

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL QUALITY

REPORT ON THE STATE OF PHARMACEUTICAL QUALITY: FISCAL YEAR 2020

Assuring quality medicines are available to the
American public





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Introduction

The State of Pharmaceutical Quality is the condition, constructed from various indicators, of the pharmaceutical manufacturing industry's ability to deliver quality drug products to U.S. patients and consumers. This U.S. Food and Drug Administration (FDA) Report on the State of Pharmaceutical Quality from the Center for Drug Evaluation and Research (CDER) covers fiscal year (FY) 2020¹ and presents information on quality in the U.S. drug supply chain. Quality drug products are safe and effective and free of contamination and defects. Like the rest of the world, FDA and pharmaceutical industry were together forced to adapt in FY2020, due to the COVID-19 public health emergency, to assure quality medicines were available to the American public. While facing challenges, we prioritized meeting our commitments while maintaining our high standards and responsibility to public health and the safety of our staff. Our commitment to provide this report summarizing key indicators of the pharmaceutical manufacturing industry's ability to deliver quality drug products to U.S. patients and consumers has not changed. There is an important consideration regarding the information provided in this report. This information is limited to FDA-registered human drug manufacturers² and drugs regulated by CDER, legally marketed in the U.S. Here we report on the evolving global pharmaceutical landscape examining manufacturing site demographics, impacts of COVID-19, manufacturing site compliance, drug product demographics, drug product quality, and regulatory innovations. We provide information on, for example, inspectional classification outcomes, product performance, product testing results, and recalls.

FDA uses the State of Pharmaceutical Quality, in part, to inform regulatory decision making and surveillance activities. We provide this information to the public so that all stakeholders can better understand the quality of the U.S. drug supply, an especially important consideration during a global public health emergency.

¹ From October 1, 2019 to September 30, 2020

² Manufacturer is defined as anyone engaged in manufacturing, preparing, propagating, compounding, processing, packaging, repackaging, or labeling of a drug. However, medical gas and pharmaceutical outsourcing facilities are omitted from this report.

Manufacturing Site Demographics

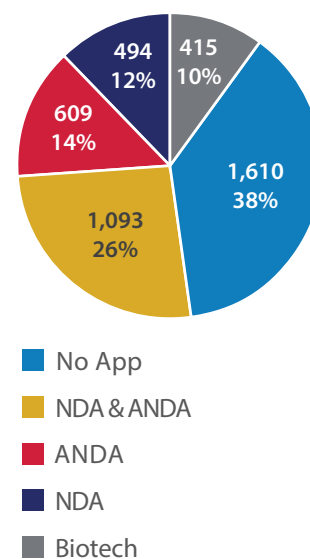
The FY2020 CDER Site Catalog³ has 4,221 drug manufacturing sites, a small decrease (-1.2%) from 4,273 in FY2019.⁴ It is important to note that this count excludes medical gas manufacturers and newly registered hand sanitizer manufacturers, the latter of which are covered in the next section of this report.⁵ Of this total, 1,610 (38%) drug manufacturing sites are in the “No Application” sector, which indicates that all products manufactured at the facility are those marketed without an approved application, including over-the-counter (OTC) monograph products, unapproved products,⁶ and homeopathic products. The remaining 2,611 (62%) sites are involved in the manufacture of at least one application product:

- Biological products licensed under Biologics License Applications (BLAs)⁷
- Innovator products approved under New Drug Applications (NDAs)
- Generic products approved under Abbreviated New Drug Applications (ANDAs)

As in previous years, in FY2020 there are more sites involved in the manufacture of both innovator and generic products (1,093) than there are sites involved in the manufacture of either innovator (494) or generic (609) products exclusively (Figure 1).

The top five countries by number of manufacturing sites in the FY2020 CDER Site Catalog were the United States, India, China, Germany, and Canada (Table 1). All had a net decrease in the number of sites, considering those added and removed⁸, and these were the same top five countries as in FY2019⁹. Of these, the U.S. accounted for the highest number of sites removed (286). China had the highest percentage of sites removed (-19.1%) and the highest net decrease (-10.1%). Of all

Figure 1. Distribution of the FY2020 Site Catalog by Application Type



³ The CDER Site Catalog of manufacturers is the curated list of registered sites, vetted by the FDA as legally manufacturing human drugs for the U.S. market; thus, not all human drug registrants qualify as “manufacturers” in the catalog.

⁴ FY2020 CDER Site Catalog as of November 2020

⁵ This report covers CDER-regulated products and excludes products regulated by the Center for Biologics Evaluation and Research (CBER), e.g., vaccines including those related to COVID-19.

⁶ <https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs>

⁷ Therapeutic Biological Products under CDER — <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/transfer-therapeutic-products-center-drug-evaluation-and-research-cder>

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

⁹ <https://www.fda.gov/media/138711/download>

countries with at least 50 sites, Mexico had the largest net decrease of sites (-13%) and the UK and France had the smallest net decrease. The South Korean site inventory was most dynamic (loss of 34% and gain of 32%), indicating its status as an emerging source of pharmaceutical products.

Table 1. FY2020 Manufacturing Site Inventory

Country	Sites in FY2020	Sites maintained	Sites Removed	Sites Added	Percentage Shift		
					% Removed	% Added	% Net
UNITED STATES	1780	1644	286	136	-16.1%	7.6%	-8.4%
All Others	1266	1152	170	114	-13.4%	9.0%	-4.4%
INDIA	502	457	53	45	-10.6%	9.0%	-1.6%
CHINA	367	334	70	33	-19.1%	9.0%	-10.1%
GERMANY	160	150	26	10	-16.3%	6.3%	-10.0%
CANADA	146	137	19	9	-13.0%	6.2%	-6.8%
TOTAL	4221	3874	624	347	-14.8%	8.2%	-6.6%

Impacts of COVID-19

In FY2020, FDA worked in many ways to protect our nation during the COVID-19 public health emergency by assuring quality drugs to treat COVID-19 patients were available as soon as possible, monitoring the nation's supply of medicines, and taking action to mitigate or prevent drug shortages. The agency [published over 60 guidance documents](#) related to the public health emergency in an unprecedented effort to provide information to industry, including insights into drug and biological product development during the pandemic, and guidance on informing the agency of any interruptions in manufacturing operations which could result in supply chain disruptions. FDA efforts also focused on approving and authorizing medicines to treat patients with COVID-19, addressing the increased demand for alcohol-based hand sanitizer during the public health emergency, and assuring the availability of container closures for drugs and vaccines in light of dramatically increased demand for parenteral products.¹⁰

¹⁰ This effort identified risks of global shortages on glass tubing, glass containers, and rubber components that could result from the increase in demand triggered by the COVID-19 pandemic, and which in turn could cause risk of drug shortages in other U.S. drug products.

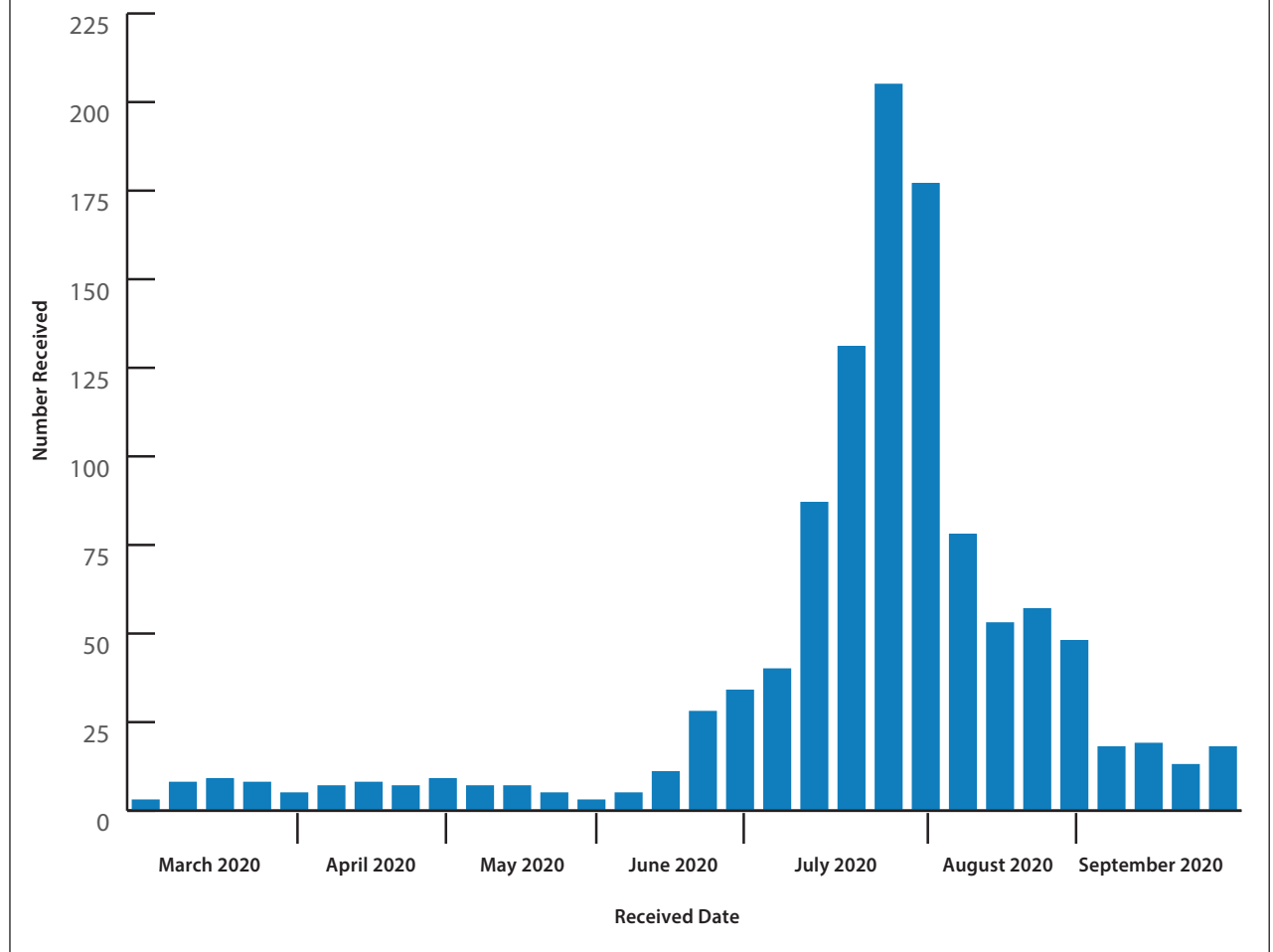
Hand Sanitizers

As part of the response to the pandemic, FDA issued guidance detailing a [temporary policy on the preparation of alcohol-based hand sanitizers during COVID-19](#). This guidance outlines the conditions for thousands of distilleries and other industrial manufacturers of alcohol to register and produce alcohol-based hand sanitizers to meet demand for these products within the U.S. There was a concomitant and significant increase in overall registered facilities with 6,743 new registrants in 2020, compared to 740 in 2019. The majority of these new registrants were hand sanitizer manufacturers, 3,688 of which de-registered after FDA outreach to confirm registrants and products. At present, there are 1,623 new registrants from around the globe considered “manufacturers” in the FY2021 CDER Site Catalog, 94% of which are hand sanitizer manufacturers.

Product Quality Monitoring

With the introduction of new registrants came many hand sanitizer manufacturers who had no previous experience manufacturing hand sanitizers. To tackle the influx of new hand sanitizer registrants, FDA tested imported hand sanitizers and issued a statistically designed domestic surveillance sampling and testing assignment covering around 300 firms and based on several risk factors. In partnership with the National Poison Data System (NPDS), the agency also monitored increased reports of ingestion of hand sanitizers, some of which were fatal or led to permanent disability due to the presence of methanol, a contaminant found in some hand sanitizers that did not conform to standards. The suspected quality issues led to additional for-cause sampling assignments based on these reports and other product complaints submitted to the agency. Product complaint reports peaked in July 2020 with more than 125 complaints (Figure 2). There was then a sharp decrease in complaints for these products following agency-coordinated voluntary recalls by some manufacturers. Many hand sanitizer products were added to the [FDA’s Should Not Use list](#) based on FDA testing. FDA also initiated the first human drug related “country-wide import alert” for hand sanitizers from Mexico due to the large number of failures found upon import testing.¹¹

¹¹ Occurring in FY2021. This type of Import Alert has been used for other commodities such as food. With this type of Import Alert, manufacturers can only import from Mexico if the agency accepts their petition to be on a list.

Figure 2. Number of Consumer Complaints Received for Hand Sanitizers, FY2020

Site Quality Monitoring and Application Approvals During COVID-19 Pandemic in FY2020

During the global public health emergency, many FDA inspections were not possible. In 2012, the Food and Drug Administration Safety and Innovation Act gave FDA new authorities under the Food, Drug, and Cosmetic Act §704(a)(4) to request records or other information from firms in advance of or in lieu of an inspection.¹² Although the number of surveillance inspections conducted significantly dropped in March 2020, FDA used this authority to obtain records for sites that would have had surveillance inspections. FDA also expanded the Mutual Recognition Agreements (MRAs) with the European Union and the United Kingdom to include inspections performed in countries other than their own.

¹² For more information about FDA's use of this authority, see [Staff Manual Guide 9004.1 POLICY AND PROCEDURES FOR REQUESTING RECORDS IN ADVANCE OF OR IN LIEU OF A DRUG INSPECTION](#)

The FDA used several strategies to assess and act on regulatory submissions that would typically have needed a pre-approval inspection (PAI) or pre-license inspection (PLI). FDA surveillance history, requests for records, and inspection reports obtained through the MRAs were used to mitigate risk and enable regulatory actions. For submissions that were deemed mission-critical, some inspections were still performed under difficult COVID-19 travel restrictions. As a result of utilizing all of these approaches, CDER completed facility assessments to meet User Fee dates over 90% of the time and reduced the need to conduct PAIs 58% of the time in FY2020 Q3, and 64% of the time in FY2020 Q4.¹³

Manufacturing Site Compliance

As a response to the global pandemic, in March 2020 the U.S. Department of State enacted restrictions on travel to China which caused FDA to postpone all non-mission-critical site inspections there. This postponement eventually extended to all countries, including the U.S. Typically, these inspections enable FDA to monitor compliance with CGMP and identify quality problems. Nevertheless, FDA still performed 562 drug quality assurance inspections¹⁴ (i.e., surveillance and for-cause) in FY 2020. Although most of these inspections were performed prior to the public health emergency, FDA continued to conduct mission-critical inspections during the pandemic. In addition, MRA authority was used to assess 183 sites through MRA inspection reports for a total of 745 sites (18% of the FY2020 CDER Site Catalog). For comparison, in FY2019 1,258 drug quality assurance inspections were performed and an additional 109 sites were assessed using MRAs for a total of 1,367 sites (32% of the FY2020 CDER Site Catalog).

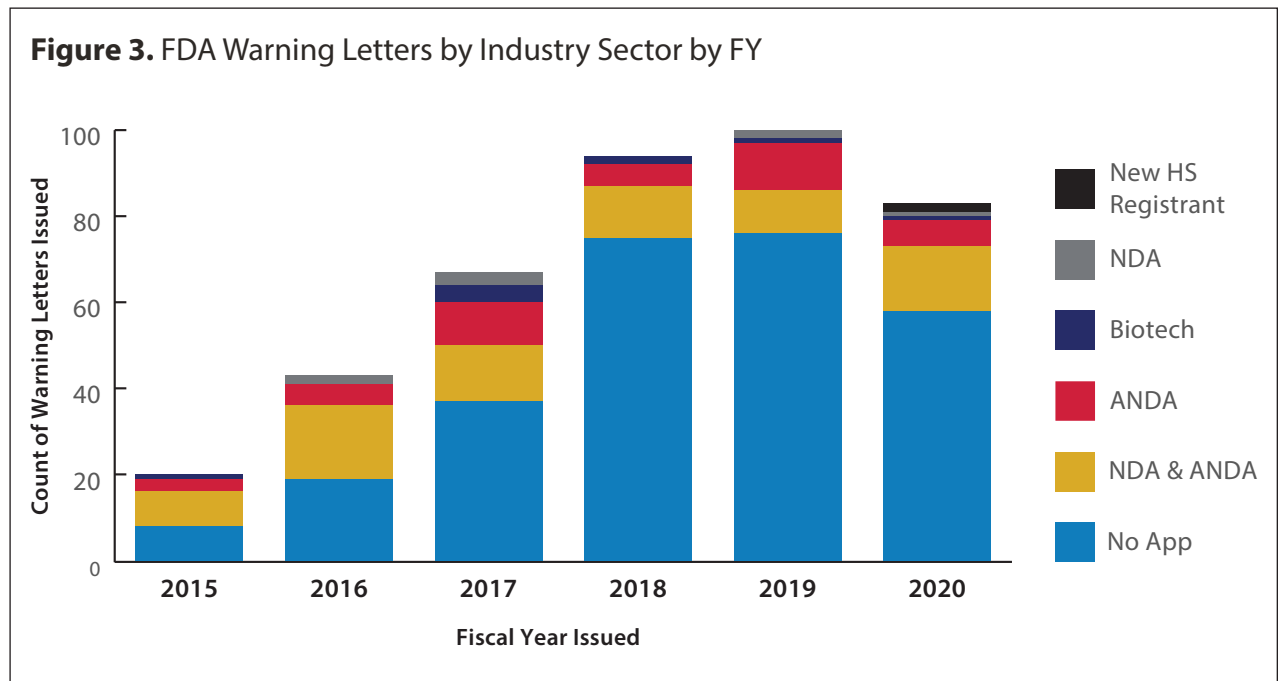
Warning Letters / Import Alerts

CGMP violations that are observed either through an inspection; violative evidence collected from a record request; or failing analytical sampling and testing, may result in a regulatory action including Warning Letters¹⁵ and Import Alerts. The number of Warning Letters issued in FY2020 was slightly lower than in FY2018 or FY2019, but still over four times higher than in FY2015 (Figure 3). As in past years, the majority of Warning Letters in FY2020 were issued to sites with non-application products (69%), and especially those that manufacture finished dosage form (FDF), non-sterile, non-application products (41% of all Warning Letters).

¹³ <https://www.fda.gov/industry/fda-user-fee-programs/cders-work-meet-user-fee-goals-during-pandemic>

¹⁴ [Compliance Program 7356.002 – Drug Quality Assurance.](#)

¹⁵ From FY2015 to FY2020, 9 individual Warning Letters included more than 1 FEI (as many as 3). For the purposes of this analysis, these still count as 1 Warning Letter issuance and the first FEI listed will link to Region and Sectors.



FDA protects the American public by issuing Import Alerts that help prevent targeted products from entering the U.S. market.¹⁶ Import Alerts doubled to 128 in FY2020 (Figure 4). Latin America had the most sites on Import Alert for the first time in FY2020, due to an unprecedented number of new hand sanitizer registrants from Mexico that failed to meet quality standards. Of the 55 sites on Import Alert in Latin America, 49 (89%) were for new hand sanitizer registrants. As mentioned previously, FDA eventually put all hand sanitizers from Mexico on a “countrywide” Import Alert.

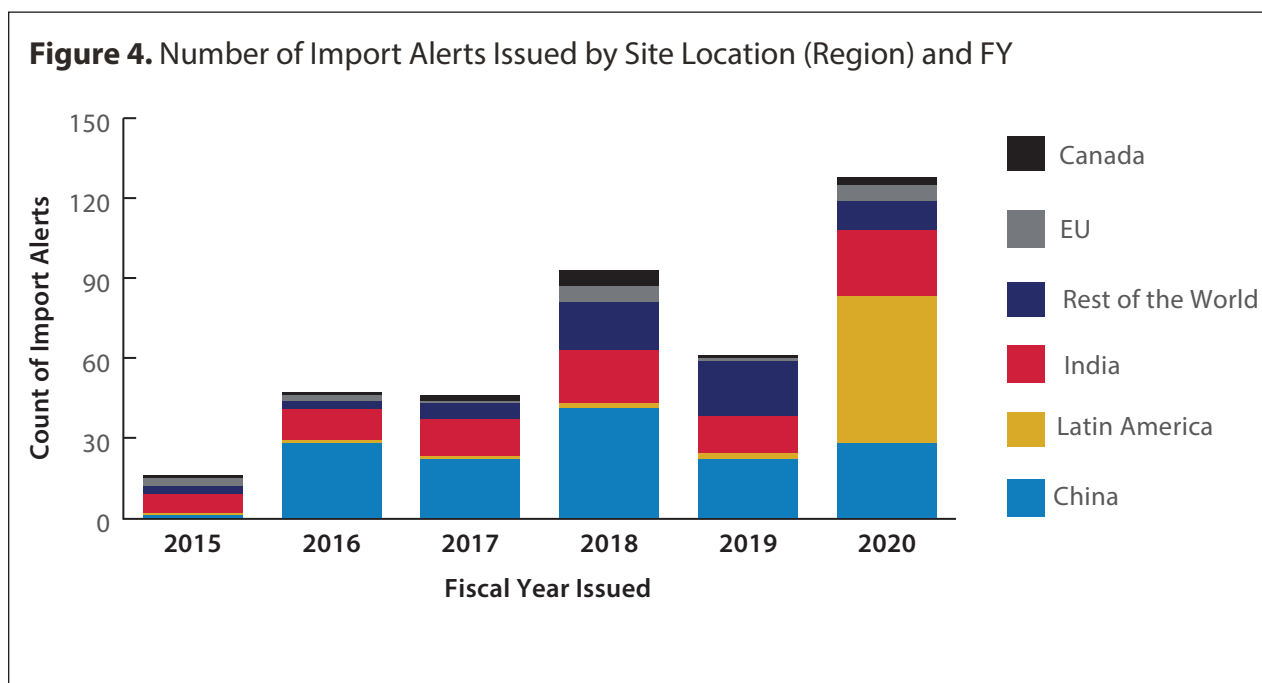
Site Inspection Score (SIS)

A site inspection score (SIS), on a scale of 1 to 10, is used as a proxy for compliance with CGMP regulations. Compliance with CGMP assures proper design, monitoring, and control of manufacturing processes and facilities, and represents the minimum standards to which sites must adhere.¹⁷ Higher SIS scores indicate better compliance with CGMP. The SIS is based on the classification of FDA drug quality assurance inspections conducted over the prior ten years,¹⁸ including inspections

¹⁶ Import alerts referenced in this section: 55–03, 55–05, 66–40, 66–78, and 99–32. https://www.accessdata.fda.gov/cms_ia/industry_60.html

¹⁷ 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).

¹⁸ The period covered by this report is FY2011 through FY2020. An algorithm determines this score (from 1–10) and assigns more weight to more recent inspectional outcomes. Due to the flux of sites in and out of the CDER Site Catalog, there may not always be FDA inspectional outcomes for all sites — for example, some newly registered sites may not yet have an initial FDA drug quality inspection.



classified under the MRA program, which allows some global regulators to recognize reports from their counterparts' inspections.

As sites are inspected and receive a classification outcome,¹⁹ these outcomes are transformed into an SIS. Since FY2019, there was a small decrease (0.10) in the mean SIS of the entire inventory of sites (7.3). As observed in years past, there are differences between geographic regions and manufacturing sectors. The mean SIS for sites in the U.S. (7.62), the EU (7.59), and Canada (7.56) remained higher than the global average, while the mean SIS for sites in China (7.23), India (6.87), and Latin America (6.69) remained lower than the global average, though the scores indicate an acceptable level of compliance to CGMP on average. When considering sectors, sites making homeopathic products have the lowest mean SIS (6.77).

Machine Learning Model to Predict SIS

An XGBoost²⁰ (eXtreme Gradient Boosting) machine learning regression model²¹ was developed to model and predict the SIS using inspection data from 10 years of inspection outcomes.²² We extracted features and feature combinations predictive of an increase or decrease in the risk factor associated with low or high SIS (Table 2). These features consid-

¹⁹ [Inspection Classification Outcomes](#)

²⁰ <https://doi.org/10.1145/2939672.2939785>

²¹ Including studying the model interpretability using Shapley (SHAP) values and analyzing critical feature interaction effects

²² Note that the following analyses do not include Medical Gas sites or newly registered sites under the COVID Temporary Guidance for Hand Sanitizers

ered included Profile Class Codes (PCCs). When a drug manufacturing inspection is performed, FDA uses PCCs to capture all product classes produced by the manufacturer as well as those covered during the inspection (e.g., tablets, capsules, ointments, sterile injectables). The number of application and non-application products being manufactured at a site were the top two most important features associated with higher or lower SIS, respectively. These types of analyses enable FDA to better target and apply surveillance resources.

Table 2. Features Identified by Machine Learning as Predictive of SIS

Factors associated with sites that have higher SIS	Factors associated with sites that have lower SIS
<ul style="list-style-type: none"> • Biotech Analysis²³ manufacturing sites with higher number of applications products • Profile class codes (PCCs) other than API and FDF (e.g., test laboratories). • Located in the region "USA." • Lower Product Quality Defects (see section 4) rates. • Higher number of NDA products manufactured. 	<ul style="list-style-type: none"> • Sites containing a Homeopathic PCC with a higher number of non-application products. • Located in the region "India." • Manufacturers of Analgesics with a lower total product count. • Sites with a higher number of total CDER PCCs (e.g., manufacturing many different types of products). • Sites located in "USA" or "India" with a high number of Physical Product Issues (e.g., cracked tablets, cloudy product, particles). • Sites located in India, Canada, or Latin America and without prescription drug listings. • Sites with no NDA listings with lower counts of PCCs.

Drug Product Demographics

Manufacturer Location by Application Type

Many establishments are involved in the manufacture of more than one drug product and more than one application type. To better understand risk in the supply chain, it is necessary to determine how many times a site is referenced in all applications. Quality issues at a site referenced in many applications may introduce substantial risk to the supply chain. Drug applications reference specific manufacturing operations undertaken at manufacturing sites (e.g., finished dosage formulation,

²³ Harboring laboratories that test at least one biotechnology product

API manufacturing, testing, labeling, repacking) to make the final drug. U.S. sites are referenced the most in approved ANDAs (37,411 times) followed by India (13,253 times). U.S. sites are also referenced the most in approved NDAs (13,357 times) followed by the EU (5,464 times), while sites in India (837 times) are referenced less than the U.S., EU, Canada, and the rest of the world (Figure 5).

Distribution of Approved Applications per Site

Comparing the number of applications referenced per manufacturing site shows that the individual site referenced in the most applications is a U.S.-based repacker (and that four sites in the U.S. are referenced in over 1,000 applications); but that the median number of application references per site in the U.S. is only 2.0 (Figure 6). In contrast, no site in India is referenced more than 1,000 times; but the median number of application references per site is 16.5 — over eight times higher than the U.S. median. This suggests that, in general, sites in India are responsible for more products than are sites in the U.S. Hence, sites in India tend to have more profile class codes, and processes, to cover on inspection.

Figure 5. Number of Times a Site is Listed in Applications, by Region, FY2020

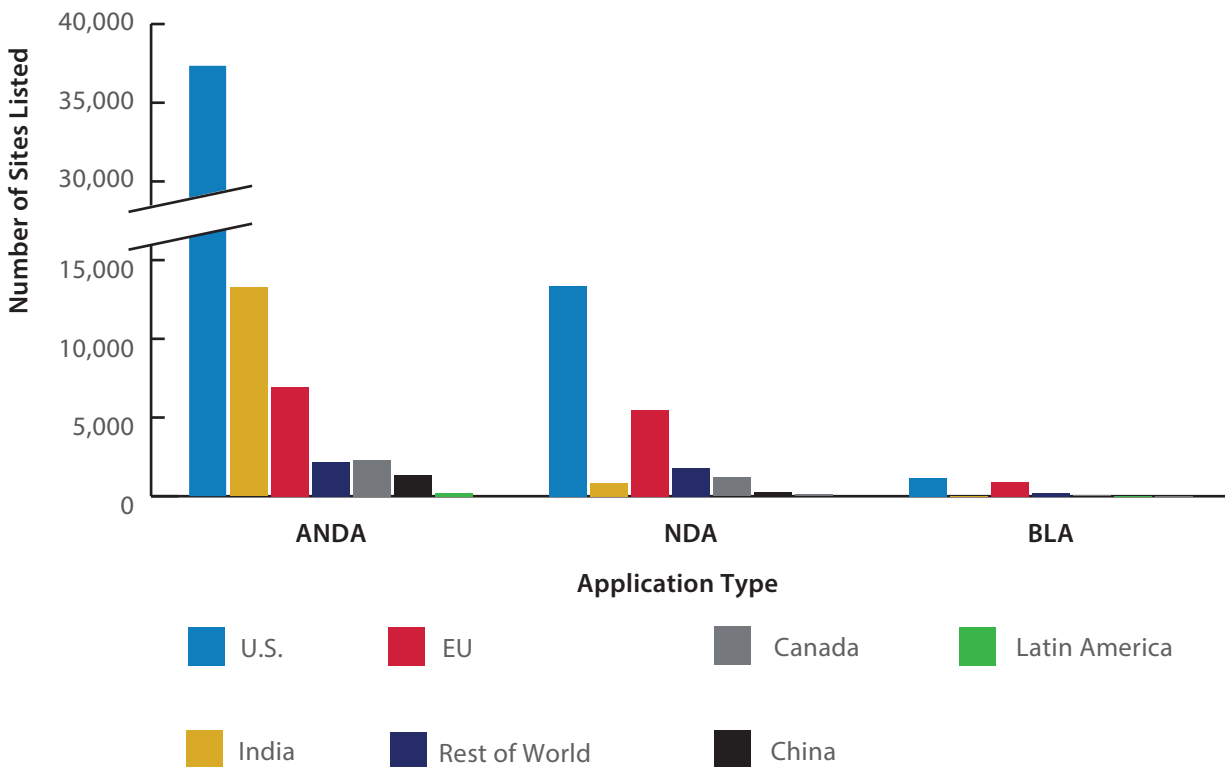
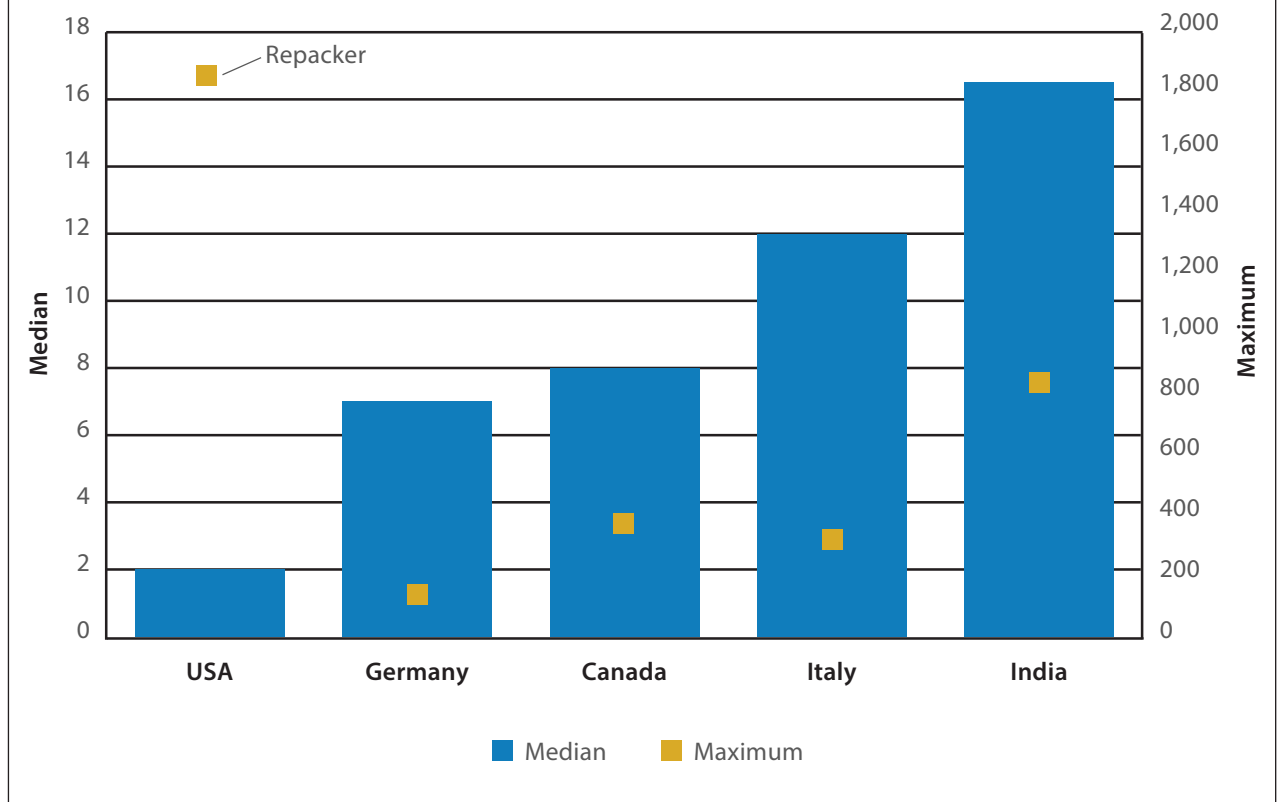


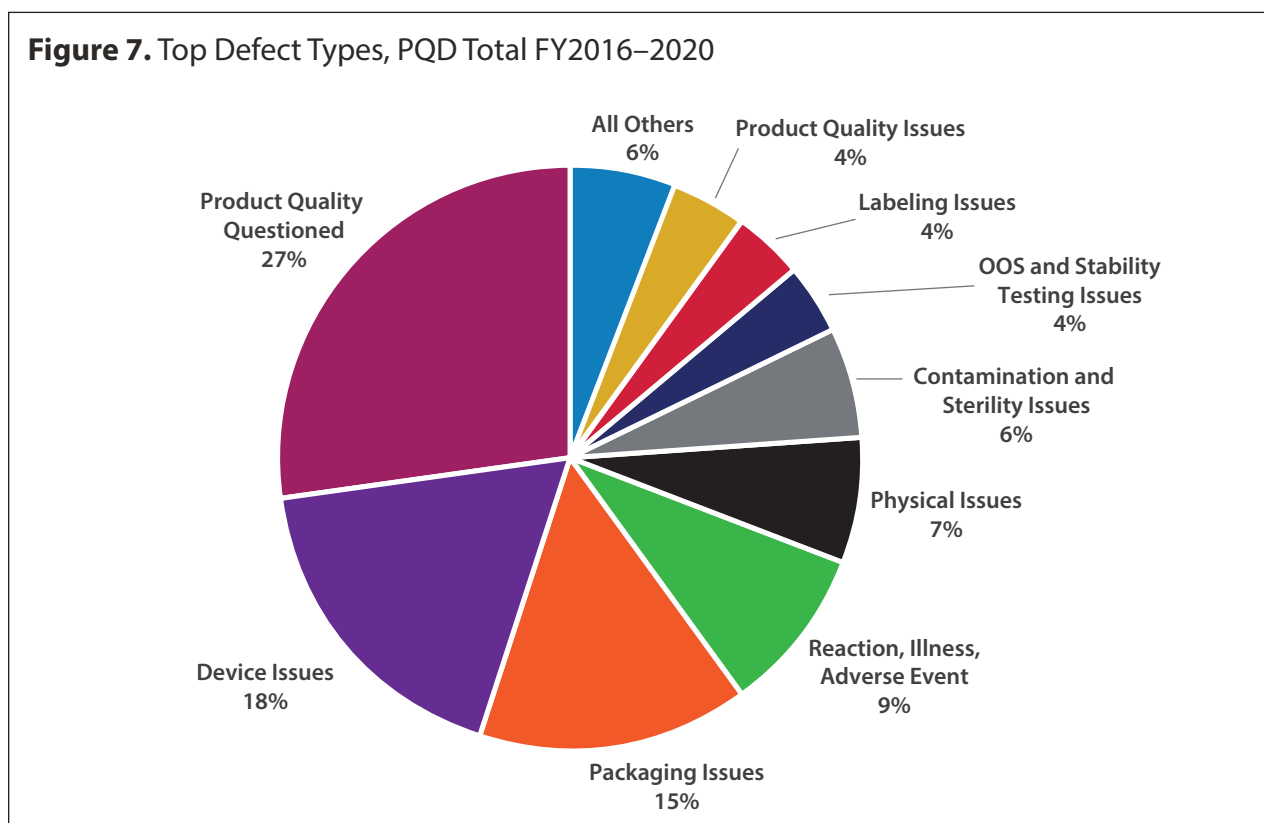
Figure 6. Number of Application Products Referenced per Site

Drug Product Quality

Product²⁴ quality concerns were measured through Product Quality Defect (PQD) reports comprising 11,932 Med Watch (MW) reports, 4,308 Field Alert Reports (FARs), 253 Consumer Complaints, 263 Biological Product Deviation Reports (BPDRs), and 2,623 tested samples over a 5-year period (FY2016–FY2020). FARs are submitted for drug products subject to NDAs and ANDAs and BPDRs only apply to biological products subject to BLAs. Adverse events or other problems with FDA-regulated products can be reported by the public through MedWatch or Consumer Complaints. As a result of more reporting mechanisms for application drug products, they account for 88% of PQDs in FY2020. Nevertheless, due to issues related to hand sanitizers, in FY2020 there was a four-fold increase in the number of PQDs

²⁴ In this report, “product” refers to both drug product and drug substance.

reported for the No Application industry sector when compared to the average PQDs of FY 2016–2019. PQD reports are grouped in 20 defect categories. For FY2016–FY2020, three defect categories account for 60% of all defects reported: Product Quality Questioned, Device Issues, and Packaging Issues (Figure 7).



Over this time period, all types of reports increased except for Consumer Complaints. A change in the number or type of PQDs received could be due to several factors, some outside of the intrinsic quality of product, such as increased sales volume or improved awareness of FDA’s process for reporting quality issues. For example, the most notable increase in FY2020 was in BPDRs received (263) compared to FY2019 (83). This increase is largely due to the transition of 97 NDAs to BLAs on March 23, 2020.²⁵ Concerns about these products would have been previously reported as FARs.

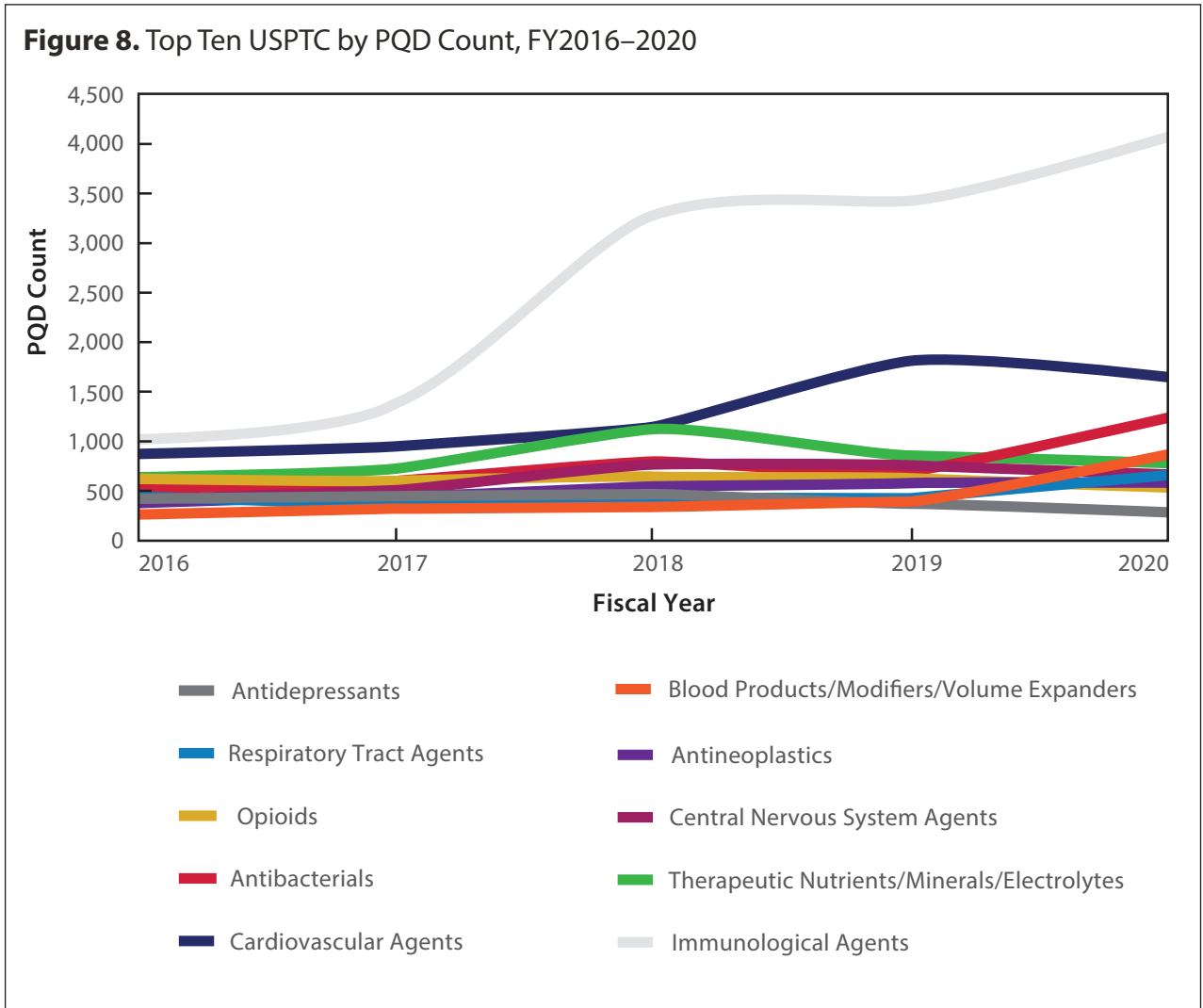
²⁵ [“Deemed to be a License” Provision of the BPCI Act](#)

Product Quality Defects by USPTC

In FY2020, the number of PQDs increased for five [United States Pharmacopeia Therapeutic Categories](#)²⁶ (USPTCs) (Figure 8). Most of these increases may be due, in part, to expanded use of drug products used to treat patients with COVID-19²⁷ (Table 3). In 2020, Immunological Agents continued to account for the highest number of PQDs (24%). Immunological Agents are often sterile injectable products which may have a device constituent, such as an autoinjector. While the SIS for

26 <https://www.fda.gov/regulatory-information/fdaaa-implementation-chart/usp-therapeutic-categories-model-guidelines> These categories, created by USP under Food and Drug Administration Amendments Act of 2007, are used to organize products into 50 therapeutic groups for comparative analysis.

27 Products were listed either on the NIH website Therapeutic Management of Patients with COVID-19 or identified on a list of 40 critical COVID-19 Drugs on the Resilient Drug Supply Product: Critical Acute Drug List & Critical COVID-19 Drug List Drug Shortages Reported by ASHP & FDA.



this product category (7.8) is above the overall average (7.3), the device constituent is not typically covered in a drug surveillance inspection. FDA monitors these surveillance signals has formed an interdisciplinary group to address potential underlying issues with these products.

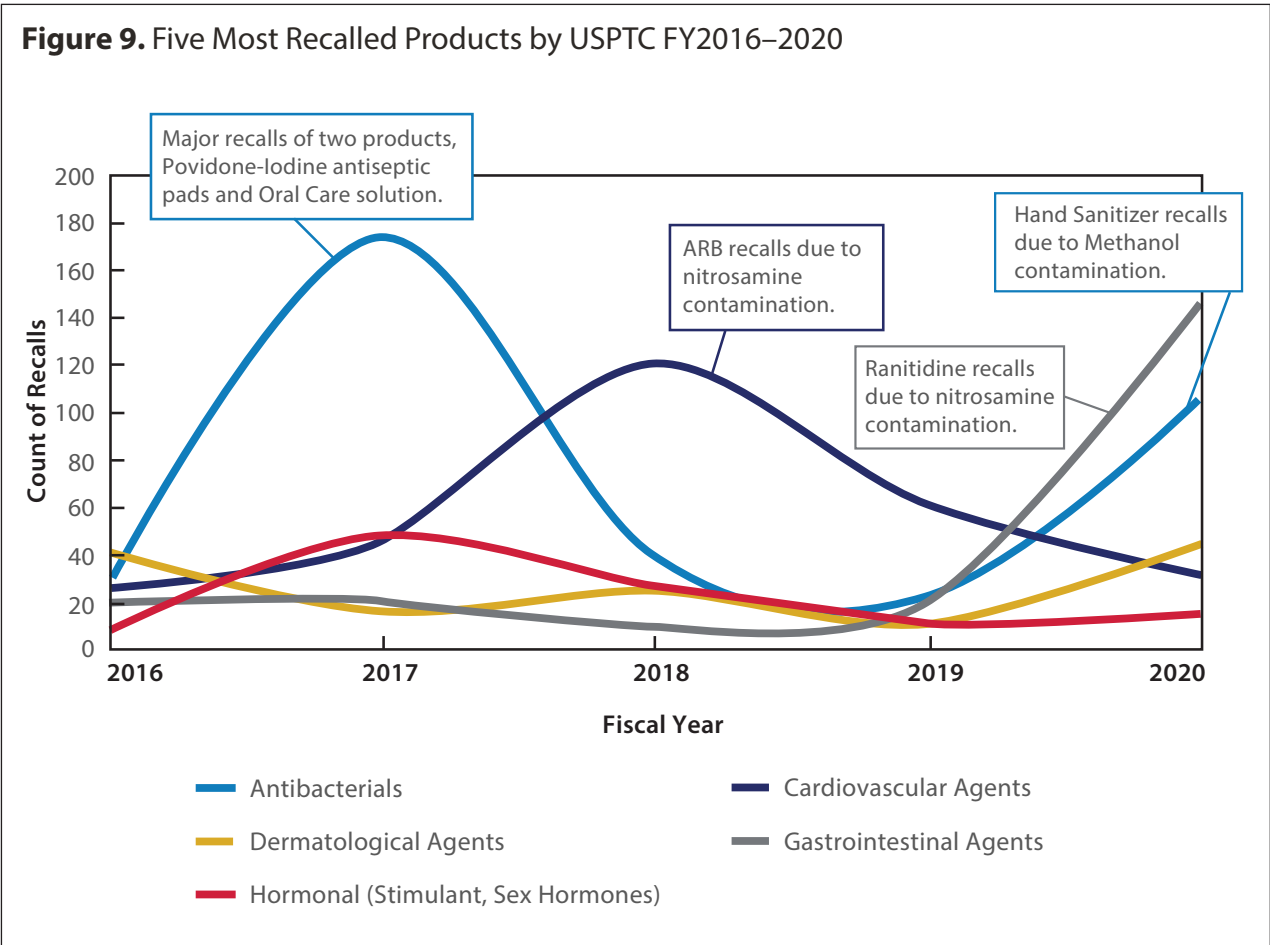
Table 3. USPTCs with Increased PQDs in FY2020

USPTC with Increased PQDs	Product in USPTC linked to treatment of COVID-19 related symptoms
Immunological Agents	interferon products
Antibacterials	hand sanitizers linked to increased demand during COVID-19, azithromycin, doxycycline
Antineoplastics	N/A
Respiratory Tract Agents	montelukast, fluticasone propionate, fexofenadine hydrochloride
Blood Products/Modifier/Volume Expanders	heparin, enoxaparin

FY2020 Recall Analysis

In FY2020, the number of recall events²⁸ increased for the second consecutive year. The most recalled products by USPTC reflect the major quality issues over the past five years (Figure 9). In FY2017, microbial contamination led to recalls of antibacterial products (e.g., povidone-iodine antiseptic pads and oral care solutions). The presence of nitrosamine impurities in a number of cardiovascular products led to recalls in FY2018. In FY2020, increased recalls for gastrointestinal products and antibacterial products were related to nitrosamine impurities found above the acceptable limit in H₂ Blockers (e.g., ranitidine) and contamination in hand sanitizers, respectively. The most substantial increases in the number of recalls by industry sector in FY2020 were in the No Application and NDA & ANDA (i.e., sites manufacturing for both application types) sectors (Figure 10). In FY2020, the Biotech and NDA sectors again had the fewest recalls. The average SIS of sites reporting at least one recall continues to be below the overall average SIS, highlighting the relationship between recalls and CGMP compliance. Each major recall over the last five fiscal years was associated with microbial or chemical contamination/impurities; a focus area for the industry to improve quality.

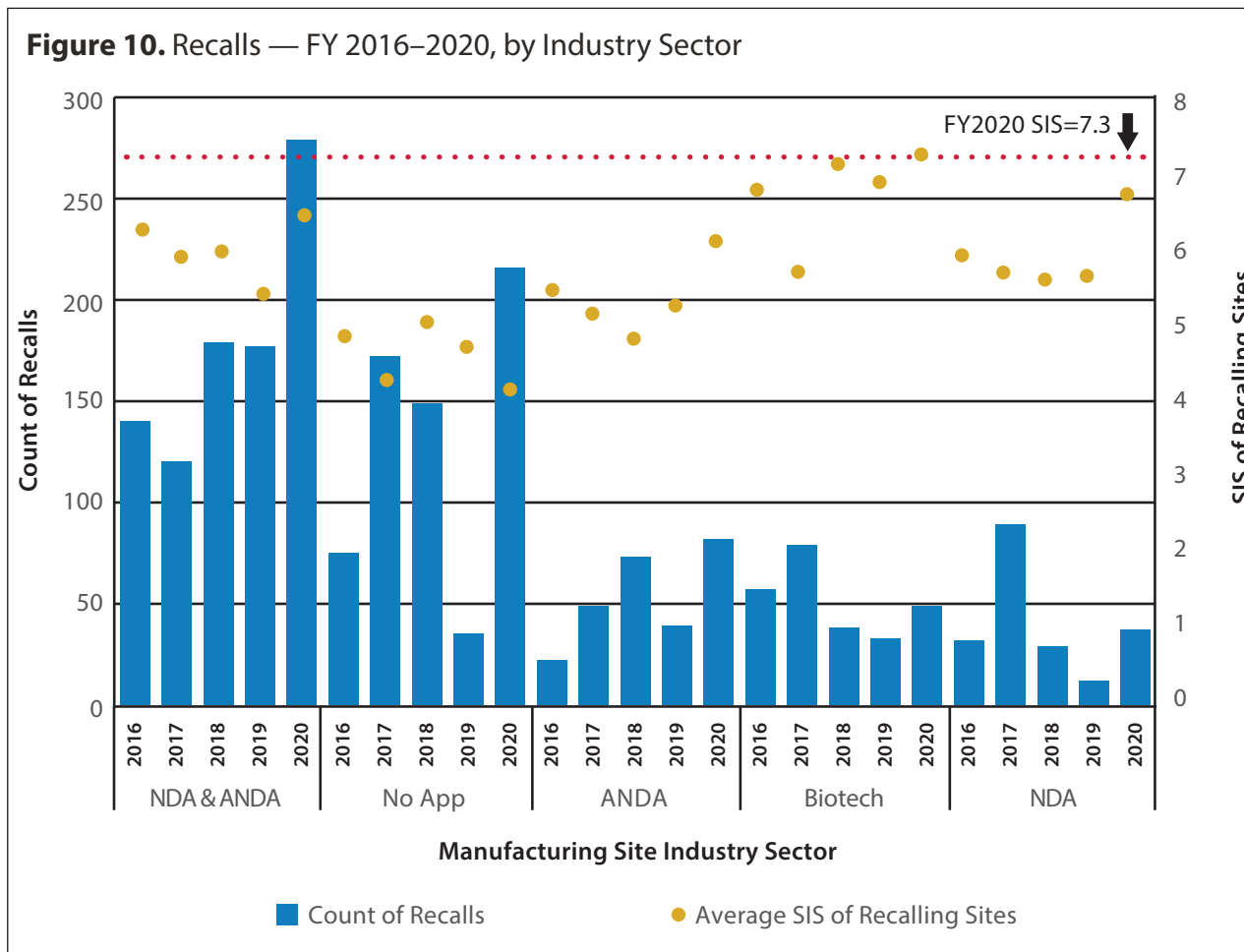
²⁸ All recall classes (I, II, III) included. <https://www.fda.gov/safety/industry-guidance-recalls/recalls-background-and-definitions>



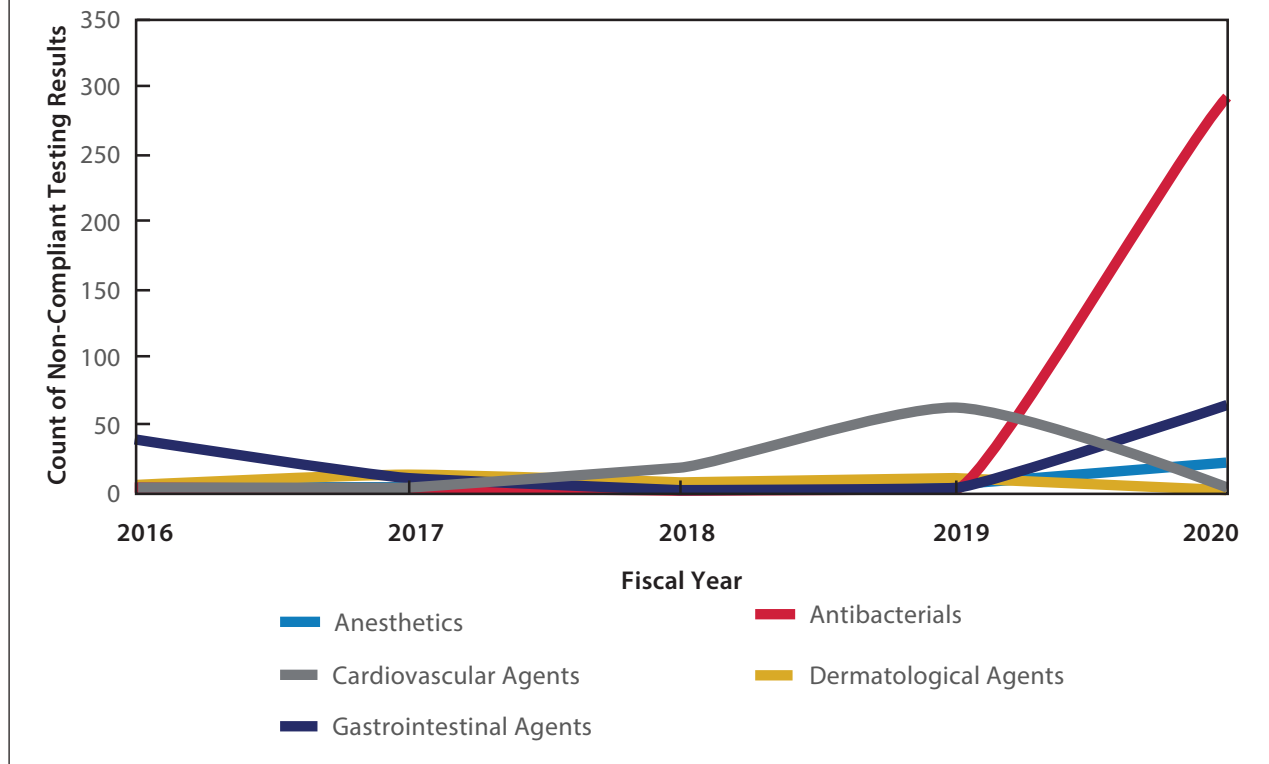
FY2020 Sampling and Testing

FDA conducts routine surveillance sampling and testing of drugs on the market as well as targeted sampling and testing of drugs with potential risks — based on information and data collected from inspections, manufacturers, distributors, wholesalers, and consumer complaints. This contributes to the agency’s effort to minimize public exposure to non-compliant or poor-quality products. Product sampling is therefore often associated with investigations and incidents, which introduces an inherent bias to these data.

Five years (FY2016–2020) of product sampling data included a total of 5,465 unique drug samples collected and classified as compliant (passing results) or non-compliant (violative or failing testing results for at least one critical quality attribute tested). The highest non-compliant rate (30%) in FY2020 is seen for Antibacterial (e.g., hand sanitizers) samples collected in response to the COVID-19 pandemic (Figure 11).



Also notable are the increased non-compliant rates for Gastrointestinal Agents which led to the recalls of ranitidine and nizatidine products with nitrosamine impurities, followed by the eventual [withdrawal of all ranitidine products](#) from the U.S. market in April 2020. An example of the use of surveillance tools to protect patients is reflected in the increased recalls for Anesthetics in FY2020. After a §704(a)(4) request for information from a firm identified CGMP concerns and product sampling identified sub-potent product from the firm, FDA placed the firm on import alert, protecting patients from sub-potent medicine.

Figure 11. Non-Compliant Testing Results for Sampled Products, FY2016–2020

Commitment To Quality

CDER provides this annual Report on the State of Pharmaceutical Quality for CDER-regulated drugs legally marketed in the U.S. These analyses, as part of a comprehensive surveillance program, provide the public with an understanding of the pharmaceutical industry and enable FDA to proactively address potential pharmaceutical quality issues before patients and consumers are impacted. This surveillance function helps assure quality medicines are available to the American public. During FY2020, the demands of the COVID–19 public health emergency emphasized the criticality of this mission. FDA responded by introducing new, and adapting existing, surveillance tools to watch over the drug supply chain while non-mission-critical inspections were postponed due to travel restrictions.

The number of MRA inspection reports reviewed increased substantially, allowing inspectional resources to be reallocated to other high-risk activities. OPQ also made increasing use of FDA’s authority under §704(a)(4) of the FD&C Act to request records from regulated firms. FDA recently published guidance on [Remote Interactive Evaluations](#)²⁹

²⁹ <https://www.fda.gov/media/147582/download>

to enhance surveillance oversight while decreasing risks of exposure during a pandemic. These tools have allowed many products to be approved, without PAIs or PLIs, before their User Fee dates and prevented many inferior products from entering the U.S. market.

CDER continues to be at the forefront of outreach to industry and to the public. Over the past year, throughout the pandemic CDER has provided supply chain information, addressed emerging product quality concerns, and interacted with global stakeholders. Our FY2020 efforts include:

- Authoring a [peer-reviewed study](#)³⁰ on comparing difficult-to-make drugs manufactured in various parts of the world and marketed in the U.S.
- Sponsoring a workshop on [Understanding How the Public Perceives and Values Pharmaceutical Quality](#)³¹, held by Duke University's Margolis Center for Health Policy.
- Holding a [Pharmaceutical Quality Webinar for Global Stakeholders](#)³² beginning at midnight Eastern Standard Time to allow international stakeholders to attend during their workday (90% of online attendees were from India and China).

Through proactive efforts CDER seeks to improve the future state of pharmaceutical quality and to minimize long-standing problems such as drug shortages due to quality issues. These efforts include:

- **New Inspection Protocol Project (NIPP):** This project is aimed at using standardized electronic inspection protocols to collect data in a structured manner. The protocols promote consistent and comprehensive coverage of critical areas of drug manufacturing and provide structured, data-rich reports. The protocols include questions related to quality culture observed in facilities. In the future, FDA will have the ability to better understand how certain variables (e.g., location of the establishment, type of establishment) affect quality. As more data are collected through NIPP, these types of insights can inform future inspections, identify policy/outreach opportunities, and influence application-related decision making.

³⁰ <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2769690>

³¹ <https://healthpolicy.duke.edu/events/understanding-how-public-perceives-and-values-pharmaceutical-quality>

³² <https://www.fda.gov/drugs/news-events-human-drugs/pharmaceutical-quality-webinar-global-stakeholders-07232020-07232020#event-information>

- **Quality Management Maturity:** To characterize quality management maturity among human drug manufacturers, FDA funded Dun & Bradstreet and the University of St. Gallen to study over 200 pharmaceutical manufacturing establishments. The researchers found that quality has a positive correlation with performance, as there was a high degree of positive correlation between: (i) Delivery Indicators such as order fulfillment, customer complaint rate, and adherence to standard lead time; and (ii) measures³³ of the degree to which an organization adheres to best-practice maturity principles. These findings support the hypothesis that a high degree of quality management maturity has a positive impact across an organization, including on the fundamental ability to deliver supply. FDA is moving toward a rating system that incentivizes drug manufacturers to invest in quality and achieve higher levels of quality management maturity. This concept was proposed in the multi-agency report for Congress [*Drug Shortages: Root Causes and Potential Solutions*](#).

Regardless of the circumstances, U.S. patients and consumers deserve confidence in their next dose of medicine. FDA will continue engaging with stakeholders, responding to changing circumstances based on science and risk, developing innovative programs, and sharing information on the State of Pharmaceutical Quality, all in an effort to assure that safe, effective, quality medicines are available to the American public.

³³ Enablers of work areas well-suited for visual control and lean production (i.e., 5S implementation) such as utilization of Statistical Process Control, proactiveness related to process bottlenecks, and Corrective Actions and Preventive Actions effectiveness.



U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
www.fda.gov

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993