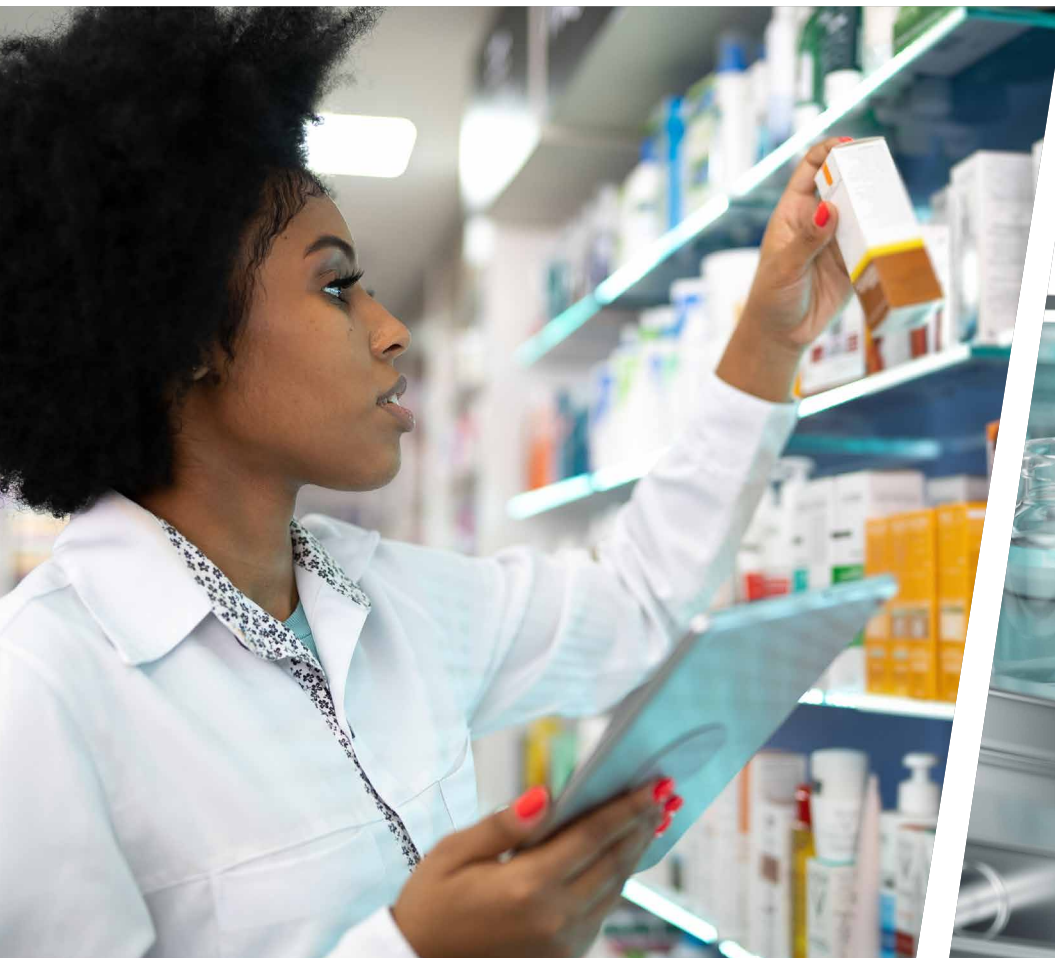


CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL QUALITY

REPORT ON THE STATE OF PHARMACEUTICAL QUALITY: FISCAL YEAR 2021

Assuring quality medicines are available to the
American public



August 2022
www.fda.gov



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Introduction

The Office of Pharmaceutical Quality (OPQ) in the U.S. Food and Drug Administration's (FDA's or the Agency's) Center for Drug Evaluation and Research (CDER) is responsible for ensuring that drugs legally marketed in the U.S. are safe, effective, and meet quality standards. For FY2021¹, the fourth annual Report on the State of Pharmaceutical Quality presents key data used to characterize drug and site quality for consumers and patients in the U.S. This report covers FDA-registered drug manufacturers² and drugs, including biological products, regulated by CDER³ to inform stakeholders about the quality of the U.S. drug supply.

This report presents the findings of recent OPQ research that reveal insights about pharmaceutical manufacturers and their products, adherence to manufacturing compliance standards, and opportunities for improvement. In addition, this report highlights two initiatives that will enable new approaches to inspect, characterize, and advance quality: New Inspection Protocol Project (NIPP) and Quality Management Maturity (QMM). These initiatives are building a framework for a future where inspections and assessments produce data that capture a broader and more profound understanding of site quality. NIPP and QMM will empower FDA to make better, more informed, and timelier decisions while encouraging drug manufacturers to continually improve.

This report also describes aspects of OPQ's quality surveillance during the COVID-19 public health emergency (PHE). The lessons learned during the PHE will impact how OPQ surveils quality long after the PHE has ended. Overall, the data and analyses in this report provide a picture of a high state of pharmaceutical quality for U.S. consumers and patients with the expectation for continuing improvement.

¹ FY2021 was from October 1, 2020 to September 30, 2021.

² A "manufacturer" is anyone engaged in manufacturing, preparing, propagating, compounding, processing, packaging, repackaging, or labeling of a drug.

³ This report covers CDER-regulated products and excludes products regulated by FDA's Center for Biologics Evaluation and Research (CBER), e.g., blood, vaccines, tissues, and certain other biological products.

Manufacturing Site Demographics

The FY2021 CDER Site Catalog (current as of November 2021)⁴ has 4,451 drug manufacturing sites⁵ ([Table 1](#)), which is a 3% increase over FY2018. During FY2020 and FY2021, most of this increase was due to newly registered sites that manufacture non-alcohol-based hand sanitizers (e.g., benzalkonium chloride) or hand sanitizer in dosage forms other than topical solutions (e.g., wipes, aerosols). Of the total drug manufacturing sites in FY2021, 39% are in the “No Application” sector, which indicates that all products manufactured at the site are marketed without an approved FDA application. This sector includes over-the-counter (OTC) monograph products, marketed unapproved prescription drug products⁶, and homeopathic products. The remaining 61% of sites manufacture at least one application product, including one or more of:

- Biological products licensed under Biologics License Applications (BLA)⁷
- Innovator products approved under New Drug Applications (NDA)
- Generic products approved under Abbreviated New Drug Applications (ANDA)

The top five countries based on the number of sites in the inventory (U.S., India, China, Germany, and Canada) all had net increases, based on new registrations and removals⁸, in the number of manufacturing sites over the past three years. Understanding the locations of drug manufacturing sites and their trends helps FDA better plan for future surveillance and outreach.

⁴ The CDER Site Catalog is the curated inventory of registered manufacturing sites, vetted by FDA as legally manufacturing human drugs for the U.S. market. Hence, not all human drug sites that register qualify as “manufacturers” for the CDER Site Catalog.

⁵ Although they meet the definition of “manufacturer,” this count and the analyses presented in this report exclude medical gas manufacturers (based on existing CDER Site Catalog policy), newly-registered sites (those registered after the FDA published hand sanitizer guidance on March 20, 2020) that exclusively manufacture alcohol-based hand sanitizers (due to the many sites that registered to meet COVID-19 PHE needs and whose registrations were expected to be temporary), and pharmaceutical outsourcing sites (under the Federal Food, Drug, and Cosmetic Act section 503B).

⁶ [Unapproved Drugs](#)

⁷ [Explanation of which therapeutic biological products are regulated by CDER](#), for the original transfer and [for those deemed to be BLA products](#).

⁸ FDA removes sites from the CDER Site Catalog if they are not currently engaged in the manufacture of human drugs for the U.S. market and therefore are not subject to routine CGMP inspection. This commonly occurs when sites deregister or are no longer active in an approved application.

Table 1. Inventory shift over FY2018-FY2021 for Countries with Greater than 50 Sites

Country	Sites in FY2021 Catalog	3-Year Change for Sites in the Catalog					
		Sites Maintained	Sites Removed	Sites Added	% Decrease	% Increase	% Net Change
U.S.	1,910	1,657	159	253	-8%	13%	5%
India	531	492	19	39	-4%	7%	4%
China	383	328	47	55	-12%	14%	2%
Germany	179	164	7	15	-4%	8%	4%
Canada	149	138	9	11	-6%	7%	1%
Italy	142	137	11	5	-8%	4%	-4%
France	136	127	4	9	-3%	7%	4%
Japan	130	123	8	7	-6%	5%	-1%
UK	106	99	11	7	-10%	7%	-4%
Spain	83	75	6	8	-7%	10%	2%
South Korea	79	64	22	15	-28%	19%	-9%
Switzerland	75	68	5	7	-7%	9%	3%
Ireland	58	54	1	4	-2%	7%	5%
Mexico	57	51	5	6	-9%	11%	2%
All Others	433	383	44	50	-10%	12%	1%
Total	4,451	3,960	358	491	-8%	11%	3%

Quality Surveillance with Foreign Regulatory Authority Inspection Reports and Record Requests

While COVID-related travel restrictions continued to limit FDA's ability to inspect sites in FY2021, alternative tools were used to provide quality surveillance. These tools enabled FDA to assess sites that would otherwise have been out of reach. In particular, the Mutual Recognition Agreement (MRA)⁹ program enabled FDA to receive and rely on inspection reports from MRA partner agencies. This includes inspections conducted both within and outside their countries. During FY2021, using inspection reports from MRA partners, FDA reviewed and classified 139 site inspections in 18 MRA partner countries and six other countries. FDA also used

⁹ [Mutual Recognition Agreement \(MRA\)](#)

its authority under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) to request records and other information in lieu of or in advance of inspections to assess compliance with Current Good Manufacturing Practice (CGMP) requirements for sites that FDA would otherwise have been unable to assess. During FY2021, FDA conducted 288 surveillance systems-based assessments, using information from 704(a)(4) requests, that resulted in 21 Import Alerts (see also [Import Alerts and Recalls](#) section).

Drug Product Demographics

The CDER Product Catalog includes all registered products, which consist of application products (NDAs, ANDAs, and BLAs) and non-application products (including OTC monograph, marketed unapproved prescription drugs, and homeopathic products). For FY2021, the Product Catalog contains 12,428 ANDAs, 3,537 NDAs and 315 BLAs. Each of these applications may include multiple products of different strength, concentration, or sizes. The Product Catalog contains more than 140,000 non-application products with a unique National Drug Code (NDC), including 75,300 OTC and 15,640 homeopathic products. Manufacturers of all drug products are required to maintain product quality throughout each product's life cycle.

Essential Medicines

In October 2020, in response to Executive Order 13944¹⁰, FDA published a List of Essential Medicines, Medical Countermeasures, and Critical Inputs (described herein as EM)¹¹. In order to protect the American public against outbreaks of emerging infectious diseases, such as COVID-19, as well as chemical, biological, radiological, and nuclear threats, this executive order seeks to ensure sufficient, reliable, and long-term domestic production of these products and minimize potential shortages. The published EM list contains 227 drug and biological product essential medicines and countermeasures, including analgesics, antivirals, anticoagulants, antihypertensives, and antimicrobials. The CDER Site Catalog includes approximately 1,100 sites that manufacture at least one product on the EM list. An analysis of

¹⁰ [Executive Order 13944 List of Essential Medicines, Medical Countermeasures, and Critical Inputs](#)

¹¹ [Drug and Biologic Essential Medicines, Medical Countermeasures, and Critical Inputs for the List Described in Section 3\(c\) of the Executive Order 13944](#)

Site Inspection Score (SIS)

- Range: 0-10
- Used as a proxy for compliance with CGMP regulation¹²
- Higher scores indicate better CGMP compliance
- Based on classifications of FDA drug quality inspections over the prior ten years¹³

active pharmaceutical ingredient (API) and finished dosage form (FDF) sites found that the median Site Inspection Score (SIS) for EM manufacturers (7.45) is significantly higher ($p < 0.0001$) than for non-EM manufacturers (7.00). This observation indicates that sites manufacturing EM products have a higher level of adherence to manufacturing compliance standards than sites that do not manufacture EM products.

[Figure 1](#) shows the regional distribution of sites that manufacture API and FDF¹⁴ for all products and for EM products. There are 1,686 sites that manufacture API and 354 of these sites manufacture API for EM products. Currently, 23% of API manufacturing sites are located in the U.S.; for EM this drops to 19%. The 27-member EU and the UK¹⁵ have more API manufacturing sites than any other region and India has the most for any single country. 48% of FDF manufacturing sites for all products are in the U.S. while 44% of the EM FDF sites are in the U.S.; a further 20% are in India. These data illustrate that only a minority of drug manufacturing sites are domestic. Overall, API and FDF manufacturing are heavily dependent on foreign manufacturing sites. In recognition of this, the 100-Day Review under Executive Order 14017 (“America’s Supply Chains”)¹⁶ directed the U.S. Department of Health and Human Services to identify products for which onshoring may be advisable. Site analysis is based on FDA’s information about the location of manufacturing sites but does not address the amount of product produced at sites. Section 510(j)(3) of the FD&C Act, which was added by the recent CARES Act¹⁷ requires registered sites to report annually the amounts of drugs manufactured for U.S. commercial distribution. These data will enable FDA to make better informed manufacturing site surveillance decisions by understanding manufacturing amounts from each site.

¹² Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers adequately control manufacturing operations (see 21 CFR 210.1).

¹³ This includes inspections classified under the MRA program, which enables FDA to rely on inspection reports from foreign regulatory authorities that FDA has determined are capable of conducting inspections that meet U.S. requirements.

¹⁴ For Figure 1, sites that produce both API and FDF are included as both API sites and FDF sites.

¹⁵ The United Kingdom (UK) was a European Union (EU) member until January 2020. This report’s regional assessments group the EU and the UK together. The U.S. FDA has established Mutual Recognition Agreements with both the EU and the UK.

¹⁶ [Building Resilient Supply Chains, Revitalizing American Manufacturing, and Fostering Broad-Based Growth, June 2021](#)

¹⁷ [Coronavirus Aid, Relief, and Economic Security Act \(CARES Act\) Drug Shortage Mitigation Efforts](#)

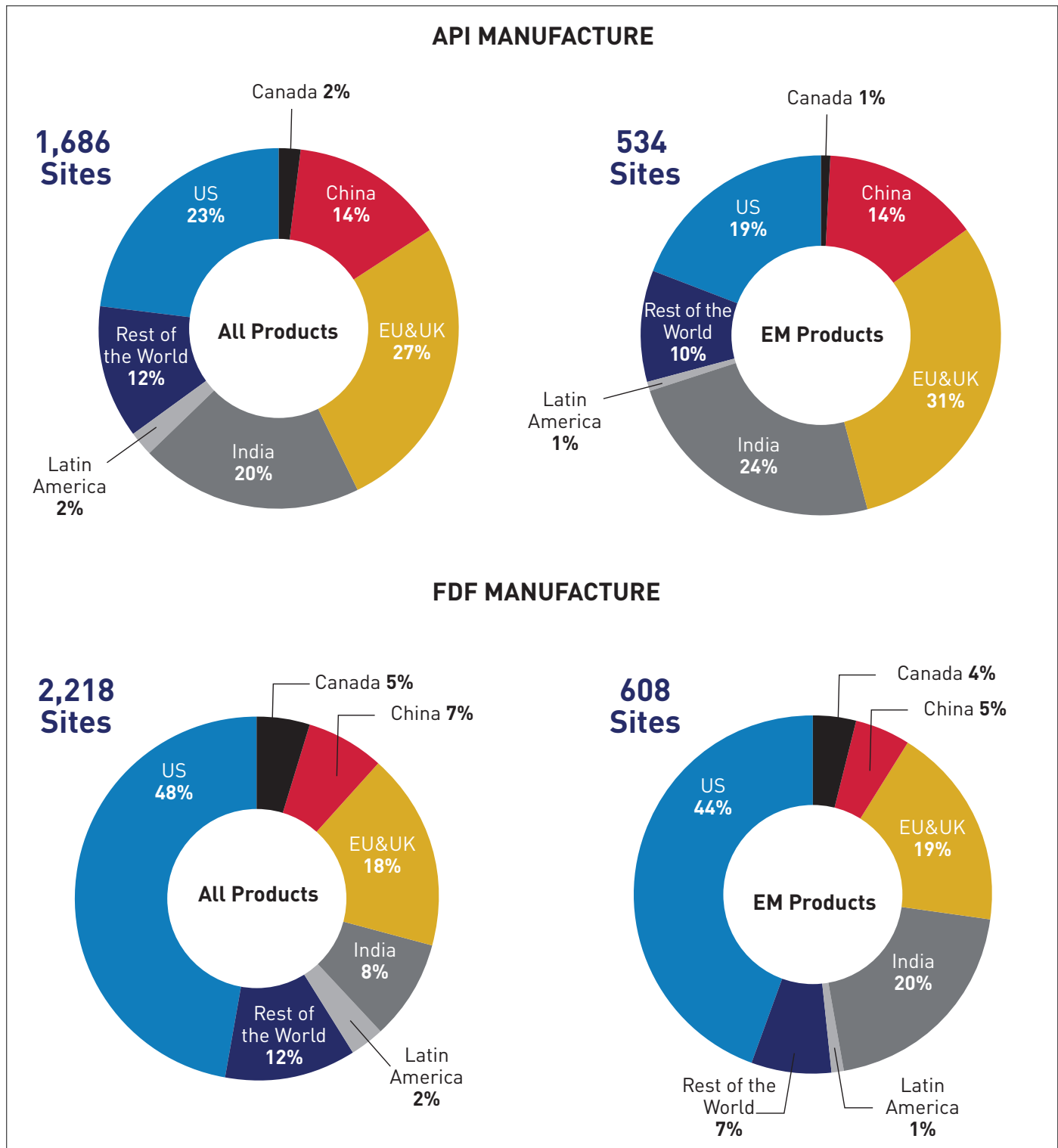


Figure 1. API and FDF Manufacturers by Region for All Products and for EM Products

Product Quality Defects (PQDs)

The Agency receives and evaluates mandatory, as well as voluntary, post-market quality reports. FDA's post-market regulations¹⁸ require that application owners notify FDA about significant product quality defects¹⁹ in marketed products within three working days for Field Alert Reports (FARs) and 45 days for Biological Product Deviation Reports (BPDRs). Voluntary reports include MedWatch (MW) and consumer complaints (CC) that can be submitted by consumers, patients, and healthcare professionals when product quality fails to meet expectations. During FY2021, CDER received 11,512 quality-related MW, 4,115 FARs, 273 CC, and 205 BPDRs, which are similar quantities to FY2020. These reports provide FDA a rich source of post-market information to prioritize surveillance actions, including identifying products for laboratory testing. In the future, amount reporting as required by CARES Act will enable FDA to normalize PQDs by the amount of each product manufactured for commercial distribution, allowing for better evaluation of the impact and magnitude of PQDs.

Import Alerts and Recalls

During FY2021, FDA placed import alerts²⁰ on 49 sites²¹ for refusing inspections, refusing 704(a)(4) records requests²², non-compliant laboratory testing, and non-compliant findings from inspections and record requests ([Figure 2](#)). The location and type of import alerts show where FDA identified risks and acted to protect the public. The largest number of import alerts were for sites in China and Latin America. Manufacturers of hand sanitizer products accounted for all import alerts issued for non-compliant laboratory testing. FDA's efforts to assure access to safe and quality hand sanitizer products are discussed more below (see The Quality of Hand Sanitizer Products section).

Recalls are an important public health action that remove violative, defective, or potentially harmful products from the market.

¹⁸ The FAR and BPDR regulations are found in 21 CFR 314.81(b)(1) and 21 CFR 600.14, respectively.

¹⁹ [Additional information and examples of "significant chemical, physical, or other change or deterioration in the distributed drug product" are provided in the guidance Field Alert Report Submission: Questions and Answers \(July 2021\)](#)

²⁰ Import alerts empower FDA to detain imports without physical examination and place the burden on importers to provide evidence that overcomes the appearance of violation. Otherwise, these products are subject to refusal into the U.S.

²¹ [Import alerts include 66-40 \(CGMP-based\), 66-78 \(testing-based\), and 99-32 \(for refusals\). As of January 2022, refusals by drug sites to permit entry or inspection receive the new Import Alert 66-79, reserving Import Alert 99-32 for food sites.](#)

²² [Policy and Procedures for Requesting Records in Advance or In Lieu of a Drug Inspection](#)

Although most recalls are voluntary, they may be driven by a company's own initiative or by an FDA recommendation.²³

For the second year, the number of total recalls and Class I recalls increased ([Figure 3](#)). The increase in Class I recalls was largely due to market removals for hand sanitizer products that contained methanol and for consumer products, including sunscreen, with benzene contamination. In recent years, Class II recalls²⁴ have not shown any trends. Instead, they tend to be event-driven and reflect emerging knowledge of product defects. Class III recalls, those with the least public health impact, have been steady.

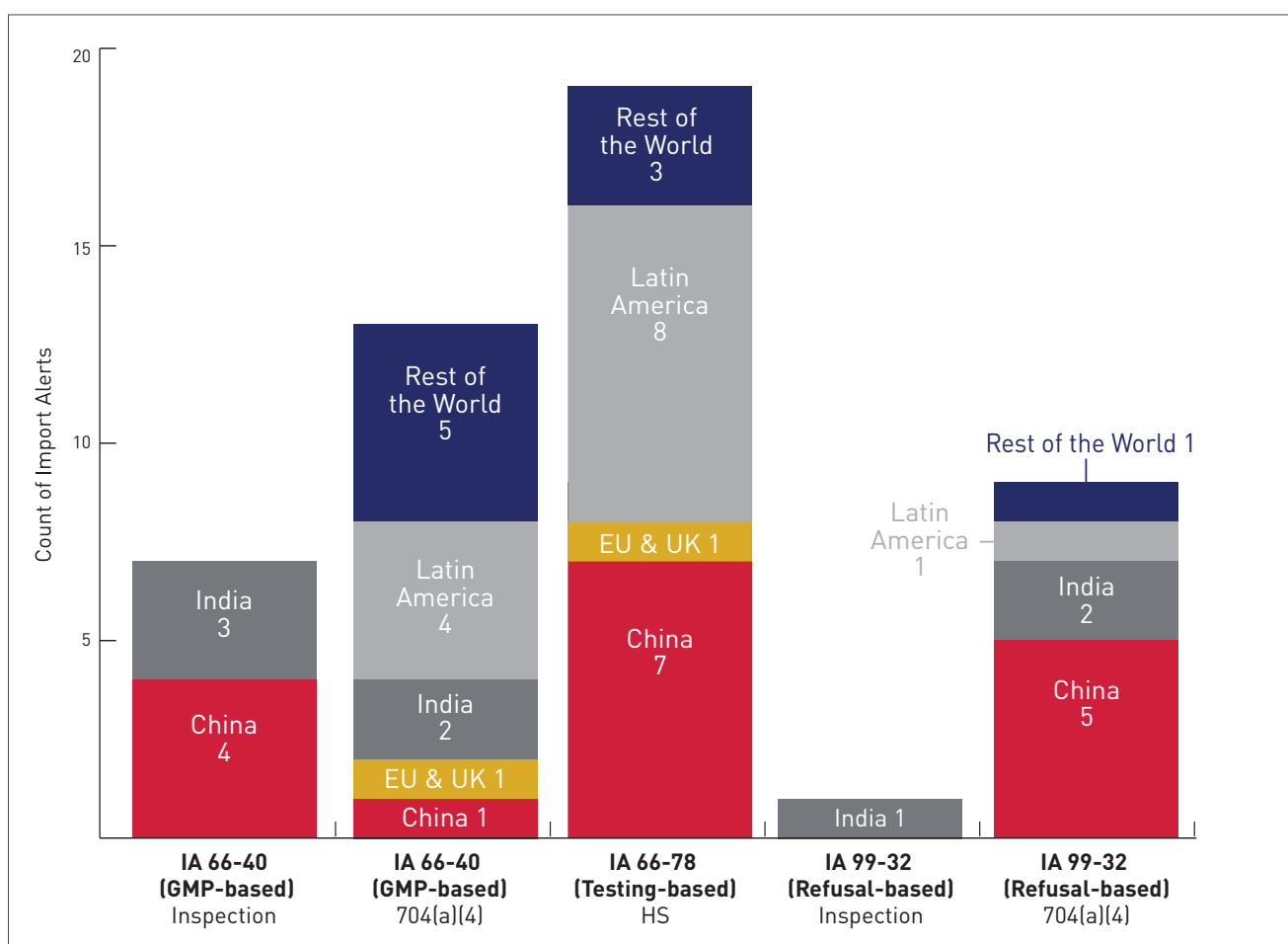


Figure 2. FY2021 Import Alerts (IA) by Type and Region

²³ When FDA determines that a distributed drug product violates the law, it may recommend that the firm cease distribution and recall the product. Guidance for industry is provided in Initiation of Voluntary Recalls Under [21 CFR Part 7, Subpart C](#).

²⁴ A Class I recall is a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. See 21 CFF 7.3. For [additional information follow link](#)

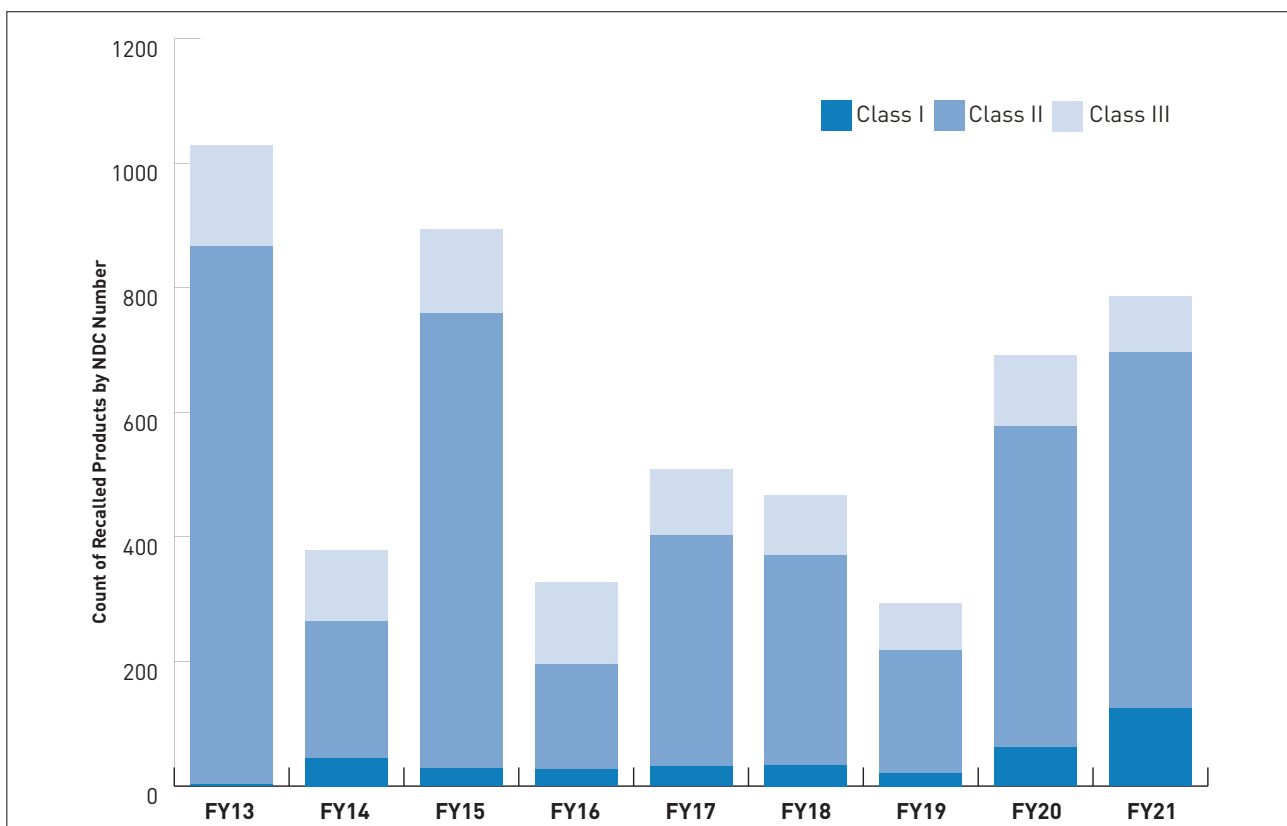


Figure 3. Recalls by Classification for FY2013-FY2021

Research on the State of Quality

FDA conducts research to understand where pharmaceutical manufacturing is adhering to compliance standards and where opportunities exist for improvement. This report presents research on the state of quality as it relates to recalls, complex products, FAR submissions, hand sanitizer products, organic impurities in OTC monograph products, as well as findings from CDER's ongoing sampling and testing program.

The Relationship Between Inspections and Recalls

To better understand recalls, OPQ analyzed the temporal relationship between FDA site inspections and subsequent recalls. Using FY2017–FY2021 data for 1,220 recall events (113 Class I, 761 Class II, and 346 Class III)²⁵ and 5,609 inspections (89% surveillance, 11% for-cause), several statistically significant associations were found:

²⁵ [FDA's Role in Drug Recalls](#)

- Regardless of the inspection outcome, there were more Class II recalls in the 12 months following surveillance inspections than occurred outside of that 12-month window ($p=0.0095$).
- For Voluntary Action Indicated (VAI)²⁶ outcomes, there were more Class III recalls in the six months following surveillance inspections than occurred outside of that 6-month window ($p=0.0094$).
- Class I recalls are more likely to be associated with two inspection outcomes: final Official Action Indicated (OAI) classification and an initial OAI classification that was reclassified to VAI after resolution of violations.

These associations between inspections and recalls attest to the benefits of inspections. They can reveal that potentially defective products were marketed and can prompt firms to identify potentially defective products. Recalls provide removal and potential correction for these defective products. In the absence of inspections, many of these situations, and possible public harm, could have gone undetected. Nevertheless, drug manufacturers are required to ensure the safety and quality of their drugs. FDA reminds manufacturers of drugs marketed under approved applications and manufacturers of other drugs, including over-the-counter monograph drug products, of their obligation to ensure that their products conform to the appropriate quality specifications.

Complex Products and Quality

Using the FY2021 CDER Product Catalog and CDER Site Catalog²⁷, all sites were classified as “Complex” or “Non-Complex” to indicate whether they produce at least one complex product²⁸. Only 3% of sites produce complex products exclusively but 32% of sites produce at least one complex product (Table 2). The median SIS of sites that produce at least one complex product is significantly higher ($p < 0.0001$) than sites making only non-complex products (Table 2). This indicates that manufacturers of complex products have a better inspection history than sites that do not produce complex products. Overall, manufactur-

Complex Products

Include products with complex:

- Active pharmaceutical ingredients
- Formulations
- Dosage forms
- Routes of administration
- Drug-device combinations

Examples of complex generic products:

- Inhalers
- Topical products
- Extended release injectables

²⁶ Inspection outcomes are described in: [Inspection Classification Outcomes](#) and [Investigations Operations Manual](#)

²⁷ This analysis considered only currently approved applications and excluded medical gas sites and those identified as hand sanitizer manufacturers.

²⁸ Complex products are defined as described in the [GDUFA II Commitment Letter](#).

ers of complex products have a higher level of adherence to manufacturing compliance standards than sites that do not manufacture complex products. The global distribution of sites that manufacture complex products differs from sites that do not manufacture complex products ([Figure 4](#)). While the U.S. has the largest number of sites that manufacture complex products, sites that manufacture any complex products are more concentrated in the EU and UK than sites that manufacture only non-complex products.

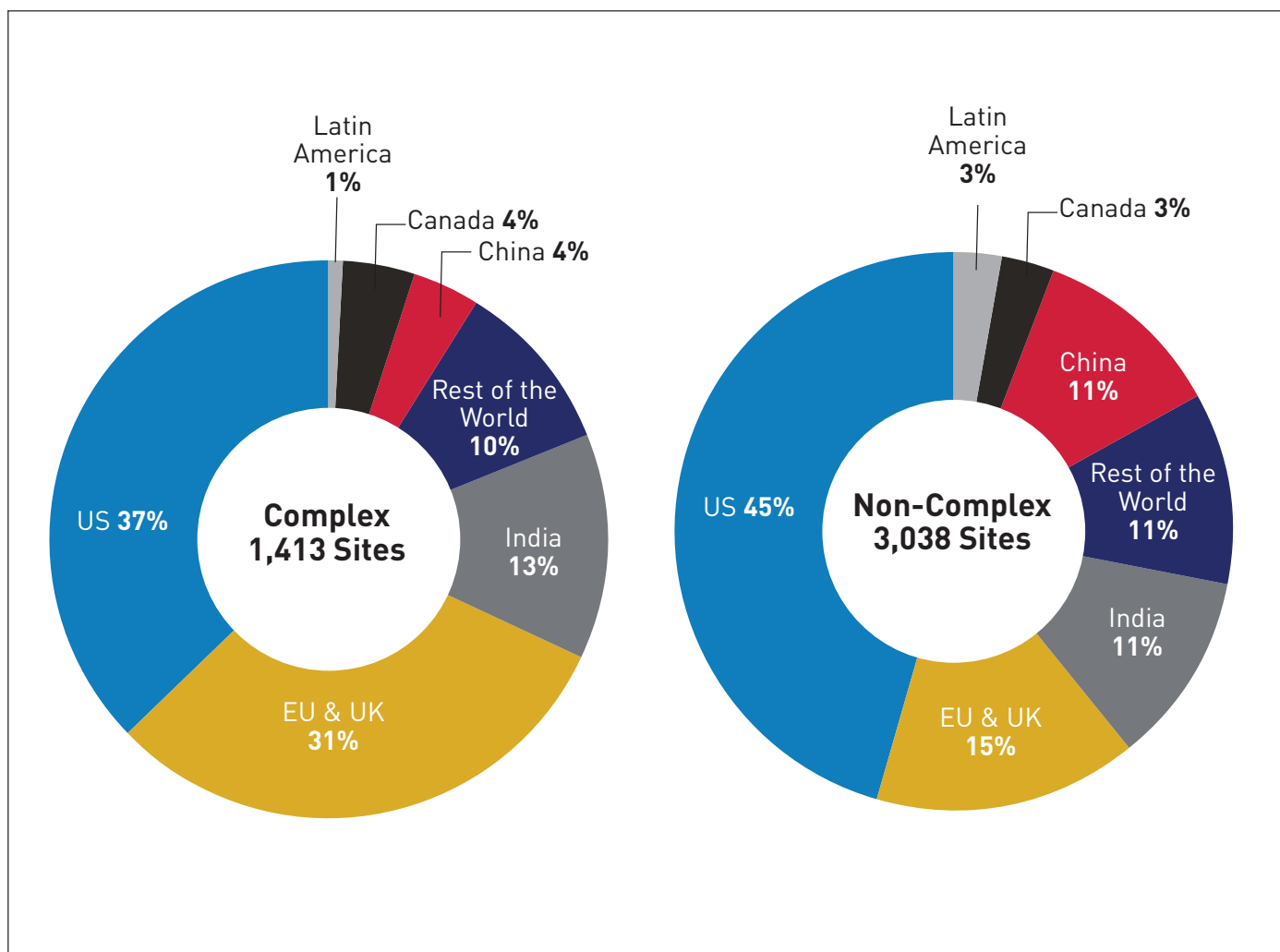


Figure 4. Sites by Region for Complex Products

Table 2. Sites by Product Type with Median SIS (all business operations)

	Site Count	Percent of Total	Median Score
Complex	1,413	32 %	7.65
Non-Complex	3,038	68 %	7.00

FAR Submissions and Site Quality

FDA explored data about FAR submission rates to better understand the factors that correlate with FAR submissions and how those factors reflect site quality. This study included all 1,143 sites that were eligible to submit a FAR during FY2018–FY2021, i.e., sites with at least one FDE, NDA, or ANDA with postmarket reporting requirements under 21 CFR 314.81(b)(1)). [Table 3](#) summarizes key characteristics of sites that did and did not submit at least one FAR during those four years. Sites that did not submit FARs tend to be foreign, producing non-sterile products, and have fewer approved applications.

Table 3. Characteristics of FARs Reporting and Non-Reporting Sites

	Sites that Did Not Submit FARs (49.1%)	Sites that Submitted FARs (50.9%)
Site Location (%)		
Domestic	38.9	43.6
Foreign	61.1	56.4
Manufacturing Sector (%)		
Non-Sterile	64.9	52.2
Sterile	35.1	47.8
Application Count (sum of NDAs and ANDAs)		
Median	3	21
Mean (Standard Deviation)	8.12 (17.4)	46.23 (78.1)
Min, Max	0, 233	0, 1092
Interquartile Range	1 to 7	7 to 56

While sites are required to submit an initial FAR after receiving information concerning significant quality problems with distributed drug products, there is no similar requirement to submit a follow-up or final FAR. Nevertheless, doing so is recommended because it indicates that the firm completed

an investigation into the quality problem and implemented corrective actions and preventative actions (CAPA) where appropriate. Hence, it is a positive sign about industry quality management practices that 97% of sites that submitted an initial FAR submitted at least one follow-up or a final FAR.

In general, OPQ recognizes FAR submissions as an attribute of a healthy pharmaceutical quality system. OPQ has found that the probability for a site to submit a FAR is influenced by multiple factors. The most significant factors that led to higher FAR submissions are:

- the total number of application products associated with a site;
- the number of profile class codes²⁹ at a site; and
- how many times a site was inspected within the past ten years.

A better understanding of the characteristics of sites that submitted FARs can be used to identify outreach opportunities and assure that manufacturers understand their postmarket reporting requirements.

MW reports are submitted by healthcare professionals, patients, and consumers, giving everyone the opportunity to help identify quality problems. For sites that submitted a FAR, FDA received an average of 6.4 MW reports per year. In contrast, for sites that did not submit a FAR, FDA received an average of 0.62 MW reports per year. Sites that were identified with MW reports were 5.0 times more likely ($p < 0.001$) to submit at least one FAR. The strong positive association between FAR submissions and MW reports confirms that these programs complement each other as part of FDA postmarket quality surveillance.

The Quality of Hand Sanitizer Products

FDA's continued close monitoring of hand sanitizers in FY2021 identified products containing methanol and other toxic substances. These products were identified in FDA's list of hand sanitizers consumers should not use.³⁰ FDA's hand sanitizer web pages have received more than 20 million page views and been among FDA's most visited web pages.

²⁹ FDA uses profile class codes to classify manufacturing site operations based on FDA-defined product classes as explained in the [FDA Investigations Operations Manual](#)

³⁰ [FDA updates on hand sanitizers consumers should not use](#)

As in FY2020, the inventory of sites manufacturing hand sanitizers fluctuated significantly due to the ongoing response to market demand during the COVID-19 PHE. In FY2021, around 2,300 sites registered as hand sanitizer manufacturers, with nearly 1,500 of them being new sites. Most hand sanitizer manufacturers are located in the U.S. and China (Figure 5). CDER expects the hand sanitizer inventory to stabilize over the coming year following FDA's withdrawal of the temporary policies for alcohol-based hand sanitizers in 2021.³¹

In FY2021, CDER issued almost 400 requests under section 704(a)(4) of the FD&C Act to obtain critical quality information from hand sanitizer manufacturing sites and reviewed over 600 product quality defect reports. The most common issues in product quality reports (non-death and hospitalization) were reaction, illness, or adverse event (e.g., dizziness, headache, burning, nausea) and contamination concerns. In January 2021, FDA issued the first warning letter based solely on information received and reviewed in response to a section 704(a)(4) records request to a manufacturer of hand sanitizer products. Over the course of FY2021, FDA issued around ten more such warning letters for hand sanitizer products.

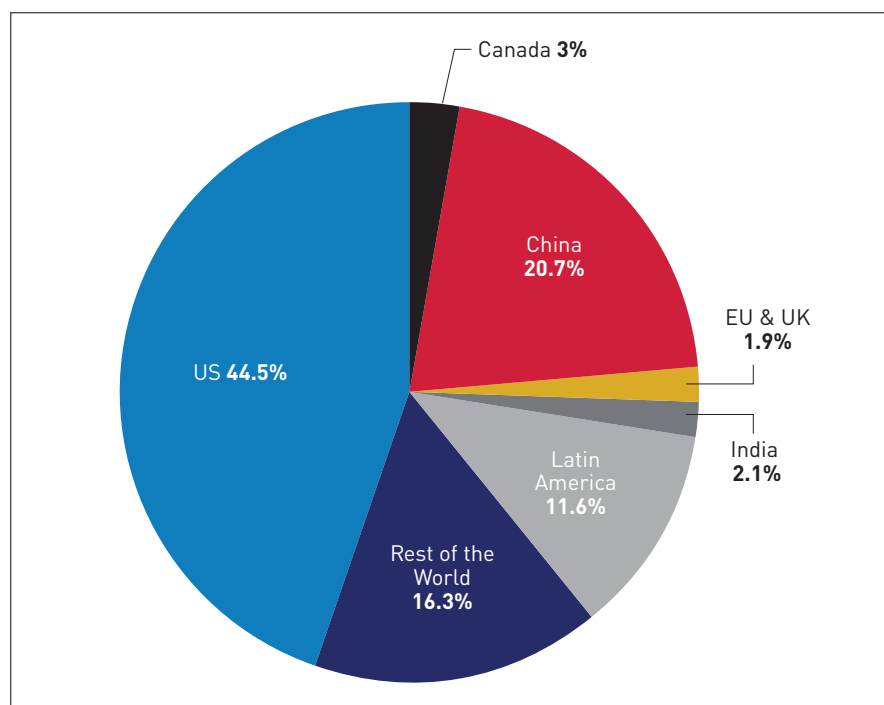


Figure 5. Regional Distribution of Hand Sanitizer Manufacturers for FY2021

³¹ [FDA In Brief: FDA Withdrawing Temporary Guidances for Alcohol-Based Hand Sanitizers](#)

FDA's response to hand sanitizer safety concerns also included surveillance sampling and testing of domestic hand sanitizer products, increased import screening and testing, and focused sampling and testing in response to adverse events and reported product quality defects. OPQ researchers developed innovative approaches for rapid screening³² and a method for determining the quality of hand sanitizers.³³ Using this and other methods, FDA tested more than 350 hand sanitizer samples, finding over 38% to be non-compliant for issues such as impurities (e.g., methanol) and sub-potency. Many of these product test results provided the basis for the warning letters. In response to the methanol risk, in January 2021, FDA issued a guidance³⁴ outlining the Agency's policy for drug manufacturers and compounders to test alcohol or isopropyl alcohol for contamination prior to using the alcohol to produce drugs, including hand sanitizer products. Hand sanitizer quality issues resulted in several FY2021 actions to protect U.S. consumers from unsafe products. As discussed previously, manufacturers recalled hand sanitizer products that could pose a danger to consumers, with most of these recalls resulting from product contamination. In addition, hand sanitizer actions represented over half of all import alerts and almost half of all warning letters issued for drug products in FY2021. Although most hand sanitizer manufacturers are located in the U.S. and China, Latin America accounted for the largest number of hand-sanitizer-related import alerts (44%) and warning letters (89%), with Mexico alone accounting for 36% of the import alerts and 69% of the warning letters. Due to ongoing concerns on the quality of hand sanitizer from Mexico, FDA imposed a countrywide import alert in January 2021³⁵—the first time the FDA has issued a countrywide import alert for any category of drug product. China accounted for an additional 32% of hand-sanitizer related import alerts and 6% of the warning letters.

Control of Organic Impurities in OTC Monograph Products

OTC products play a vital role in America's health care system because they are considered safe and effective for public use without the direction and supervision of trained healthcare

³² [Through-Container Quantitative Screening of Hand Sanitizers](#)

³³ [Development and validation of a headspace GC-MS method to evaluate the interconversion of impurities and the product quality of liquid hand sanitizers](#)

³⁴ [Policy for Testing of Alcohol \(Ethanol\) and Isopropyl Alcohol for Methanol, Including During the Public Health Emergency \(COVID-19\) Guidance for Industry](#)

³⁵ [Coronavirus \(COVID-19\) Update: FDA Takes Action to Place All Alcohol-Based Hand Sanitizers from Mexico on Import Alert to Help Prevent Entry of Violative and Potentially Dangerous Products into U.S., Protect U.S. Consumers](#)

professionals. Manufacturers of OTC products must comply with CGMP requirements as provided in 21 CFR 210 and 211 and the product must be manufactured under an OTC monograph or approved under an application. As such, all drug manufacturers have a satisfactory understanding and control of impurities, including organic impurities.^{36,37} Inadequate control of organic impurities in OTC drug products may pose a risk of toxicity to patients and customers.

OPQ recently used the FD&C Act 704(a)(4) authority to obtain data on the state of organic impurity control for non-application OTC products.³⁸ Requests were sent to 13 manufacturers of 15 commonly used nonprescription oral drug products. The results, summarized in [Figure 6](#), found a wide range of organic impurity control, ranging from adequate (i.e., impurities have been specified for finished product release and on stability) to inadequate or no organic impurity criteria.

Although possible deficiencies in organic impurity control can also be addressed during inspections, the Agency expects non-application OTC drug product manufacturers to comply with CGMP requirements. Compliance with CGMP requires that firms establish scientifically sound specifications and test methods, that may include control and testing for impurities at product release and through their labeled shelf life.

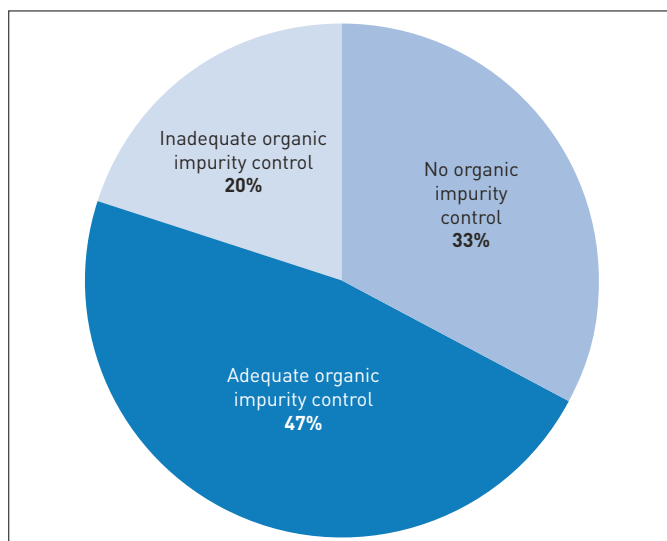


Figure 6. Organic Impurity Control for OTC Drug Products in FDA Study

³⁶ Organic impurities can arise during the synthesis, purification, and storage of a new drug substance. An impurity is any component of the new drug substance that is not the chemical entity defined as the new drug substance.

³⁷ See, for example, 21 CFR 211.160(b) and 211.165(a).

³⁸ These products include both monograph and application-to-OTC products.

Sampling and Testing

To help assure the high quality of drugs available in the U.S., CDER samples and tests drug products each year as part of surveillance and focused sampling assignments (e.g., hand sanitizer, nitrosamines, opioids, and heparin). Sampling and testing gained additional importance during the COVID-19 PHE. With many inspections postponed, FDA sampled and tested products to surveil industry and aid in identifying non-compliant products.

When non-compliant products are discovered, FDA works to protect the public from potential harm by sharing information, recommending that manufacturers initiate recalls, preventing U.S. distribution with import alerts, and monitoring the site until compliance is achieved.

For FY2017–FY2021 a total of 3,861 unique samples were collected, tested, and classified ([Figure 7](#)). In FY2021 the percent of non-compliant samples was 35%, an increase from 16% in FY2020. [Figure 8](#) shows the distribution of the FY2021 non-compliant samples. The increased rate of non-compliance is driven by focused sampling assignments with high non-compliant rates for products with nitrosamine contamination, hand sanitizers, and sampling related to COVID-19 mission critical sampling and testing, which became more

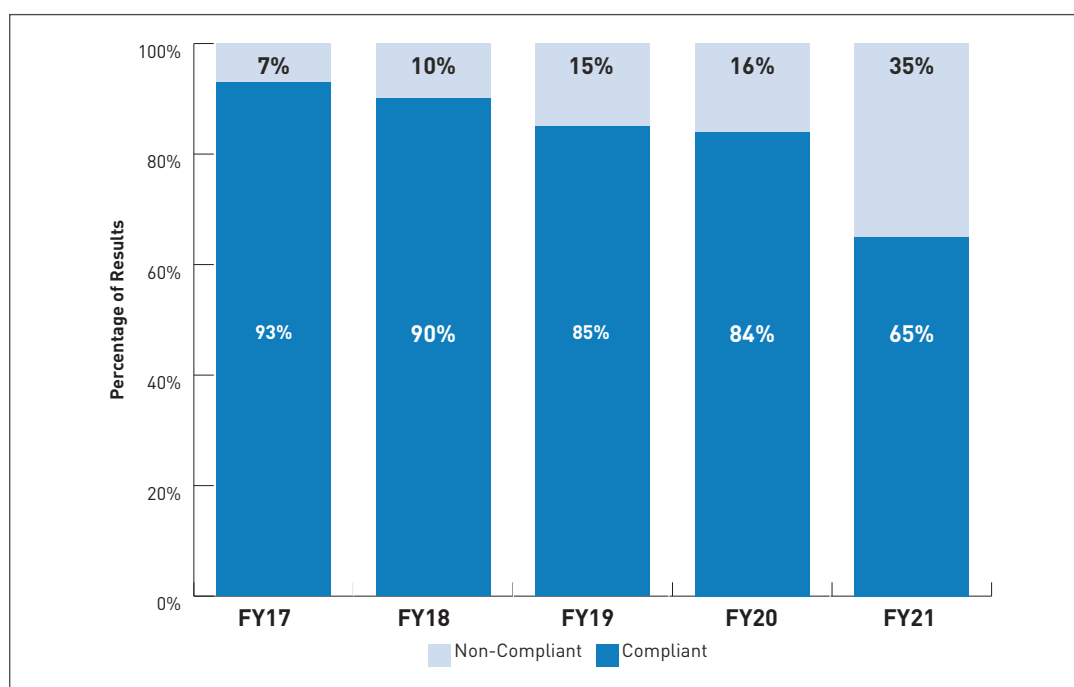


Figure 7. Sample Compliance Rates by Fiscal Year

prominent in FY2021. The top two U.S. Pharmacopeia Therapeutic Categories for non-compliant samples in FY2021 were antibacterials (hand sanitizers and COVID 19 programs) and blood products/modifiers/volume expanders (imported products with undeclared erectile dysfunction drug ingredients).

In FY2021, for the fourth consecutive year, FDA tested products for the presence of nitrosamines. This assignment began in FY2018 when it was discovered that nitrosamine impurities impacted many angiotensin receptor blockers, a class of cardiovascular drugs including valsartan and losartan. Since then, FDA has been testing products identified at risk for nitrosamine contamination. In FY2021, there was a new voluntary recall due to a nitrosamine identified in Varenicline³⁹, a smoking cessation drug. The Agency continues to monitor the presence of nitrosamines across a variety of products and is working with companies to assist them in complying with the recommendations in FDA's guidance *Control of Nitrosamine Impurities in Human Drugs*⁴⁰. This guidance requests that industry perform nitrosamine risk assessments for drugs on the U.S. market, conduct confirmatory testing for their products identified as at risk, and control the impurity to acceptable levels.

Commitment to Quality

FDA has made programmatic advances for two initiatives, NIPP and QMM, that are building better tools for characterizing the quality of drug manufacturing sites.

NIPP is modernizing FDA's inspections program by improving how data from surveillance and pre-approval inspections are recorded, assessed, and reported. Since November 2018, FDA has been using these inspection protocols for certain sterile surveillance and pre-approval inspections. Concurrently, FDA has been developing and deploying protocols for non-sterile inspections while initiating continual improvement efforts for the IT systems that support the protocols. These protocols were designed to collect structured data for each system (surveillance inspection) or for each objective (pre-approval inspection). The questions can be scored on an ordinal scale using three levels: written observation on Form FDA 483, verbal discussion item, and covered but no objectionable

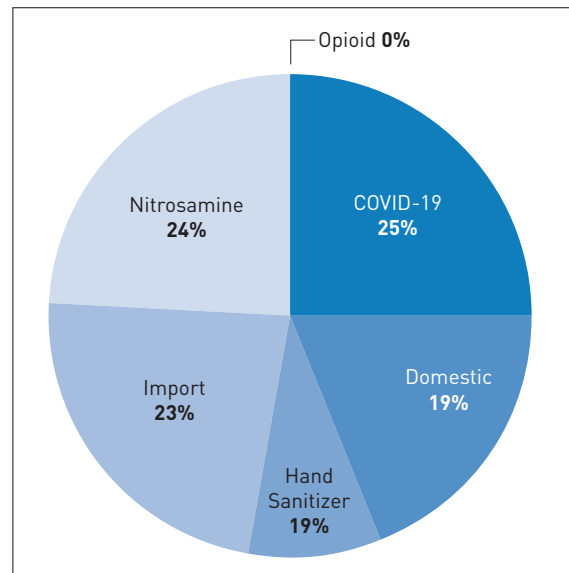


Figure 8. Distribution of FY2021 Non-Compliant Samples

³⁹ [FDA Updates and Press Announcements on Nitrosamine in Varenicline \(Chantix\)](#)

⁴⁰ [Control of Nitrosamine Impurities in Human Drugs](#)

conditions.⁴¹ Question responses can also contain a narrative describing the investigators' coverage and evaluation. Additionally, the protocols contain questions related to implementation of practices that correlate with an advanced quality system.

Collecting structured data on inspections enables more efficient and robust analytics that drive objective and data-driven decisions. The implementation of NIPP has facilitated a data mining process that can find anomalies, patterns, and correlations within the population of inspected sites. The Agency can answer critical questions related to the state of quality, for example:

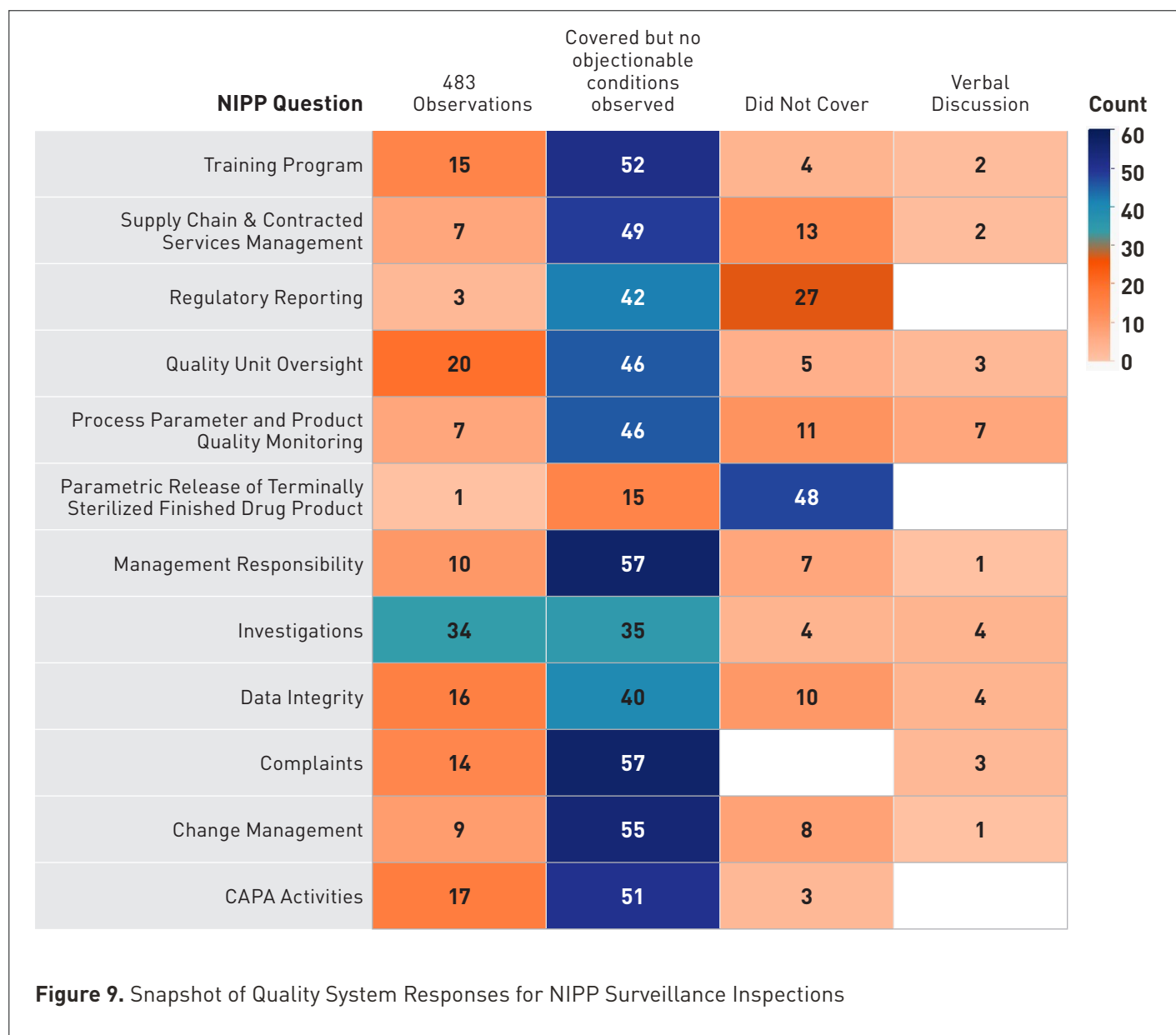
- “Is there a significant increase in deficiencies within a certain system or topic?”
- “Are the deficiencies being driven by certain characteristics of the sites (e.g., location, type of site, and size)?”

Based upon the insights gained through these analyses, the Agency can enhance identification of when pre-approval inspections are warranted and when outreach opportunities with the regulated industry could proactively mitigate systemic issues. NIPP also provides the Agency with a mechanism to identify areas for new policy or policy revisions based on the performance of the population of drug manufacturing sites.

These structured data may expand predictive capabilities for quality surveillance and help protect patients from potential supply disruptions. The data from approximately 75 surveillance inspections that utilized NIPP inspection protocols indicate a higher number of FDA Form 483 observations for the protocol question related to the coverage and evaluation of the firm's handling of investigations than for questions on other subjects ([Figure 9](#)). These data can be analyzed to identify potential associations between site characteristics and the distribution of observations. For example, associations can be identified to indicate increased or decreased likelihood of certain deficiencies based upon historical data. Natural language processing, a branch of artificial intelligence, is used to mine through the text data, detect emerging trends, and extract useful information (e.g., coverage within a specific topic). NIPP protocol data (e.g., indicators

⁴¹ Form FDA 483 and verbal observations are discussed in section 5.11.4.3 of the [Investigations Operations Manual](#).

of quality maturity) can also help support the implementation International Council for Harmonisation (ICH)^{42,43} and facilitate approval of regulatory flexibility when evidence of a mature and effective quality system is available.



⁴² [ICH guidance Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management \(2021\)](#)

⁴³ [ICH Q12: Implementation Considerations for FDA-Regulated Products \(2021\)](#)

Extensive research has validated the use of robust quality metrics programs as the foundation for continual improvement of product and process quality. As the underlying knowledge of effective quality management has evolved, we have recognized the importance of a holistic approach that integrates quality metrics with attributes of effective QMM. The 2019 report *Drug Shortages: Root Causes and Potential Solutions*⁴⁴ by the multi-agency Federal Drug Shortages Task Force reported that 62% of drugs that went into shortage between calendar years 2013 and 2017 were associated with manufacturing or product quality problems (e.g., substandard manufacturing sites or processes or quality defects in the finished product). These problems necessitate remediation, which can take time to address, interrupting production and leading to shortages. The Drug Shortages Task Force found one of the root causes of drug shortages is the fact that the market does not recognize and reward manufacturers for having mature quality management practices, and recommends an enduring solution focused on the development of a ratings system to incentivize drug manufacturers to invest in quality management maturity for their sites. As described in OPQ's recent QMM White Paper, QMM is the state attained by having consistent, reliable, and robust business processes to achieve quality objectives and promote continual improvement.⁴⁵

During FY2021–FY2022, FDA, in collaboration with external contractors, executed two pilot programs (one for foreign API manufacturers and one for domestic FDF manufacturers) to further develop the criteria and methods used to objectively measure a manufacturing site's QMM. These pilot programs utilized unique methods including self-surveys, facilitated interviews based on the assessment rubric, and focused presentations delivered by the site. Each approach sought to balance the burden on the site while achieving objective and accurate scores. The pilot programs assessed site maturity levels as evidenced by proactive management of product availability risks, effective application of quality risk management across business units, investments into digitalization, and advanced analytics. The pilot programs also provided evidence for operationalizing an assessment framework that can accurately and objectively discern between maturity levels within and across practice areas. FDA is continuing to collaborate with impacted stakeholders (e.g., manufacturers,

⁴⁴ [Report | Drug Shortages: Root Causes and Potential Solutions](#)

⁴⁵ [Quality Management Maturity: Essential for Stable U.S. Supply Chains of Quality Pharmaceuticals](#)

wholesalers, group purchasing organizations, and payors) to assure the program maximizes desired impact for all stakeholders – providing a competitive advantage through transparency in the marketplace, facilitating a focus on continual improvement, providing purchasers and payors more insights into maturity and performance, and most importantly, ensuring availability of medicines to patients and healthcare professionals.

The NIPP and QMM initiatives demonstrate FDA’s commitment to innovative quality programs now and in the future. Through them, inspections and assessments will produce richer, more analyzable data that can empower insights about drug quality and better oversight of the sites that manufacture them. Using these data and advanced analytic tools, FDA will be prepared to engage with manufacturers to assure the availability of quality products. Enhanced management of knowledge and an emphasis on risk-based approaches will enable FDA to target its regulatory resources more effectively, better protect the public from non-compliant products, and provide consumers and patients confidence that legally marketed drugs in the U.S. consistently exhibit a high state of quality.



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