . Failing to conduct biennial inspections of domestic drug firms, the FDA responded with the introduction of a risk-based site selection model in 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, 2004a). 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 site selection model (SSM) ranks manufacturing sites for inspection.

Specifically, 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, 2004b). 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, 2004b). This step was intended to be an initial brainstorming stage. It identified 70 potential risk factors (FDA, 2004b). Next, the potential risk factors were filtered, eliminating duplicates, and difficult to quantify factors. 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 divides the site into three general groups: Process, Products, and Facility. Further division of these general groups then takes place 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. Such risk factors include a facility's production type (e.g., packing facility, API production, labeling facility) and a process' vulnerability to environmental contaminants (e.g., the process uses 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, 2004b). The risk potential for each general group is a combination of the weighted potential risk factors. The estimated combined risk potential for the site is then calculated through a linear combination of these groups (FDA, 2004b). 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 1 and 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 $k$ and by assuming that the assignment of weight factor $w_{i,j}$ corresponds to risk factor $v_{i,j}$, the combined weighted risk factors for group $j$ can be thought to take the form of Equation 1.

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

Where, $\vec{w}_{i,j}$ is the row vector representation for weight factors, $w_{i,j}$ corresponding to risk factors $\vec{v}_{i,j}$. Then $R_j$ represents the mathematical combination of weighted risk factors belonging to group $j$ (e.g., Process, Products, or Facility). It should be noted that the weighted risk factors are

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numerical discrete values and the weight factor assigned to select risk factors are determined by expert opinion, empirical evidence or a mixture of both (FDA, 2004b).

Then the potential risk of site $S_k$ 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 groups 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 is 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 to fail 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-inspection by the FDA over manufacturer B. Hence, the SSM allows FDA investigators to focus their efforts on critical firms.

## Analytical Testing

Pharmaceutical manufacturing has some of the highest quality standards of any industry. However, batch to batch and sometimes item to item variation is an inescapable element of manufacturing. To mitigate these inconsistencies, drug manufacturers are tasked with testing each batch to ensure a quality pharmaceutical product (e.i., a product free from contaminants and reproducibly delivers the therapeutic benefit described on the label (Woodcock, 2004). Despite this requirement, impurities are not always captured before distribution. Such events occur in other types of manufacturing, such as food, where a defective fruit product, for example, may slip into distribution. However, this is typically less of an issue. A defective orange can be inspected at the consumer level for quality. This is not the case for drug products where visual detection of adulterated or contaminated drugs is nearly impossible. Instead, specialized equipment must be used that the everyday patient does not have access to, such as infrared spectrometry. Hence, it is critical the FDA conduct quality testing for patients. In FY2019 FDA, laboratories analyzed 734 drug samples (FDA, 2020a). Included in the drugs tested was Valsartan, a common blood pressure medication. After they received notice that, Valsartan was potentially contaminated with N-nitrosodimethylamine (NDMA), an impurity with potential carcinogenic properties. 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. This prompted a recall of many ARB's in the US, including Valsartan, Losartan, Irbesartan, and Olmesartan. Following this, 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-Citiz en-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, which 61% of received a report of OAI or official action indicated. This suggested 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 active pharmaceutical ingredient 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). 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 this time 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-28 69-0001.

Given that arguably the two largest 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 drug supply chain. Luckily, Valisure has inspired other quality testing pharmacies to emerge such as the University of Kentucky (UK). Here, 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 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

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the FDA may need to investigate (FDA, 2020b). MedWatch accepts reports regarding prescription and over-the-counter medicines, biologics, medical devices, combination products (e.g., nasal spray), cosmetics, and foods. Through 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 reporter's 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 found at https://www.accessdata.fda.gov/scrip ts/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 a supply chain security tool kit for medical products (FDA, 2017a). 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 found at: http://www.nifds.go.kr/apec/SupplyChain/APEC_SupplyChain Toolkit_170317.pdf.

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## Conclusion

 Pharmaceutical manufacturers execute quality control and other good manufacturing practices (GMP) to provide safe drugs. The FDA is tasked with ensuring manufacturers are performing such procedures. Faced with limited resources the FDA has developed novel tools to aid pharmaceutical manufacturing 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 University of Kentucky (UK) to emerge. Lastly, the FDA provides tools to encourage participation and education of quality pharmaceutical manufacturing from customers and supply chain personnel.

## Acknowledgements

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