U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACEUTICAL QUALITY

REPORT ON THE STATE OF PHARMACEUTICAL QUALITY: FISCAL YEAR 2019

Assuring quality medicines are available for the American public

June 2020
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Table of Contents

Introduction

This report from the U.S. Food and Drug Administration (FDA) on the State of Pharmaceutical Quality for fiscal year (FY), October 1, 2018 to September 30, 2019, contains select quality indicators and trends that provide insight into the quality of the U.S. drug supply chain. In 2019, for the first time, the Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) produced a public report on the State of Pharmaceutical Quality for CDER-regulated drugs legally marketed in the U.S. Quality drug products are safe and effective, free of contamination and defects. The State of Pharmaceutical Quality is a summary of various measures of the pharmaceutical manufacturing industry's ability to deliver quality drug products to U.S. patients and consumers.

The information provided in this report is specific to drugs marketed in the U.S. and to FDA-registered human drug manufacturers.[1] In some instances, we use a site inspection score, on a scale of 1 to 10, which is a measure of a site's compliance to Current Good Manufacturing Practice (CGMP) regulations. CGMPs provide for systems that assure proper design, monitoring, and control of manufacturing processes and facilities.[2] CGMPs set a minimum threshold that sites must achieve in order to be allowed to supply the U.S. marketplace. The site inspection score is based on the classification of FDA Drug Quality Inspections[3] conducted over the last 10 years.[4]

A higher inspection score represents better compliance with CGMPs. Other quality indicators, such as drug quality defect reports submitted to the FDA, reveal additional information that contributes to a more complete picture of the overall quality of pharmaceutical manufacturing.

Many observations about the State of Pharmaceutical Quality will not change significantly from year-to-year. In this report, we generally focus on observations that either were not covered in last year's report or were associated with new developments and trends in FY2019. The

1 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.

2 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).

3 Following Compliance Program 7356.002 — Drug Manufacturing Inspections (PAC 56002 series)

4 The period covered by this report is FY2009 through FY2018. 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 FDA 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.

FDA uses the State of Pharmaceutical Quality, in part, to inform regulatory decision-making and surveillance activities. We provide this information publicly so our external stakeholders can better understand the quality of the U.S. drug supply. Although the FDA has rich sources of quality data, we want to provide this public information to introduce more transparency for patients and consumers. Where there are actionable findings from this report, we want to engage the pharmaceutical manufacturing industry in a further commitment to quality. It is our public health mission to assure patients and consumers have access to safe, effective, *quality* medicines.

Manufacturing Site Demographics

Manufacturing site demographics reflect the distribution and diversity of site characteristics across the pharmaceutical industry. The FDA's catalog of drug manufacturing sites is dynamic as sites are continually added and removed. At the end of FY2019 there were 4,273 drug manufacturing sites in the catalog, as compared to 4,676 at the end of FY2018 (Figure 1).[5] This was a net 8.6% decrease in the total number of sites despite the addition of 382 sites, as many sites were also removed. Of those added, 250 sites had already been in the catalog with a previous FDA inspection. The overall change in the FY2019 number of drug manufacturing sites was largely driven by a net decrease of 10.3% in sites that do not manufacture FDA-approved application products ("No Application"). This "No Application" sector includes over-the-counter (OTC) monograph, unapproved drugs[6], and homeopathic drug products. Registered sites performing only packaging and labeling operations also decreased substantially in FY2019 (13.4%). These decreases in site counts may be indicative of industry trends toward consolidation and/or the result of the FDA's increasing efforts to more accurately curate facilities[7] in the U.S. drug supply chain.

Manufacturing Site Compliance

In 2019, FDA investigators performed 1,258 Drug Quality Surveillance Inspections (Figure 2).[8] These inspections are one of the fundamental ways the FDA monitors conformance to CGMP requirements and identifies quality problems and adverse trends at facilities that may require

Figure 1.
Drug Manufacturing Site Catalog at the End of FY19

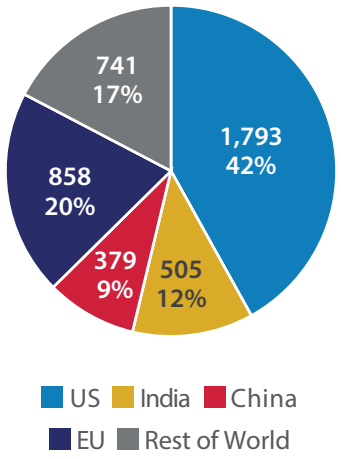
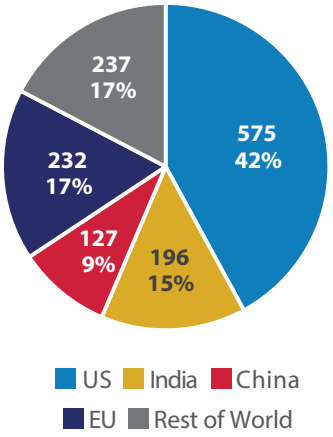


Figure 2.
Drug Manufacturing Site Inspections Including Those Reviewed and Classified Under the MRA in FY19



5 The site catalog is an inventory of registered human drug manufacturers in US commerce. Most medical gas and pharmaceutical outsourcing facilities are omitted from this analysis.

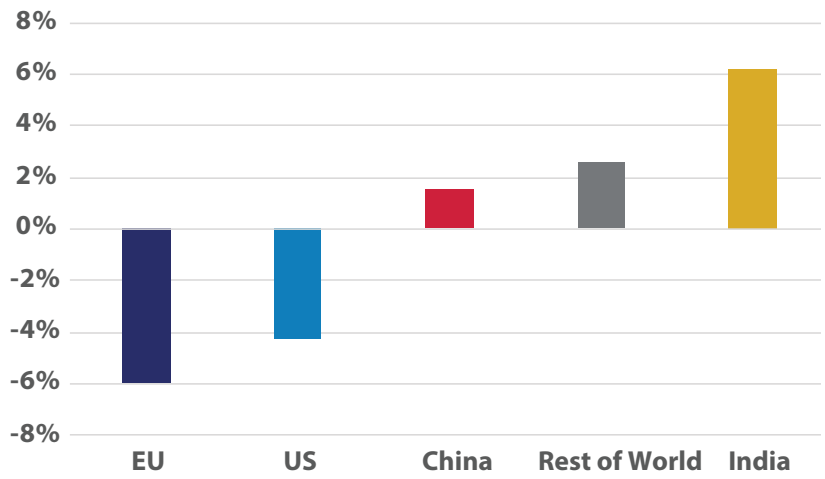
6 https://www.fda.gov/drugs/enforcement-activities-fda/unapproved-drugs

7 These include prioritizing uninspected inventory, continuing to refine and integrate IT tools to help detect data quality issues, and using other surveillance tools.

8 PAC 56002 series as relevant.

mitigation. The FDA's Mutual Recognition Agreement (MRA)[9] with the European Union (EU) allows regulators to recognize reports from their counterparts' drug quality surveillance inspections conducted within their own borders. In addition to the inspections performed by FDA inspectors, there were 109 drug quality inspections performed by EU investigators that were reviewed and classified by the FDA under the MRA. The collective inspections by FDA investigators and EU investigators under the MRA provided coverage of 32% of the total global site catalog in FY2019. The growing ability to rely on the MRA enables the FDA to allocate its resources elsewhere by conducting an increasing percentage of inspections in other parts of the world (Figure 3).

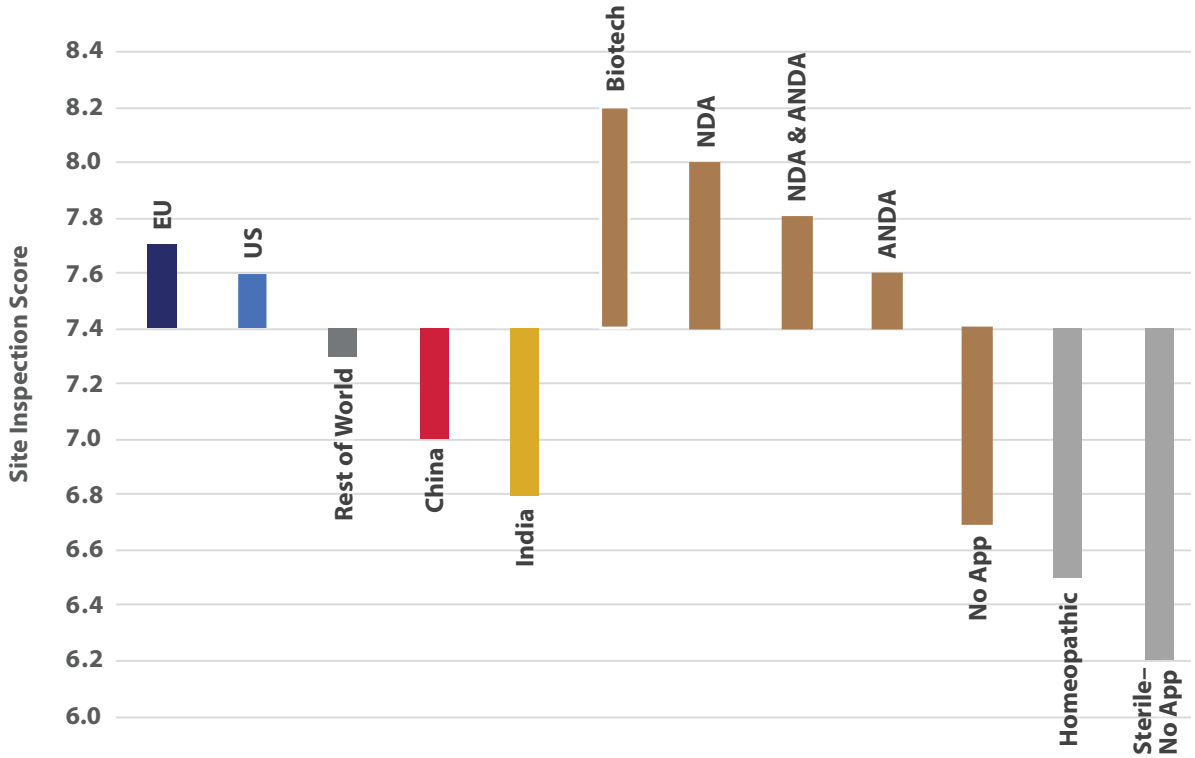
Figure 3.
Change in Percentage of Annual Drug Manufacturing Site Inspections Performed by FDA Over Two-Year Period (FY17-19)



9 https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra

The site inspection score provides one measure of a site's compliance to CGMP regulations. The average score of all sites in FY2019 was 7.4, not significantly different than FY2018 (7.5). Still, there are some differences between geographic regions, application types, and manufacturing sectors (Figure 4). For example, the average scores for sites in the EU (7.7) and U.S. (7.6) are statistically higher than the global average, while the average score for sites in China (7.0), India (6.8), and Latin America (6.8) are statistically lower than the global average. All of these scores indicate an acceptable level of compliance to CGMPs[10] on average. When considering application types, the No Application sector (6.7) significantly brings down the global average. Within this No Application sector, sites making homeopathic products (6.5) and OTC sterile products (6.2) scored lowest.

Figure 4.
Site Inspections Scores for Geographic Regions, Application Types, and Manufacturing Sectors

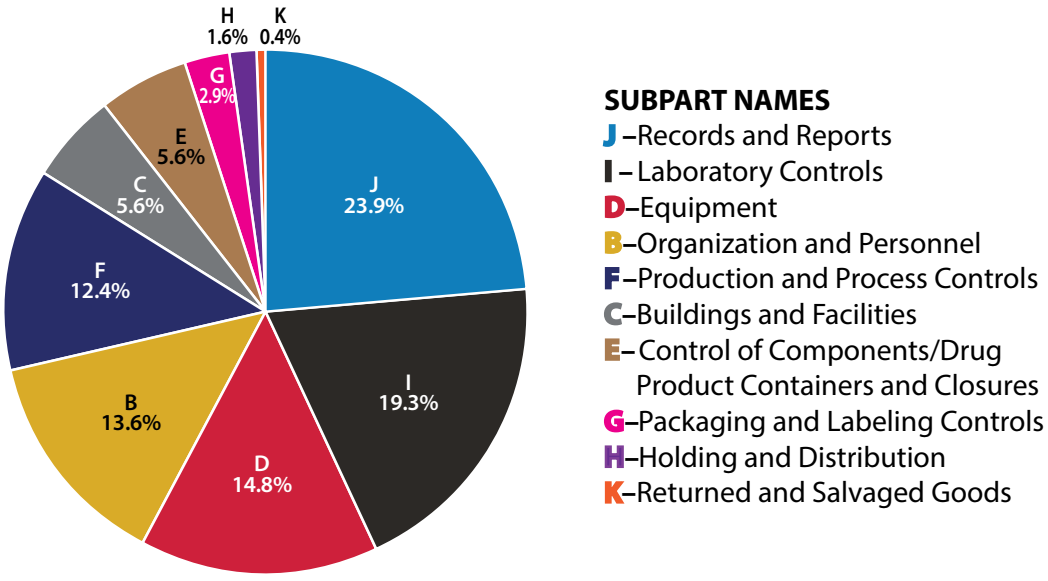


10 As communicated in the FMD-145 letter to sites post inspection closure. https://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm056246.htm

Inspection Findings

When CGMP violations are observed on an inspection, they are noted on Form FDA 483 referencing the specific violation to the Code of Federal Regulation (CFR).[11] A data mining process analyzed and grouped a subset of FY2019 observations by CFR sub-part and section. Most observations (58%) were related to sub-parts covering Records and Reports, Laboratory Controls, and Equipment (i.e., subparts J, I, and D; Figure 5). CFR Subparts are further partitioned into detailed sections which can be cited on Form FDA 483 since they describe the specific CGMP requirements for the pharmaceutical industry. The most cited sections were related to 211.192 (Production Record Review, 8%), 211.22 (Responsibilities of the Quality Unit, 8%), and 211.160 (General Requirements / Scientifically Sound Laboratory Controls, 5%). These sections represent some of the key elements of an effective Pharmaceutical Quality System. These are potential areas of focus for manufacturing facility management to improve overall pharmaceutical quality and inspectional outcomes.

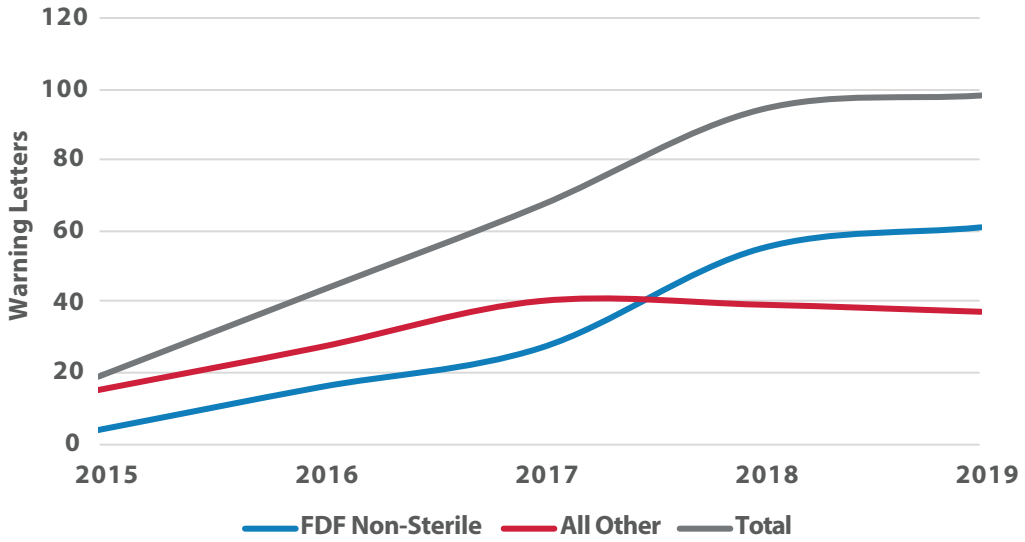
Figure 5. 21 CFR 211 Subpart Citations in FY19



11 These documented observations use specific citations from the Code of Federal Regulations, 21 CFR 211 Subparts B through K (API inspections result in observations, not CFR citations).

A possible outcome of a problematic inspection finding is the issuance of a Warning Letter. The number of Warning Letters issued by the FDA has increased significantly since 2015, driven largely by Warning Letters issued to sites manufacturing non-sterile finished dosage products (Figure 6). Notably, sites manufacturing products for the No Application sector accounted for over 70% of all Warning Letters issued in both FY2018 and FY2019. This finding correlates with the lower site inspection score for this sector. As expected, the observation that facilities inspected for the first time tend to have worse inspection outcomes (6.0) than those inspected previously (7.2) continues to hold in FY2019. This observation emphasizes the importance of FDA efforts to prioritize and inspect sites newly engaged in manufacturing for the U.S. market.

Figure 6.
Warning Letters Issued FY15–19



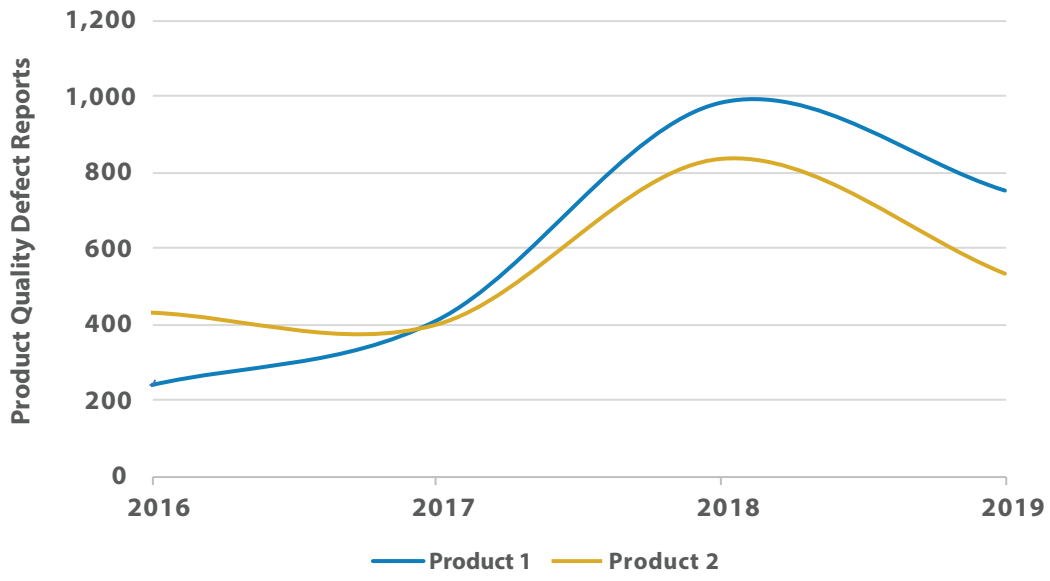
Drug Product Quality

A quality drug product is safe and effective with every dose, free of contamination and defects. The FDA receives industry, healthcare provider, and consumer feedback on product quality via product quality defect reports. These include, but are not limited to, Field Alert Reports (FARs), MedWatch Reports (MWs), and Biological Product Deviation Reports (BPDRs).

Immunological products continue to be significantly overrepresented in product quality defect reports. Though these products represent only 2.1% of all approved applications, they account for 19% of all product quality defects reports. Two popular immunological products, considered

combination products[12], account for most of the product quality defects reported for this class. Many of these issues relate to the "device" constituent part. Notably, both immunological products showed a decrease in the number of reports submitted beginning in early FY2018 and continuing into FY2019 (Figure 7). This trend could be due to several FDA-approved changes to the devices, labeling, and assembly sites.

Figure 7.
Product Quality Defect Reports for the Top 2 Immunological Products from FY16–19



Applicants are required to submit FARs to the FDA within three days of receiving information concerning significant quality problems[13] with a distributed drug product. MWs that concern possible defects are voluntarily submitted to the FDA by consumers and healthcare providers. We investigated the correlation between MWs and FARS as it would stand to reason that when patients, consumers, and healthcare providers submit several MWs for the same drug and same defect issue, these issues could also be reported by the manufacturer in FARs to the FDA. In FY2019, 145 applications (69% Abbreviated New Drug Applications (ANDAs) and 31% New Drug Applications (NDAs)) had more than eight MWs with identifiable trends and no submitted FARs. This observation could indicate an actionable area for both manufacturers and the FDA to explore in order to better understand signals of potential quality issues and deficiencies in pharmaceutical quality systems.

12 https://www.fda.gov/combination-products/about-combination-products/combination-product-definition-combination-product-types

13 As discussed in sections 1a and 1c in the published FAR Guidance: https://www.fda.gov/media/114549/download

Drug Sampling & Testing

The FDA has a long-standing program to regularly sample and test marketed drugs for conformance to specifications. In June 2018, the FDA received notification of the unexpected presence of N–nitrosodimethylamine (NDMA) impurities in some approved drugs used to treat high blood pressure and heart failure. These drugs—including valsartan, losartan, irbesartan, and olmesartan—are Angiotensin II Receptor Blockers (ARBs) widely used in the U.S. The FDA rapidly developed a sensitive method to detect and quantify NDMA and other nitrosamine impurities at very low levels in ARBs. In FY2019, 734 drug samples, including ARB samples, were analyzed in FDA labs. Results of these tests prompted the FDA to request several ARB recalls to protect public health which created a shortage of valsartan and losartan.

In July 2019, NDMA was found in ranitidine, a drug approved to prevent and relieve heartburn associated with acid ingestion and sour stomach. FDA scientists quickly published a testing protocol that could be used to detect and quantify NDMA impurities in ranitidine. In total, FDA scientists developed testing methods that are capable of measuring eight nitrosamine impurities in ten different drug products. After initial testing, the FDA issued a public statement[14] on ranitidine, alerting patients and healthcare professionals that some ranitidine drug products contained NDMA impurities at low levels. Many companies initiated voluntary recalls. After a thorough scientific investigation, the FDA determined that NDMA could form in ranitidine beyond an acceptable daily intake limit over time during the labeled shelf-life or if exposed to temperatures higher than ambient. With this scientific evidence, the FDA recently requested a market withdrawal of all ranitidine products.[15]

To better understand the presence of nitrosamines in the U.S. drug supply chain, the FDA dispatched investigators to 23 manufacturing sites around the world in FY2019. As there are multiple root causes[16] of these impurities in multiple drugs,[17] FDA subject matter experts participated in several of these inspections to thoroughly assess site and process risks related to the formation of nitrosamines based on their assessment of the regulatory submissions. Most of these inspections

14 https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-ndma-zantac-ranitidine

15 https://www.fda.gov/news-events/press-announcements/fda-requests-removal-all-ranitidine-products-zantac-market

16 https://www.fda.gov/media/122643/download

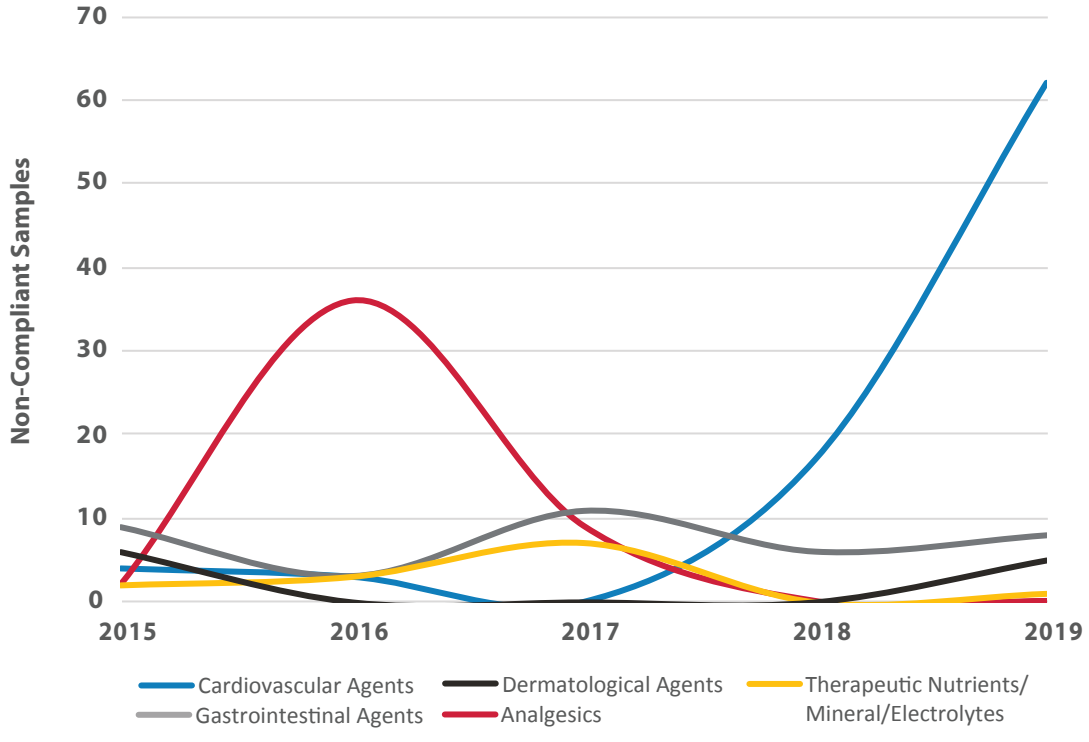
17 https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications

(61%) had Official Action Indicated (OAI)[18] outcomes, contributing to the high rate of non-compliant inspections in India in FY2019 compared to the overall average across all regions evaluated.

When looking at sites that manufacture all products sampled and tested by the FDA—related to nitrosamine investigations or otherwise—those manufacturing products deviating from acceptable standards had a lower site inspection score (4.9) than those that did not deviate from acceptable standards (6.4). This disparity is expected as many collected samples related to specific existing concerns. At minimum this indicates that inspection findings and product testing practices represent complimentary indicators of product quality. As a corollary, the 10 sites with the highest number of overall recalls collectively had a lower than average site inspection score (5.0).

Year-to-year data on sampled products with non-compliant testing results are indicative of the major trends negatively impacting product

Figure 8.
Non-Compliant Testing Results of Sampled Products
FY15–19



18 https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions#classification

quality (Figure 8). For example, an increase in non-compliant gastrointestinal agents was observed in FY2016–FY2017 due to docusate sodium samples analyzed in response to a multi-state outbreak of Burkholderia cepacia microbial contamination. An increase in non-compliant cardiovascular agents was observed in FY2018–FY2019 in response to the presence of nitrosamine impurities in these products. The most recalled drug class in FY2019 was cardiovascular agents. Of recalls in this class, 52% were related to the ARB nitrosamine impurities.

Engaging Stakeholders in a Commitment to Quality

The FDA uses the findings detailed in this report, in part, to identify better ways to engage stakeholders and drive improvements in the overall quality of pharmaceuticals and in manufacturing facilities. Advances in manufacturing and quality management are needed to continue assuring a reliable supply of safe, effective, quality drugs for U.S. patients. In this era of globalization, engaging stakeholders is essential to furthering the global commitment to pharmaceutical quality. The FDA's stakeholder engagements include:

- The FDA planned a public Pharmaceutical Quality Symposium,[19] which was held in October 2019 to discuss the latest developments in pharmaceutical quality. FDA experts provided case studies to illustrate the most effective ways to address quality issues and interact with the agency. Over 2,200 attendees participated online or in person, including 32% from outside the U.S.

- In FY2019, the FDA prepared the Drug Shortages: Root Causes and Potential Solutions report[20], which was released to the public in October 2019. The report identifies root causes for drug shortages including that the market does not recognize and reward manufacturers for "mature quality systems" that focus on continual improvement and early detection of supply chain issues. The report also recommends enduring solutions including developing a rating system to incentivize drug manufacturers to invest in quality management maturity for their facilities. Currently stakeholders generally rely too heavily on inspection classifications to gauge a site's state of quality, perhaps because it is among the few quality data publicly available.

19 All materials and recordings are available online: https://sbiaevents.com/pqs2019/

20 https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions

- The FDA launched the New Inspection Protocol Project (NIPP)[21] for sterile drug manufacturing facility inspections in October 2018. NIPP uses standardized electronic inspection protocols for FDA investigators to collect data in a structured manner for more consistent oversight of facilities and more efficient analysis of findings. The protocols also include questions related to quality culture observed in facilities and may incorporate questions which will help the FDA evaluate compliance and quality management maturity in the future.

- In February 2019, the FDA launched a pilot program on established conditions[22] (ECs) to gain experience receiving, assessing, and engaging with applicants on this new topic. ECs are the descriptions in an approved application that assure process performance and product quality that, if changed after approval, must be reported to the FDA.[23] Nine participants were accepted into the pilot to provide a better understanding of which elements of applications constitute ECs. This program should allow for a more efficient regulatory strategy after application approval.[24]

- The FDA designed a Site Engagement Program (SEP)[25] to address facilities with a drug product vulnerable to shortage. The goal of the SEP is to mitigate any potential quality issues that could lead to a drug shortage. If needed, this can also initiate a dialogue to collaborate on emerging quality issues beyond shortages. Participants in the FY2019 SEP pilot engaged in collaborative discussions with the FDA about process controls, metrics, quality management practices, and FDA quality data.

- The FDA's Emerging Technology Program[26] promotes the adoption of innovative approaches to pharmaceutical product design and manufacturing. Through the program, industry representatives can meet with the FDA to discuss potential technical and regulatory issues prior to filing a regulatory submission. Continuous manufacturing is an important emerging technology

21 https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-steps-strengthen-and-modernize-agencys-oversight

22 https://www.federalregister.gov/documents/2019/02/15/2019-02364/established-conditions-pilot-program

23 https://www.fda.gov/media/113483/download

24 ICH Q12, Technical and regulatory considerations for pharmaceutical product lifecycle management

25 https://www.fda.gov/drugs/pharmaceutical-quality-resources/site-engagement-program-sep

26 https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm523228.htm

that eliminates breaks between steps during drug manufacturing to reduce errors related to the stops and starts of a process. In FY2019 significant work went into the eventual approvals of three applications as part of the Emerging Technology Program, including a continuous manufacturing process for the active ingredient used in an inhaler. This continuous manufacturing process was the first ever approved for making an active ingredient.

- In FY2019, the FDA worked collaboratively with international regulators to compare validated testing methods for nitrosamine impurities and share inspection information. Among other positive outcomes, FDA established science-based acceptable daily intake levels for nitrosamine impurities. International knowledge-sharing enabled a more effective and scientifically robust response to the problem. Such interactions are key to the future of global quality surveillance.

As part of the FDA's engagement with stakeholders, we provide this annual public report on the State of Pharmaceutical Quality for CDER-regulated drugs legally marketed in the U.S. Though this annual report strives to provide a panoramic view of the pharmaceutical manufacturing industry, FDA oversight of quality is multi-faceted. Many approaches and factors are important in determining the State of Pharmaceutical Quality. This report demonstrates that regulatory tools do not stop at the monograph or drug application approval process. Regular inspections of drug manufacturing facilities ensure compliance with manufacturing requirements and focus on the facilities and drugs with the potential to be most problematic, based on scientific expertise. The FDA regularly tests products on the market in our state-of-the-art laboratories to confirm they meet quality standards. If there are reports of defects or recalls, the FDA monitors manufacturers to ensure they fix the problems in a timely manner. Surveillance programs identify possible problems so manufacturers can address them before the problems cause potential harm to patients. No regulatory tool is sufficient on its own, but when used collectively and inclusive of a surveillance program, they provide good confidence in the quality of the U.S. drug supply.

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