
quality assurance

COVID-19'S IMPACT ON FDA INSPECTIONS
AND MANUFACTURER RISK

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This article discusses the recent decreases in the FDA's manufacturing inspections due to COVID-19 and explains how USP's programs and resources can help drug-product manufacturers and ingredient suppliers manage potential quality risks in the global supply chain.

C COVID-19 has impacted virtually every industry, and drug manufacturing is no exception. While changes in the demand for certain drug products is reshaping the industry and capturing headlines, another issue permeating the conversation is how the pandemic has disrupted the Food and Drug Administration's (FDA's) inspection process. As of August 11, 2020, the FDA reported more than 18,000 inspections of domestic and foreign pharmaceutical manufacturers in 2019, the last year untouched

by the pandemic, compared to only 4,180 inspections through June 11, 2020 [1]. The decrease in on-site inspections has the potential to increase quality risks to the global supply chain and puts more of the burden on manufacturers and suppliers to ensure the quality of their drug products and ingredients.

Per a July 10, 2020 FDA statement, the agency “determined that for the foreseeable future, prioritized domestic inspections will be pre-announced” [2]. Also, the FDA has been forced to use different tactics for foreign manufacturers to ensure safety and is relying on methods such as denying entry of unsafe products into the US, conducting physical examinations and/or product sampling at US borders, reviewing a firm’s previous compliance history, using information sharing from foreign governments as part of mutual recognition and confidentiality agreements, and requesting records “in advance of or in lieu of” on-site drug inspections [3].

The cost of disruption

The global drug supply chain is complex and has always been vulnerable to disruptions. In fact, the past 200 years have been defined by a series of disruptions to the industry. The 40 years preceding COVID-19 were characterized by growth, distribution, and consolidation—all potential drivers of disruption [4]. Today, more companies manufacture drug products outside the US, and only 28 percent of active pharmaceutical ingredient (API) manufacturing sites are in the US [5]. Many intermediaries play a role in a drug products’ production, distribution, and delivery. In fact, a 2011 survey showed that 79 percent of manufacturers of pharmaceuticals rely on at least one component, manufacturing material, or finished product from a non-US supplier [6].

The COVID-19 pandemic is a disrupter unlike any the global supply chain has seen, and with increased disruption comes increased risk. Manufacturers must streamline and simplify operations more than ever before, which could come at a cost to quality assurance. Additionally, high demand for certain ingredients and products are causing shortages, which, in turn, are leading to surges in production of those ingredients or products [7]. While shortages are worrisome, so are surges—materials coming from new suppliers to combat shortages may lack quality. For the same reason, there is increased risk of adulteration by bad actors motivated by economic gain and not dedicated to quality [8].

Country of origin and supply chain complexities are two major external risk factors for manufacturers working to produce quality drug products and ingredients. Other external risk factors include material value and economic motivation for adulteration, the reputation of manufacturers and distributors, and transportation practices. Internal factors can also increase risk, including source of material, amount and type of processing, lack of compendial standards, complexity of material, and product variability due to season or temperature conditions.

For example, nizatidine capsules were voluntarily recalled in 2020 due to contamination of the API with N-nitrosodimethylamine (NDMA) to prevent any potential adverse events [9]. These risks can also lead to serious consequences. Recently, the excipient, propylene glycol, contained in ColdBest-PC cough syrup, was contaminated with chemical diethylene glycol (DEG)—causing the death of nine children [10]. Manufacturers must mitigate these internal and external risks and prevent them from compromising the quality of their products and impacting people’s lives.

Prioritizing quality

With the industry facing so many concerns, many manufacturers are seeking solutions to ensure that consumers can trust their products. Quality standards serve as a roadmap for helping to ensure quality and prevent fraud.

The *United States Pharmacopeia—National Formulary (USP-NF)* is a comprehensive source for medicine quality standards including more than 5,000 quality standards for chemical and biologic medicines, APIs, and excipients (inactive ingredients) [11]. The standards in *USP-NF* are used to help ensure the quality of medicines and their ingredients and to protect the safety of patients.

In fact, USP is an official quality standard for medicines marketed in the US and is used in over 140 countries worldwide and integrated into the laws of more than 40 countries. *USP-NF* includes three types of quality standards for medicines and dietary supplements: monographs, general chapters, and material reference standards. Material reference standards are used in conjunction with monographs and general chapters to verify that a medicine and its ingredients can pass tests to ensure adherence to quality requirements.

USP is committed during these extraordinary times to supporting manufacturers by providing auditing and testing services to verify ingredient quality through the USP Ingredient Verification Program. USP recognizes that the increased demand for certain ingredients might require manufacturers to source ingredients from new suppliers.

Although pharmaceutical manufacturers must validate test results indicated on suppliers’ certificates of analysis, USP-verified ingredients can offer manufacturers a reliable way to verify the ingredient quality and a means of qualifying new ingredient suppliers. Ingredient manufacturers who participate in the USP Ingredient Verification Program have undergone extensive Good Manufacturing Practice (GMP) facility audits, quality control and manufacturing (QCM) evaluation, and laboratory testing of their ingredients for full compliance to specifications.

The program helps manufacturers ensure that proper quality controls are in place to make the API and excipient quality visible. The program:

- confirms a company’s compliance with applicable GMP requirements;
- verifies conformance to appropriate specifications for identity, strength, purity, and quality;

- confirms that ingredients meet acceptable limits for impurities and contaminants; and
- ensures ingredient consistency from batch to batch.

To further support the public health response to the coronavirus, USP is helping to accelerate the work of scientists and manufacturers developing vaccines and treatments, supporting front-line workers impacted by shortages of critical drugs and personal protection equipment, and helping to build a more resilient global medicines supply chain. For example, a new white paper provides regulators in low- and middle-income countries with recommendations to mitigate the impact of the pandemic, ensure access to quality medicines, support local manufacturers' use of quality standards, and keep patients safe [12].

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For more information about USP's Ingredient Verification Program, contact Danita Broyles (danita.broyles@usp.org).

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