

REPORT ON THE STATE OF PHARMACEUTICAL QUALITY

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF PHARMACEUTICAL QUALITY

DATED MAY 13, 2019

Introduction

The Office of Pharmaceutical Quality (OPQ) in the Center for Drug Evaluation and Research (CDER) in the U.S. Food and Drug Administration (FDA) monitors the quality of CDER-regulated drugs legally marketed in the U.S. A quality drug is consistently safe and effective, free of contamination and defects. Patients and consumers expect quality drugs with every dose they take. The ‘State of Pharmaceutical Quality’ is a yearly snapshot of the pharmaceutical manufacturing industry’s ability to deliver quality pharmaceutical products.⁵

We gauge this objective assessment using quality indicators based on available FDA drug product-specific and manufacturing site-specific data (Table 1).⁶ This information is specific to drugs marketed in the U.S. and to registered human drug manufacturers⁷ engaged in U.S. interstate commerce (medical gas and pharmaceutical compounding and outsourcing facilities are omitted). We do include data from foreign agency site inspections recognized under the Mutual Recognition Agreement⁸. Drug product performance data were drawn from application submission data and product quality defect reports which capture industry, healthcare provider, and consumer feedback. To the extent it is informative, we evaluated manufacturing site data by

Drug Product Data	Manufacturing Site Data
<p>Recalls</p> <p>Product Quality Defect Reports Field Alert Reports MedWatch Reports Consumer Complaints Biotechnology Product Deviation Reports</p> <p>Drug Shortages</p> <p>Application Stats Submissions Refuse-to-Receive Refuse-to-File Approvals Complete Responses</p>	<p>Geographical Regions U.S., European Union, India, China, Canada, Latin America, Rest of World¹</p> <p>Inspectional Outcomes</p> <p>Application Type Manufactured Biotech² Biologics License Application (BLA) New Drug Application (NDA) Abbreviated New Drug Application (ANDA) NDA & ANDA No Application³</p> <p>USP Therapeutic Category Manufactured⁴</p> <p>Manufacturing Sector Biotech Biotech Analysis Sterile PET: Positron Emitting Tomography products Non-sterile Finished Dosage Form Non-sterile Active Pharmaceutical Ingredients Analysis Primary Packaging and Labeling</p>

Table 1. Key drug product and manufacturing site data used to determine the State of Pharmaceutical Quality in the U.S.

¹ Rest of World contains all countries not included in the other regions.

² Sites having one or more FDA-approved biotech application products - and possibly other types of applications

³ Sites not flagged as having any FDA-approved application products (e.g., OTC monograph, unapproved, homeopaths)

⁴ [FDAAA Reference for USPTC](#)

⁵ This report is an analysis of fiscal year 2018, the latest complete fiscal year.

⁶ The analyses use FDA data from fiscal years 2009 – 2018 for inspection classification outcomes, fiscal years 2013-2018 for recalls, fiscal years 2016-2018 for product quality defects, fiscal years 2017-2018 for the Site Catalog, and fiscal year 2018 for the Product Catalog.

⁷ Manufacturer is defined as anyone engaged in manufacturing, preparing, propagating, compounding, processing, packaging, repackaging, or labeling of a drug

⁸ <https://www.fda.gov/internationalprograms/agreements/ucm598735.htm>

geographic region, therapeutic category, application type, and manufacturing sector. We use a site inspection score, on a scale of 1 to 10, as a measure of a site's compliance to Current Good Manufacturing Practice (CGMP) regulations based on the classification of FDA Drug Quality Inspections⁹ conducted over the last 10 years.¹⁰ Compliance with CGMPs provides assurance the drug product consistently meets the intended specifications. This inspection score is only used for comparison purposes to look for trends and target resources. In short, a higher inspection score represents better compliance with respect to CGMPs.

OPQ uses the State of Pharmaceutical Quality to, among other things, inform regulatory decision-making and surveillance activities. OPQ also provides this information to internal FDA business partners to inform their operations. We are now providing this information publicly so our external stakeholders can better understand the quality of the U.S. drug supply, we can better engage the pharmaceutical manufacturing industry in a commitment to quality, and we can better inform patients and consumers. 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 manufacturing site characteristics across the industry. Here they consider application type, manufacturing sector, and geographic region. Year-to-year demographic trends, including significant shifts in the number and types of sites, can yield important information about the State of Pharmaceutical Quality. At the end of FY2018 there were 4,676 drug manufacturing sites in our site catalog.¹¹ 42% of those do not manufacture application products for the U.S. market (i.e., they are the “No Application” sector, which includes over the counter (OTC) monograph, unapproved¹² and homeopathic products). The remaining 58% of sites manufacture one or more application products.¹³ Of the sites manufacturing application products, a large percentage (46%) manufactures products of both New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs) (Figure 1).

In FY2018, the five countries with the most drug manufacturing sites were the United States, India, China, South Korea, and Germany (Figure 2). Volatility in the site catalog (i.e., removing or adding a large portion of the site inventory year-to-year) can indicate a lack of understanding of the FDA's registration and listing requirements. It may indicate an opportunity for outreach and training. The FDA purged a large number of sites from the catalog located in India, China, and especially South Korea in FY2018 because they did not have product in the U.S. market and did not need to be FDA registered. For example, 110 sites in South

⁹ Following Compliance Program 7356.002 – Drug Manufacturing Inspections (PAC 56002 series)

¹⁰ i.e., FY2009 to 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.

¹¹ The site catalog is an inventory of registered human drug manufacturers engaged in US interstate commerce. Medical Gas, pharmaceutical compounding and outsourcing facilities are omitted.

¹² Unapproved drugs are those marketed without FDA approval:

<https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/enforcementactivitiesbyfda/selectedenforcementactionsonunapproveddrugs/default.htm>

¹³ In this report, ‘product’ refers to both drug product and drug substance/active pharmaceutical ingredients (API).

Korea (~50% of that country's total number of sites) were removed from the FDA inventory during FY2018 indicating a lack of understanding of the registration and listing requirements.

Tracking volatility is also useful to detect potential shifts in the market. For example, there was a 32.8% net increase in registration of Packaging & Labeling sites in FY2018 (Figure 3), potentially indicating an increase in outsourcing certain operations, which can increase the complexity of the supply chain. Complex supply chains require additional oversight to maintain the same level of control over quality. Similarly, there was a 29.7% net increase in the registration of "No Application" sites (Figure 4). This highlights the importance of post-market surveillance of these sites as the products and sites do not receive pre-market review.

Grouping sites based on USP Therapeutic Category shows similar trends across the countries that supply the majority of drugs to the U.S. market. In the U.S., the three sites with the most individual listed products¹⁴ account for 9.5% (3,346) of *all products* listed by U.S. sites (35,367) (Figure 5). Two of these sites make homeopathic products. This observation is similar for China and India, where the three sites in those countries with the most individual listed products account for 11.2% (of 5,734 total products) and 12% (of 15,245 total products), respectively. Indian sites also make, on average, over 2.5 times more products per site than Chinese sites, though this does not indicate the volume of production at the sites, nor the active status, only the variety of products registered to be manufactured for the U.S. market. Ultimately, these data convey insight into how a small number of sites are responsible for a large number of listed products. The number of products listed at a site is one of the risk factors in prioritizing resources for surveillance inspections.

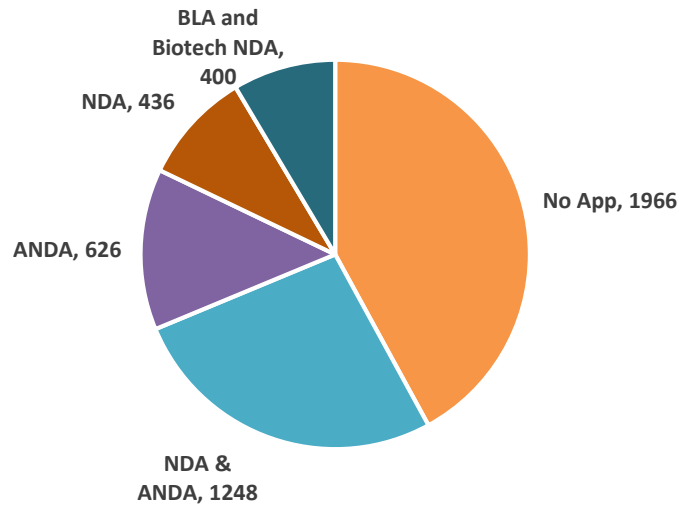


Figure 1. Drug manufacturing sites that manufacture products for the U.S. market by application type for FY2018

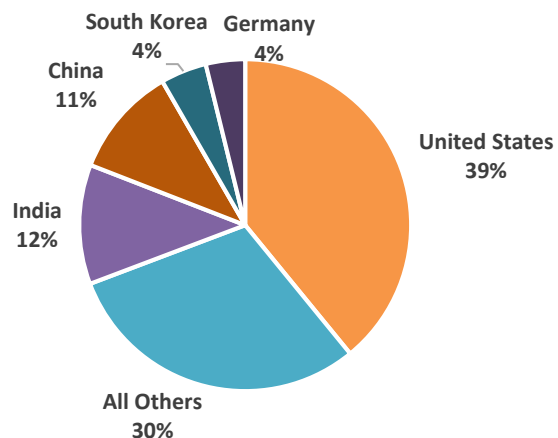


Figure 2. All drug manufacturing sites for the U.S. market by country for FY2018

¹⁴ Individual products manufactured by the site intended for the U.S. market as listed in the Electronic Drug Registration and Listing System (eDRLS)

Manufacturing Site Compliance

One of the key indicators of the State of Pharmaceutical Quality is the Drug Quality Inspection classification history of drug manufacturing sites.¹⁵ Surveillance inspections are one of the fundamental ways that the FDA monitors conformance to CGMP requirements and identifies quality problems and adverse trends at facilities so that the FDA can develop strategies to mitigate them. In FY2018 FDA investigators performed 1,346 Drug Quality Inspections¹⁶ providing coverage to about 29% of the overall site catalog.¹⁷ Of those inspections, the majority were performed outside of the U.S. (Figure 6).

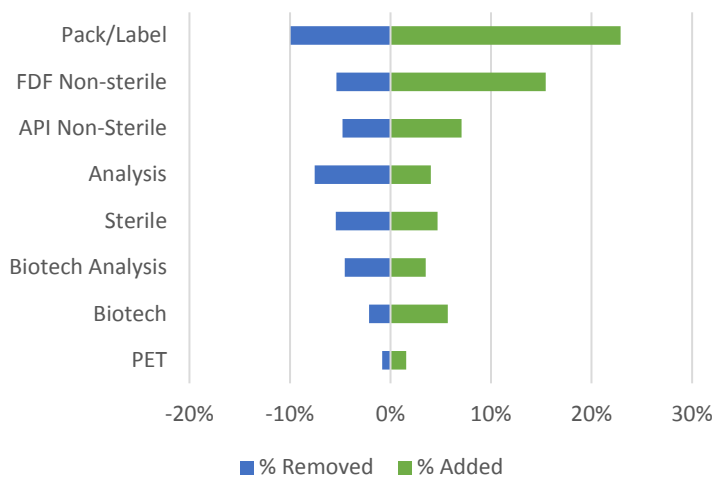


Figure 3. Overall manufacturing sector change in the site catalog from Oct 2017 to Oct 2018

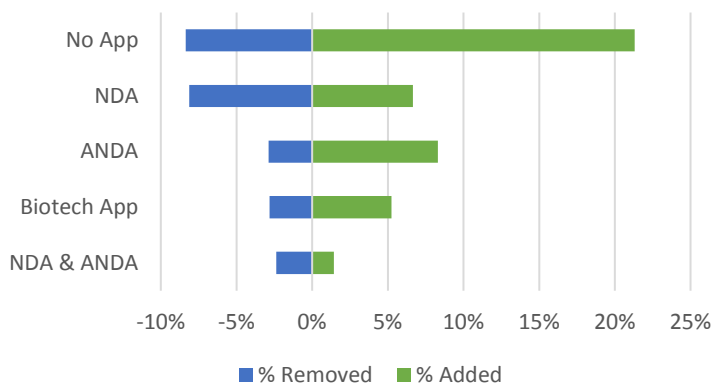


Figure 4. Overall application type change in the site catalog from Oct 2017 to Oct 2018

When considering manufacturing sites, the site inspection score is used to look for trends. The average score of all sites in FY2018 was 7.5. No trends can yet be seen for the inspection score of the overall industry¹⁸, as the score did not change significantly¹⁹ from FY2017 (7.7) to FY2018. Using this score, we do see some statistical differences between geographic regions, application types, and manufacturing sectors. For example, the score for sites in the EU (7.9) and U.S. (7.7) are higher than average, while sites in China (7.0), India (7.0), and the Rest of the World (7.2) are lower than average. Some sector and region pairs also outperform others. For instance, the score for ANDA sites in Europe (8.2) is higher than that of ANDA sites in India (7.0). These scores indicate an acceptable level of compliance to CGMPs²⁰ on average. Still, some trends highlight opportunities for increased outreach to, surveillance of, and enforcement of certain markets.

¹⁵ Site specific analyses are based on surveillance inspections which cover manufacturing process systems

¹⁶ PAC 56002 series

¹⁷ Excluding medical gas

¹⁸ Site inspection scores were first calculated in FY2017

¹⁹ All significance tests calculated at 95% confidence interval

²⁰ As communicated in the FMD-145 letter to sites post inspection closure.

<https://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm056246.htm>

When looking at application types, the average inspection score for sites that make application products (7.8) is statistically higher than for “No Application” sites (6.6). When combining industry and manufacturing sectors, sites making sterile non-application products are one of the lowest performing groups (6.7). Further statistical analysis shows that “No Application” sites consistently and significantly underperform regardless of geographic region. This again highlights the importance of post-market surveillance of these sites.

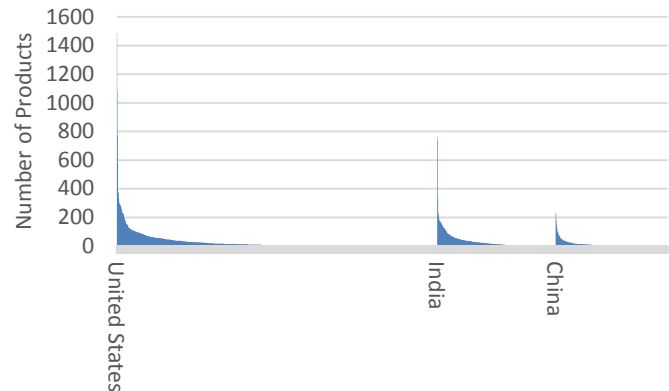


Figure 5. The number of marketed products for each site in the U.S., India, and China

There has been a concerted effort to reduce the number of drug manufacturing sites that have never been inspected.²¹ The inspection score of sites receiving an initial inspection (6.0) is much lower than that of sites that have had two or more routine inspections (7.6). This observation may be due to the fact that many of the sites recently receiving initial inspections are smaller sites producing non-application products that may be less familiar with CGMPs and U.S. regulatory requirements. These site compliance trends highlight the importance of engaging firms that are new in manufacturing for the U.S. market to make sure they understand the requirements.

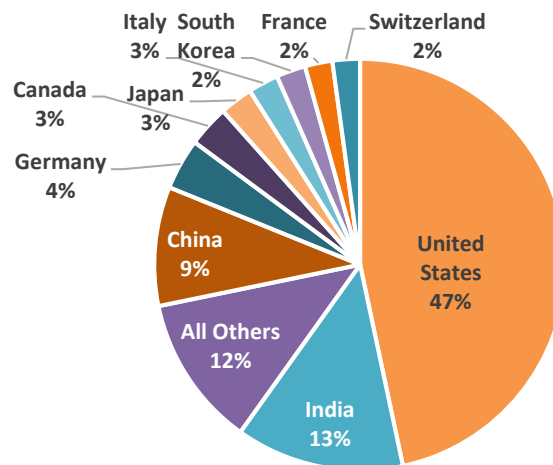


Figure 6. Drug quality inspections for manufacturing sites in FY2018 by country

Drug Product Quality

Providing a quality drug product means manufacturing every dose to be safe and effective, free of contamination and defects. To examine drug product quality, we use industry, healthcare provider, and consumer feedback from product quality defect reports received by the FDA. These comprise Consumer Complaints, Field Alert Reports (FARs), quality-related MedWatch Reports, and Biotechnology Product Deviation Reports (BPDRs). We also examine Center-classified recalls and drug shortages. These analyses include ~34,000 total reports received from FY2016-2018 and focus mainly on application products, as >95% of all such reports are for application products. In addition, FARs only apply to NDAs

²¹ <https://pink.pharmaintelligence.informa.com/PS123275/Warning-Letters-Mount-As-FDA-Completes-Initial-Inspections-Of-UnderTheRadar-Facilities>
www.fda.gov

and ANDAs, while BPDRs only apply to Biologics License Applications (BLAs). In both cases, reports are required to be submitted by the applicant/license holders. Only MedWatch and Consumer Complaints can apply to any product. These reports are voluntarily submitted to the FDA by consumers and healthcare providers.

When looking at therapeutic categories we see that while immunological products only represent 1.4% of all applications, they account for 17% of *all product quality defects* reported (Figure 7). The majority of these reports are due to complaints for two products with product quality issues. Notably, the average inspection score for sites making immunological products is 7.7, which is not significantly different than the FY2018 average for all sites.

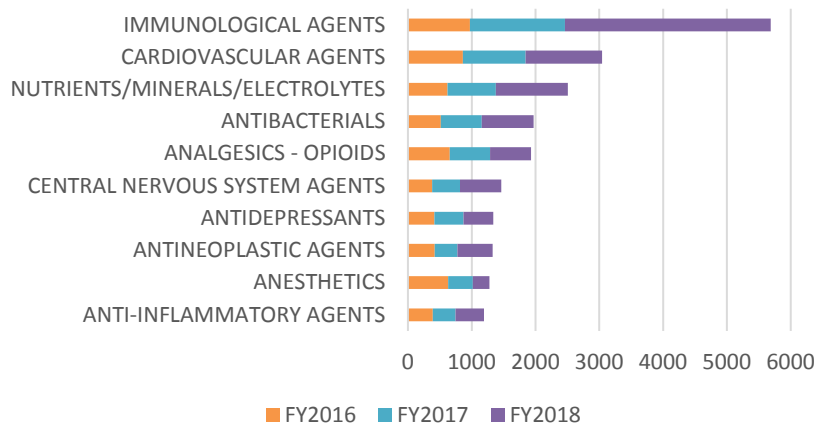


Figure 7. Product Quality Defect counts by USPTC for the past three years

The rates of defect reports were statistically different between ANDA and NDA products. When looking at all applications named in at least one such report in FY2018, NDAs had statistically higher rates of both quality related MedWatch reports (5.8 per NDA) and FARS (4.1 per NDA) as compared to ANDAs (3.4 and 1.8, respectively). This analysis did not account for whether an innovator product had a generic available, or the number of generics available. Overreporting by NDAs for MedWatch reports may be due to incorrect reporting of generic products by brand name. Improved compliance with FAR reporting is expected due to the guidance issued last year.²²

Recall rates have generally held steady over the past five years and appear specific to incidents. The recent nitrosamine impurities identified in Angiotensin II Receptor Blockers (ARBs) led to a high rate of *Cardiovascular Agent* product recalls in FY2018. 58% of the cardiovascular recalls are related to the ARB nitrosamine impurities. The overall inspection score in FY2018 for all sites manufacturing ARBs is 7.4, which is not significantly different than the FY2018 average for all sites. Note that this average does not include recent FY2019 inspections at some of these sites prompted by positive findings of nitrosamine impurities.

The average inspection score for sites involved in recalls (5.9) is significantly lower than average²³ highlighting the importance of CGMPs in assuring product quality on the market. Over 41% of recalls over the past five years are associated with sites historically not subject to routine surveillance inspections such

²² <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM613753.pdf>

²³ Recalls for CDER-regulated products, excluding compounded products and unapproved drugs (i.e. active drug substances found in dietary supplements).

as re-packers. This observation shows the value of routine inspections and the need for continued evaluation of manufacturing site risk and resource allocation. Over the last five years, 1,002 (27%) recalls are attributed to just two sites that are not in the catalog: an active pharmaceutical ingredient re-packer that had issues with cross-contamination and a secondary re-packer that had issues with labeling mix-ups.

Drug shortages are a prime concern for consumers and the FDA.²⁴ Patients and consumers need access to safe, effective, quality medicine. In general, the number of new drug shortages has declined since 2011, owing to the work of the FDA, industry, and other stakeholders. Despite these efforts, we still see shortages of medically necessary products. In FY2018, 64% of all drugs currently in shortage are sterile injectables (Figure 8) and 63% of all drugs currently in shortage are ANDA products. Quality problems at manufacturing sites are one factor that can cause supply disruptions. Given that the inspection scores of Finished Dosage Form non-sterile (7.1) and sterile sites (7.2) are statistically lower than the average, there may be opportunities to better identify sites and products at risk to potentially mitigate shortages through proactive engagement (see FDA’s engagement programs below).

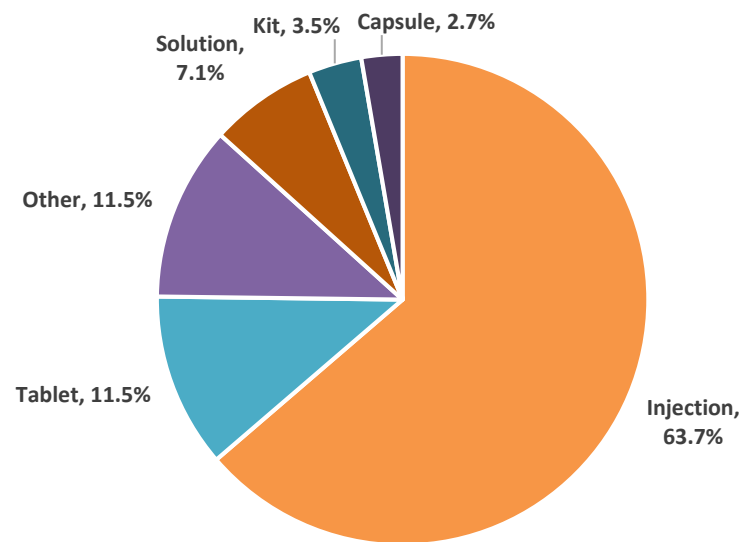


Figure 8. Shortage products by dosage form for FY2018

Drug Product Application Quality

Another important indicator of the overall State of Quality is the quality of drug product applications sent to the FDA, which may reflect a firm’s quality culture across its operations. The FDA has processes to refuse poor-quality submissions. We examined application submissions received in FY2018²⁵ to

²⁴ <https://www.fda.gov/drugs/drugsafety/drugshortages/default.htm>

²⁵ FY2018 applications include any filing type submitted in FY2018 (e.g., original NDAs, ANDAs, and BLAs; supplements to originals, and annual reports, but exclude drug master files (DMFs))

determine active status. Three years of original and supplement applications were reviewed for received-by status. Refuse-to-File (RTF)²⁶ and Refuse-to-Receive (RTR)²⁷ rates were compared between ANDAs, NDAs, and BLAs. ANDAs have a higher refusal rate (17%) than NDAs (7%) and BLAs (<1%). Note that the NDA and ANDA filing processes are different, which was not factored into this analysis. In FY2018, there was a significant increase in the NDA refusal rate (up from 1% in FY2017). Meanwhile the RTR/RTF rate for original ANDAs generally decreased since the issuance of related guidance in 2016 and continued outreach by the FDA (Figure 9).

Another significant observation was the large volume of submissions by a small group of applicants. For example, there are over 1,000 different sponsors of original and supplement submissions yet just the top ten applicants by volume of submissions account for 20% of all submissions. Further insight into submission quality is gained by looking at submission outcomes for these same ten applicants in FY2018 (Figure 10)²⁸. The highest volume applicants have a higher rate of products that are *not* approved (i.e., Complete Response outcomes). The top two applicants have more Complete Responses than approvals. This highlights the need to for applicants to focus on the quality of submission regardless of volume.

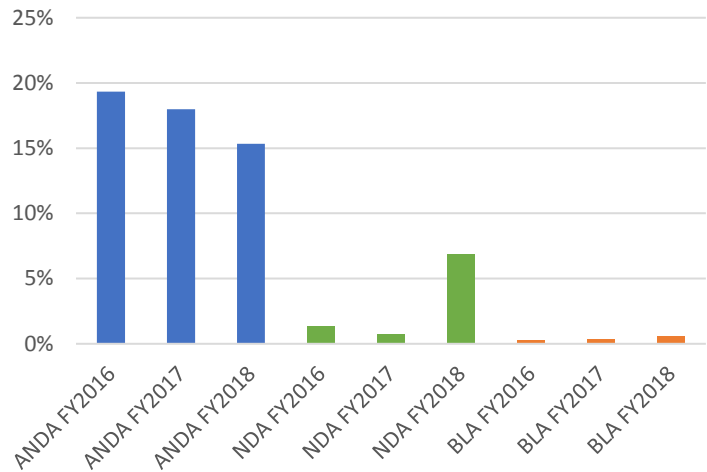


Figure 9. Percentage of applications with RTR/RTF status FY2016-FY2018

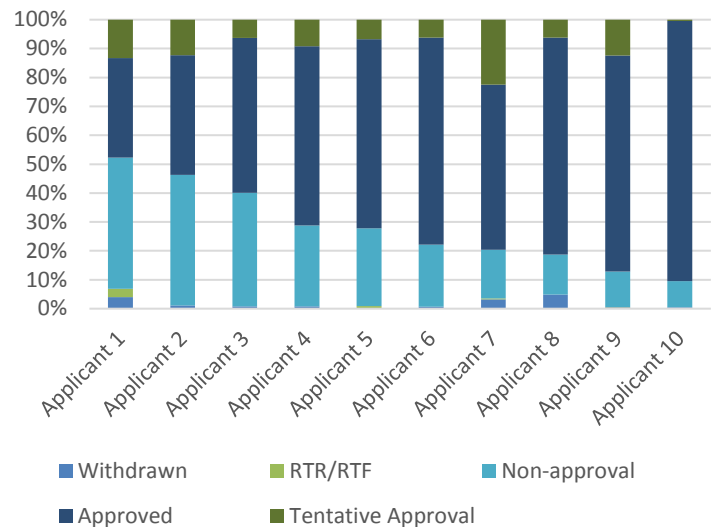


Figure 10. Comparison of application and supplement outcomes in FY2018 for the Top 10 applicants by volume of submissions

²⁶ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM588242.pdf>

²⁷ <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM370352.pdf>

²⁸ Note that counts do not necessarily reflect the timing of the decisions made, only the current status of the application. A count in CR (Complete Response) would not necessarily mean that the application received a CR in FY2018, but rather that it is the current status. Also note that reason for the CR is not specified in this analysis.

Engaging Stakeholders in a Commitment to Quality

The FDA uses the findings in this report to explore ways to best deploy FDA's resources for surveillance, training on regulations and expectations, and engaging stakeholders. Yearly assessments of our manufacturing site and product catalogs provide a panoramic view of the industry. In addition to the information presented here, FDA considers many other factors important to the State of Pharmaceutical Quality. An important impact of this report is identifying areas where FDA can further engage industry. The FDA has a portfolio of active programs specifically designed to gather additional data and engage with the pharmaceutical manufacturing industry on quality-related topics. This portfolio includes:

- A Quality Metrics Feedback Program²⁹ to gather stakeholder feedback on the use of quality metrics by manufacturers. Quality metrics are used throughout the pharmaceutical industry to monitor and continually improve product and process quality. The FDA is developing its own FDA Quality Metrics Program to evaluate a new approach for regulatory oversight of pharmaceutical products through the collection of certain quality information developed and maintained in the course of manufacturing drugs.
- A Quality Metrics Site Visit Program³⁰ to provide experiential learning opportunities to FDA staff involved in the development of the FDA Quality Metrics Program. Quality metrics are one element of companies' commitment to quality culture. This program provides stakeholders an opportunity to explain the advantages and challenges associated with implementing and managing a robust Quality Metrics Program.
- An Emerging Technology Program³¹ to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. Through the program, industry representatives can meet with FDA to discuss potential technical and regulatory issues prior to filing a regulatory submission. There has been an increase in requests from industry to include innovative elements of drug product design and manufacturing in their submissions.
- The New Inspection Protocol Project³² to use standardized electronic inspection protocols to collect data in a structured manner for more consistent oversight of facilities and faster and more efficient analysis of our findings. The protocols include questions related to quality culture observed in facilities.
- The Site Engagement Program³³ which is a voluntary program to encourage quality practices at select drug manufacturing sites with the goal of ensuring the availability of quality pharmaceuticals.

²⁹ <https://www.federalregister.gov/documents/2018/06/29/2018-14005/modernizing-pharmaceutical-quality-systems-studying-quality-metrics-and-quality-culture-quality>

³⁰ <https://www.federalregister.gov/documents/2018/06/29/2018-14006/quality-metrics-site-visit-program-for-center-for-drug-evaluation-and-research-and-center-for>

³¹ <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm523228.htm>

³² <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm625601.htm>

³³ <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm622415.htm>

Interaction with these select sites is meant to prevent or mitigate shortages that could result in high risk to patients. This program offers identified sites an additional opportunity to gain clarification on FDA's requirements and expectations for pharmaceutical quality.

The overarching goal of this portfolio of programs is to improve our ability to understand the overall condition of the industry and proactively address potential pharmaceutical quality issues *before* they impact patients and consumers.

As we continue to develop programs to promote quality, we hope for an increased commitment to quality across the industry. Patients and consumers expect safe and effective drugs with every dose they take. Manufacturers must ensure every dose is safe and effective, free of contamination and defects. We must all work together to assure patients and consumers have access to safe, effective, *quality* medicines.