U.S. FOOD & DRUG ADMINISTRATION

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality

Report on the State of Pharmaceutical Quality

FY2025



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Introduction

The Office of Pharmaceutical Quality (OPQ) in the U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), assures that drugs legally marketed in the U.S. are safe and effective, and meet quality standards. This 8th Report on the State of Pharmaceutical Quality (FY2025[1]) was produced by OPQ's Office of Quality Surveillance as part of its mission to assess and communicate the state of quality for regulated sites and products. This report provides data, trends, and insights about drug manufacturers[2] and the quality of the U.S. drug supply, including biological products regulated by CDER.[3]

1 Fiscal Year 2025 (FY2025) was from October 1, 2024, to September 30, 2025.

2 A "manufacturer" is any entity 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), such as blood, vaccines, tissues, and certain other biological products.



Manufacturing Site Demographics

Key Takeaways

At the end of FY2025, CDER's Site Catalog[4] included 5,953 manufacturing sites[5] globally, with 57% of sites located in the U.S.

This CDER Site Catalog includes 1,704 medical gas manufacturing sites (1,698 in the U.S. and 6 in Canada). This Report on the State of Pharmaceutical Quality is the first to include sites manufacturing designated medical gases or medically appropriate combinations of designated medical gases.

In FY2025, there were 1,248 drug quality assurance[6] inspections (702 (56%) in the U.S. and 546 (44%) in foreign countries). By comparison, in FY2024 there were 972 drug quality assurance inspections (432 (44%) in the U.S. and 540 (56%) in foreign countries).

Over the past four years, the number of sites in the CDER Site Catalog[7] decreased by 1%, from 5,999 sites in FY2021 to 5,953 sites in FY2025 (**Figure 1**). FDA performs continual verification of site status and outreach to maintain an accurate and up-to-date Site Catalog. Updates to the current Site Catalog are due to responses to information provided to §704(a)(4) records requests, identification of foreign sites that have no recent shipments, and sites de-registering due to fees assessed under the Over-the-Counter Monograph User Fee Act Program.

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 registered human drug sites qualify as "manufacturers" for the CDER Site Catalog.

5 Although they meet the definition of "manufacturer," registered outsourcing facilities, under section 503B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), are excluded from the counts and analyses presented in this report.

6 Drug quality assurance inspections include surveillance and for-cause inspections that are conducted under FDA Compliance Program 7356.002 and its subprograms.

7 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 surveillance inspection. This commonly occurs when sites deregister or are no longer active in an approved application.

Site counts in this report include manufacturers of designated medical gases and medically appropriate combinations of designated medical gases for FY2021 through FY2025, which were not included in prior years' reports. This provides a more complete picture of drug manufacturing. Most medical gas products supplied to the U.S. (99%) are manufactured by U.S. sites. Currently, these 1,704 medical gas manufacturing sites constitute 50.3% (1,698) of all U.S. drug manufacturing sites and 4.5% (6) of all Canadian drug manufacturing sites making products for the U.S. market.

Of all FY2025 drug manufacturing sites, 2,755 (46%) are in the "No Application" sector, indicating that all products manufactured at those sites are marketed in the U.S. without approved FDA applications. The majority of this sector is manufacturers of designated medical gases and medically appropriate combinations of designated medical gases; however, it also includes over-the-counter (OTC) monograph products, marketed unapproved prescription drug products, and homeopathic products. The remaining 54% of sites manufacture at least one application product, including:

- Biological products licensed under Biologics License Applications (BLAs)[8]
- Innovator products approved under New Drug Applications (NDAs)
- Generic products approved under Abbreviated New Drug Applications (ANDAs)

Over the past five years, the six countries with the largest net percent increases for sites in the Site Catalog were India, China, Spain, Germany, Italy, and Switzerland (**Figure 1**). For these countries combined, the number of sites increased by more than 10%. During that same period, the number of U.S. sites listed in the Site Catalog decreased by a net 5%, though the U.S. still maintains the largest number of sites. One source of change in the Site Catalog was due to manufacturers of alcohol-based hand sanitizer that registered during the COVID-19 Public Health Emergency (PHE)[9] and subsequently deregistered after demand for those products declined.

[8] See FDA's webpage for further explanation of which therapeutic biological products are regulated by CDER per the original transfer and those subsequently deemed to be BLA products.

[9] The duration of this PHE, as determined by the Secretary of Health and Human Services, was January 27, 2020 – May 11, 2023.

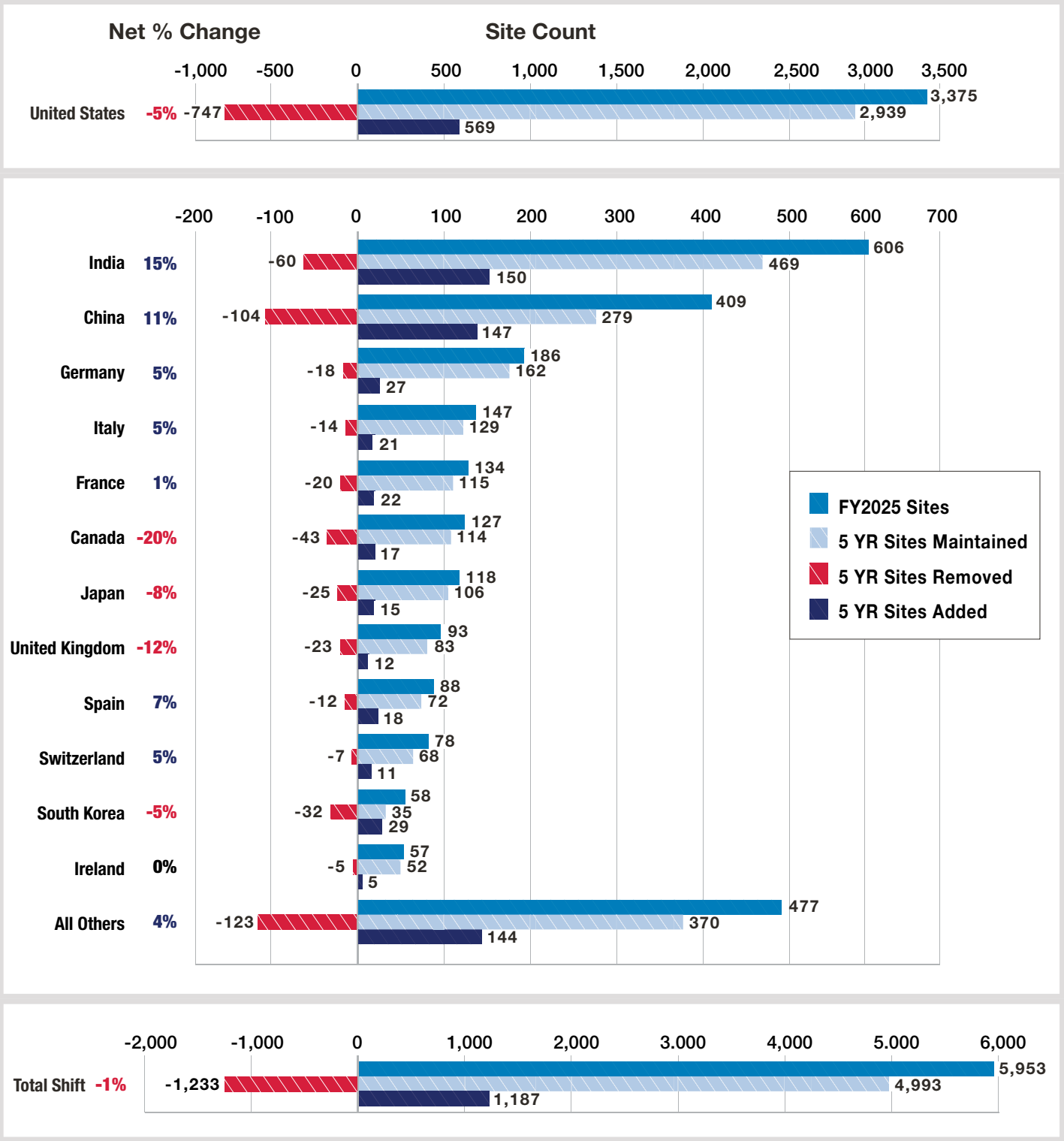

Figure 1. Inventory Shift Over FY2021-FY2025 for Countries With Greater Than 50 Sites[10]

In FY2025, there were 1,248 drug quality assurance inspections (702 in the U.S. and 546 in foreign countries), plus 61 Mutual Recognition Agreement (MRA) partner inspections, for a total of 1,309 inspections. The outcomes of these

[10] "Sites Maintained" are sites from the FY2021 Site Catalog that remain in the FY2025 Site Catalog, including medical gas facilities. "Sites Removed" and "Sites Added" are sites that were removed from, or added to, the Site Catalog during FY2021-FY2025. Some sites were added and removed during those five years (in total, there were 227 such sites). Hence, the total for FY2025 is equal to "Sites Maintained" + "Sites Added" – "Sites That Were Added and Removed."

inspections provide information about each site's ability to manufacture in compliance with applicable laws and regulations, including current good manufacturing practice (CGMP) requirements. **Figure 2** shows the distribution of outcomes for these FY2025 inspections. Inspection classifications for these 1,309 inspections were 22% no action indicated (NAI), 60% voluntary action indicated (VAI), and 18% official action indicated (OAI). A statistical examination of the distributions of outcomes revealed that China had significantly fewer OAI outcomes (8.0% vs. 18% global average), while the U.S. had significantly more OAI outcomes (21.6% vs. 18% global average), and Europe had significantly fewer NAI outcomes and more VAI outcomes than the global average.[11]

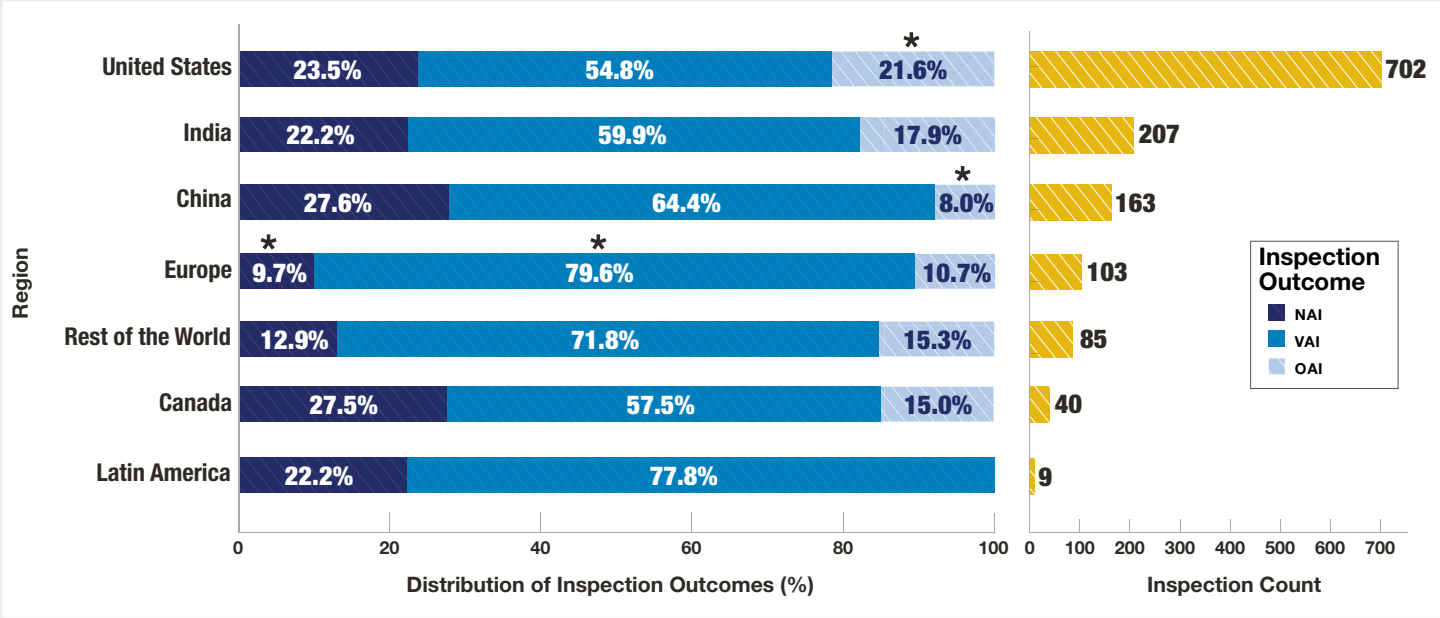

Figure 2. Distribution of FY2025 Inspection Outcomes and Inspection Count by Region

[11] A chi-squared test revealed statistically significant deviations in the distributions of inspection outcomes across the regions ($\chi^2 = 49.33$, $p < 0.001$). In Figure 2, significant deviations from expected values are indicated by asterisks. Significance is defined as residual values greater than an absolute value of 2.0.



Drug Product Demographics

Key Takeaways:

Consistent with FDA's modernization efforts, reporters of postmarket quality problems (whether members of the public, industry members, or health professionals) should use FDA's SmartHub to submit appropriate reports directly to CDER.

At the end of FY2025, CDER's Product Catalog contained 422 BLAs, including 82 biosimilar products, a 30% increase from 63 biosimilar products in FY2024.

Drug Amount Reporting improved from calendar year CY2023 to CY2024.

The CDER Product Catalog is regularly updated to include all application and non-application products. Its comprehensive product information comprises proprietary names, active ingredients, manufacturing sites, National Drug Codes (NDC),[12] and other data. At the end of FY2025, the CDER Product Catalog included 14,753 ANDAs (4.1% increase from FY2024), 3,640 NDAs (0.4% increase from FY2024), and 422 BLAs (10.2% increase from FY2024). The catalog also included 141,664 non-application product NDCs (1.1% increase from FY2024). In FY2025, the total product count, including approved applications and NDCs for non-application products, increased by 3.2%, a slower rate of growth compared to FY2024, which saw an increase of 6.3% largely due to an increase in non-application products. While 14,896 new non-application products were listed in FY2025, the increase was somewhat offset by the delisting of 13,148 non-application products following Drug Amount Reporting outreach that resulted in industry cleanup of FDA's Electronic Drug Registration and Listing System (eDRLS).

[12] The NDC is a 10- or 11-digit identifier for drugs listed with FDA that consists of three segments: "labeler code" (manufacturer or distributor), "product code" (drug product: formulation, dosage form, and specific strength), and "package code" (commercial package size and type).

Postmarket Quality Defects

FDA receives, monitors, and evaluates mandatory and voluntary postmarket quality reports. Pursuant to FDA's postmarket regulations in 21 CFR 314.81(b) and 21 CFR 600.14, application holders are required to notify FDA of any significant quality-related incident in marketed products within three working days for Field Alert Reports (FARs) and within 45 calendar days for Biological Product Deviation Reports (BPDRs). Voluntary reports include MedWatch (MW) reports that consumers, patients, and healthcare professionals can submit if product quality fails to meet expectations or an adverse event occurs.

As a part of FDA's modernization of operations, as of October 1, 2024, CDER directly receives reports of problems or adverse reactions with its regulated drug products. Using FDA's SmartHub, reporters of quality problems are directed to the appropriate webform (e.g., for human drugs, members of the public are directed to the MedWatch Voluntary Online Form – 3500B).

During FY2025, CDER received 4,059 initial FARs, 297 initial BPDRs, and 12,276 quality-related MW reports.[13] Compared to FY2024, this represents a decrease in BPDRs (-27%), an increase in FARs (+4%), and a decrease in MW reports (-2%).[14]

FAR: During FY2025, the primary reported quality defect was packaging issues (35%), which includes defects such as product commingling, product leakage, product closure issue, and package volume underfill. Additional top defects included the following:

- 17% – Physical issues, e.g., product discoloration, product adhesion issues, product odor abnormal, product cracked, product reconstitution quality issue, and product appearance cloudy.
- 17% – Out-of-specification and stability testing issues, e.g., out-of-specification test results stability, out-of-trend test results, and product impurity.
- 13% – Contamination and sterility issues, e.g., product sterility lacking, product contamination microbial, product contamination foreign material, and suspect product contamination.
- 8% – Labeling issues, e.g., product label text illegible, product barcode missing and product label damaged.

During FY2025, contamination and sterility related defects declined 20% compared to FY2024. However, FARs reporting packaging issues (+13%), physical issues (+24%), and labeling issues (+68%) increased.

[13] Quality-related MedWatch reports are voluntary postmarket reports from consumers, patients, and healthcare professionals concerning product quality issues such as defective components, contamination, poor packaging, and suspected counterfeit products.

[14] The count of 3,515 initial FY2024 FAR submissions in the FY2024 Report on the State of Pharmaceutical Quality did not account for all submissions. In FY2024, there were 3,904 FAR submissions.

BPDR: In FY2025, the primary quality defect category submitted for initial BPDRs continued to be device issues (46%), which includes defects such as device breakage, device leakage, device malfunction, component detachment, and mechanical jams. Additional top defects included:

- 18.5% – Physical issues, e.g., product appearance cloudy, product reconstitution quality, product color issue, and product residue.
- 13% – Packaging issues, e.g., product quantity empty units, product underfill, and product closure issue.

Initial BDPRs submitted for the top reported defect categories declined compared to FY2024: device issues (-5%), packaging issues (-26%), and physical issues (-51%).

MW reports: In FY2025, reported products of concern were BLAs (45%), NDAs (39%), ANDAs (13.5%), and non-application products (2.5%). The most frequent product dosage forms reported for MW submissions were injections (37%), tablets (21%), and combination product kits (17%). Device issues remained the primary quality defect category in FY2025, accounting for 41% of MW submissions. Notably, injection and kit dosage forms together represented 87% of all reported device issue defects.

Drug Amount Reporting

Pursuant to section 510(j)(3) FD&C Act, as added by the Coronavirus Aid, Relief, and Economic Security Act (CARES Act),[15] registrants under section 510, including repackers and relabelers, are required to report annually to the agency the amount of each listed drug that was manufactured, prepared, propagated, compounded, or processed for commercial distribution. This requirement is intended to enhance prevention and mitigation of possible drug shortages by augmenting its drug supply chain visibility.

Figure 3 shows the reporting rate for active CDER-regulated products listed in eDRLS, excluding certain medical gases and registrants who are repackers and relabelers.[16] CY2024 reporting rates were improved compared to CY2023 across all marketing categories; however, the reporting rate for OTC monograph products continues to trail application products.

[15] The CARES Act was enacted on March 27, 2020, to aid response and ease economic impacts of COVID-19.

[16] The last day for submitting CY2024 drug amount reports was December 31, 2025.

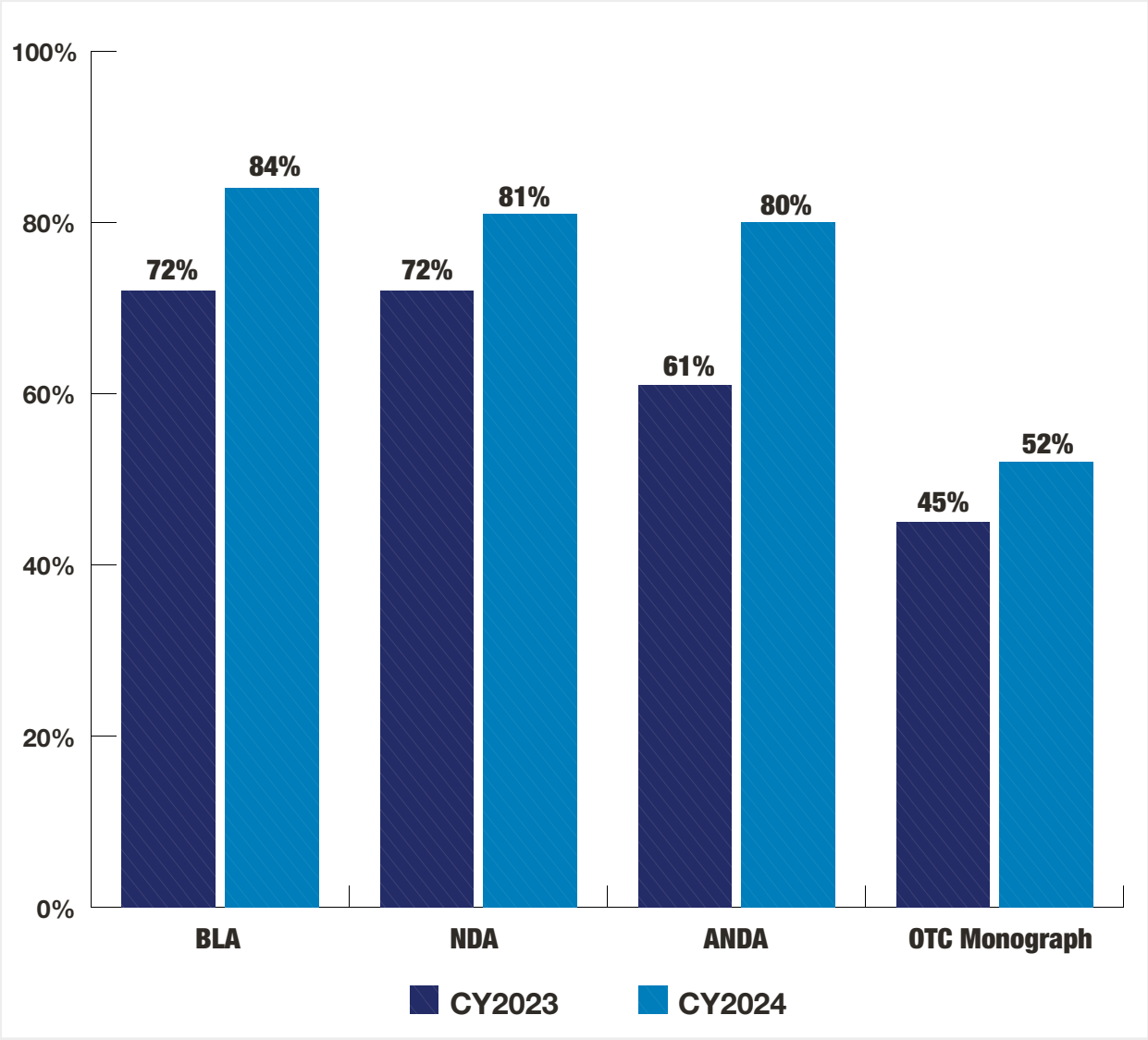

Figure 3. Percentage of NDCs for Active Listed CDER-Regulated Drugs (Excluding Certain Medical Gas) for Which Registrants (Excluding Repackers and Relabelers) Submitted Drug Amount Reports, by Marketing Category

FDA leveraged drug amount reporting data to inform the FY2026 Site Selection Model that prioritized surveillance inspection assignments. Additionally, these data have provided valuable supply chain insights for certain products, such as insulin, where drug amount reporting is more robust. Pursuant to Executive Order 14293 (May 5, 2025), on October 14, 2025, FDA notified 9,571 registrants that they had not yet submitted their required drug amount reports for CY2024. Those registrants that had still not complied with this reporting requirement by December 31, 2025, were added to FDA's public listing of noncompliant entities in March 2026.



Insights Into Research on the State of Quality

Key Takeaways:

During CY2020-CY2025, the distributions of manufacturing locations for U.S.-based application products[17] trended away from the U.S. and Europe and toward China and India.

BLAs have increased from 2.3% of all approvals in FY2016 to 4.6% in FY2025 with biosimilars representing 42% of the approved BLAs in FY2025, up from 17% in FY2016.

In FY2025, 74% of the §704(a)(4) record requests used to support application assessment were sent to foreign pharmaceutical sites, with the highest number sent to India and China.

An Evolving Manufacturing Network: Locations for U.S.-Based Application Products

Global manufacturing networks have undergone fundamental changes since the COVID-19 PHE. To illustrate one critical component of these changes, FDA examined the manufacturing networks that are specific to U.S.-based applications. FDA analyzed the active pharmaceutical ingredient (API) and finished dosage form (FDF) manufacturing locations for these U.S.-based applications and how the shares of the overall total have changed since CY2020.

[17] Application products are considered U.S.-based when the applicant is in the U.S. The sites in this analysis manufacture at least one U.S.-based application product.

Figure 4 shows the changes in distributions among the global regions for these API and FDF manufacturing locations. Overall, the distributions of these manufacturing locations increased for China and India and decreased for the U.S. and Europe. For Latin America, Canada, and other countries or regions, the changes in distributions of manufacturing sites were less significant. For these U.S.-based application products, the distribution of API manufacturing locations increased by 2.5% for China and 3.3% for India. In contrast, Europe and the U.S. had decreases of 3.2% and 1.8%, respectively, for the distribution of API manufacturing locations. The changes in distribution of FDF manufacturing locations followed a similar decreasing trend for the U.S. and Europe and an increasing trend for China and India.

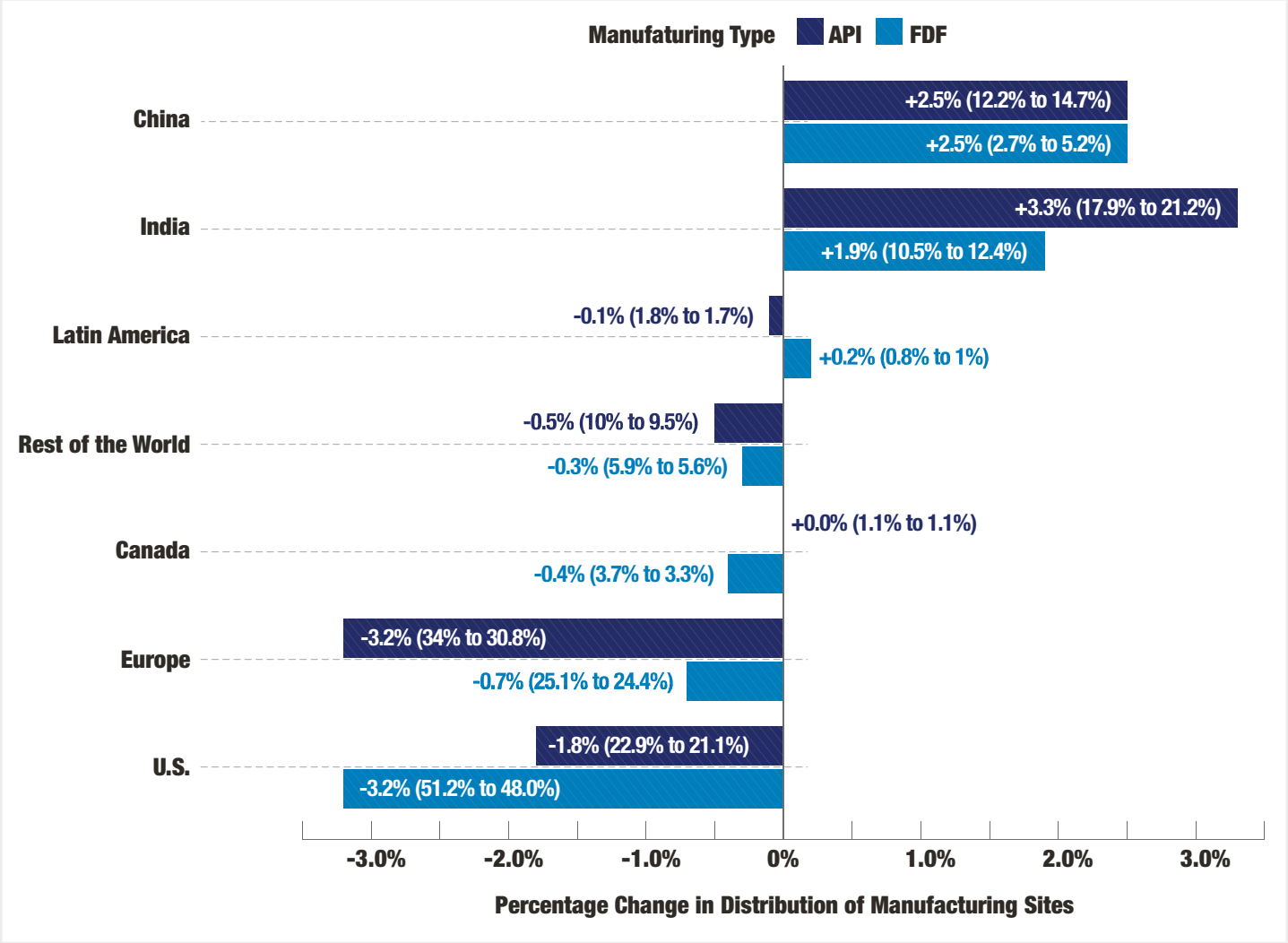

Figure 4. Changes in Distributions of Manufacturing Locations for U.S.-Based Application Products During CY2020-CY2025 (Labels Show Starting and Ending Percentages)

These changes during the past five years are attributed primarily to the addition of manufacturing sites in China and India, increasing their share of the total, while the number of sites in the U.S. and Europe remained relatively stable. It is important to note that the U.S. and Europe still retain the largest shares of API and FDF manufacturing sites respectively, as shown by the numbers in parentheses.

Approval Trends for BLAs and A/NDAs

FDA approves therapeutic products through three application types: NDAs for novel small molecule drugs, ANDAs for generic drugs, and BLAs for biological products. Historically, small molecule drugs, approved under ANDAs and NDAs, have dominated the pharmaceutical market. However, the emergence of biotechnology has introduced large molecule biological products as increasingly prominent therapeutic options. These complex proteins, monoclonal antibodies, and other biological products offer the potential to address previously untreatable conditions, particularly for oncology, immunology, and rare diseases.

To better understand these trends, FDA analyzed NDA, ANDA, and BLA approvals over the past ten years (FY2016-FY2025) (**Figure 5**). Total annual approvals ranged from 640 to 1,060, with a notable peak of 1,060 approvals in FY2019. This peak was driven by a surge in ANDA approvals, which may be attributed to FDA's ongoing efforts following the rollout of the Drug Competition Action Plan and the 2017 Generic Drug User Fee Amendments. ANDA approvals represented 85% of total approvals across this timeframe. While BLAs constituted the smallest portion of annual drug approvals, they have trended upward, more than doubling from FY2016 (18) to FY2025 (38) and representing 4.6% of FY2025 approvals. BLA approvals encompass both originator biological products approved under the 351(a) pathway and biosimilars approved under the 351(k) pathway. The recent increase in BLA approvals is attributed to increased biosimilar approvals. Biosimilars accounted for over 40% of BLA approvals in FY2024 and FY2025, reflecting the maturation of the biosimilar market as more biological products lose market exclusivity.

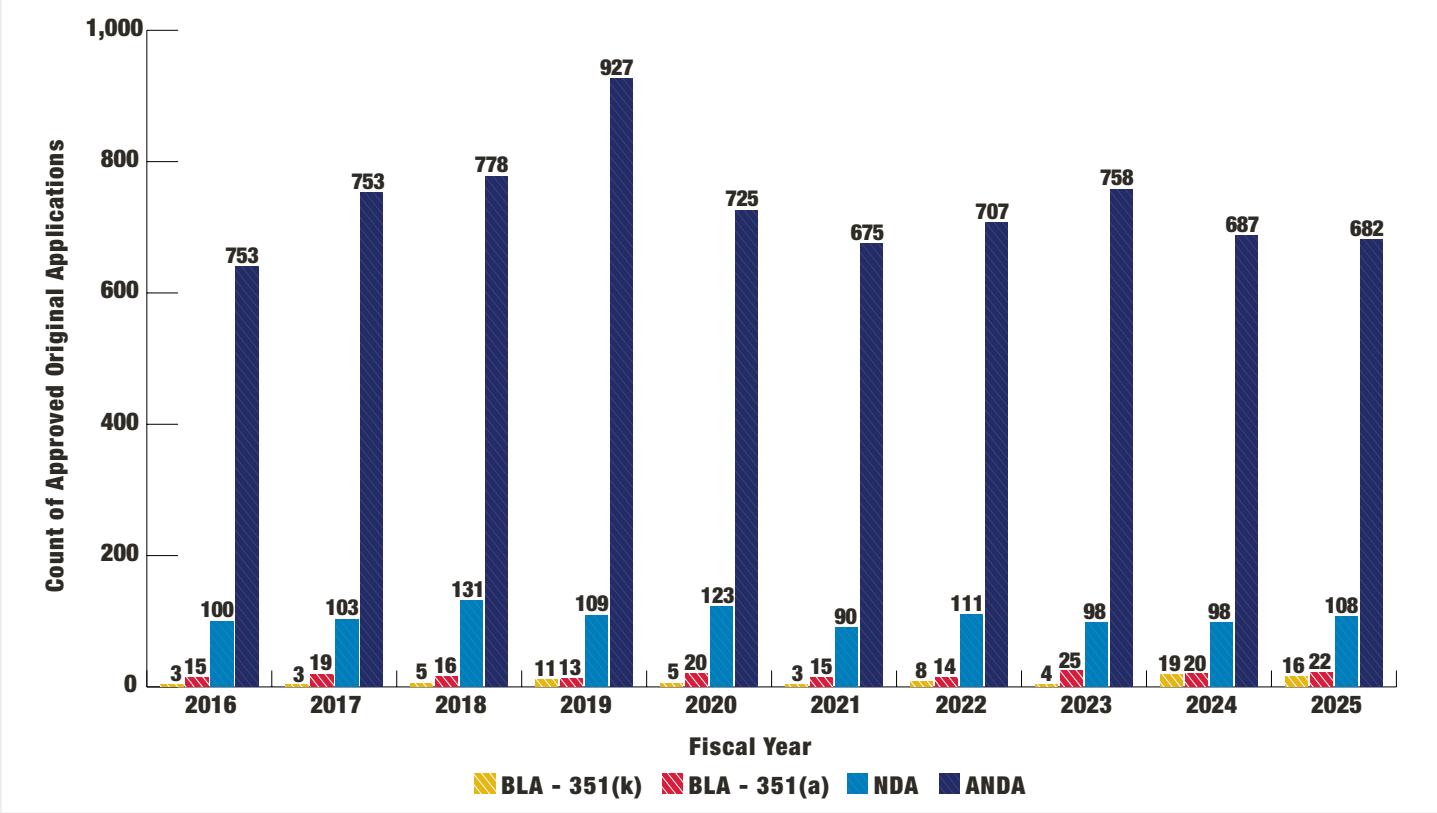

Figure 5. Distribution of Original Application Approvals by Type, Fiscal Years 2016-2025

Recent Trends in the Use of §704(a)(4) Record Request Reviews and MRAs for Risk-Based Evaluation of Drug Applications

As part of NDA, ANDA, and BLA approval processes, FDA evaluates manufacturing sites that are named in the application. Risk-based assessments consider product risk and manufacturing (process and facility[18]) risk along with the accuracy and reliability of application information. These determine whether the evaluation should be accomplished with a Pre-Approval Inspection (PAI) or Pre-License Inspection (PLI), a §704(a)(4) records request, or by FDA leveraging existing information about the facility from a previous FDA inspection or MRA partner inspection. §704(a)(4) records request reviews and MRA partner inspections serve as risk-based alternative sources of information to evaluate manufacturing sites in support of application decisions. This may reduce the necessity to conduct PAIs and PLIs or may support efficient inspection coverage. In general, sites that lack prior on-site inspections, lack demonstrated capabilities for the manufacturing responsibilities in the application, or have significant violative inspection history are deemed higher risk.

PAIs and PLIs assess CGMP compliance and readiness to manufacture safe high-quality products, conformance to application, and data integrity. PAIs are used to evaluate all A/NDA submissions and significant changes for facilities approved to manufacture licensed BLA products, while PLIs are used to evaluate new BLA product licenses. Unlike surveillance inspections, PAIs and PLIs are specific to application products. However, if during a PAI or PLI serious issues are discovered that could impact marketed products, the inspection can be expanded to surveillance coverage.

MRA inspections can provide information to demonstrate CGMP compliance and manufacturing capability relevant to the application as part of the pre-approval risk-based assessment to determine the necessity of a PAI, PLI, or §704(a)(4) records request review for facility evaluation. MRAs have been in force between FDA and the European Union, United Kingdom, and Switzerland since 2017, 2021, and 2023, respectively. In FY2025, the highest number of MRA partner inspections (69) than ever before were used to support facility evaluations for pending applications (**Figure 6**).

FD&C Act §704(a)(4) records request reviews can also be used in lieu of, or in advance of, a PAI or PLI during the application review process to obtain records normally collected during inspections to support the facility evaluation. These records request reviews can be performed for all product types across domestic and foreign sites to support application decisions. In FY2025, there were 141 §704(a)(4) records request reviews to support risk-based application decisions. More §704(a)(4) records request reviews in support of application assessment were conducted in FY2025 than in any year since FY2021.

[18] The terms "site" and "facility" are similar; but, "site" is typically used for surveillance activities and "facility" is typically used for preapproval activities.

In FY2025, 74% of these §704(a)(4) records requests to support application assessment were sent to foreign manufacturers, with the greatest portion sent to India and China (21% and 12%, respectively). Although BLAs represented only 4.5% of FY2025 FDA-approved applications, they accounted for 42% (59 of 141) of pre-approval/pre-license §704(a)(4) records request reviews. Unique to BLAs, OPQ leads site inspection activities, and these data demonstrates OPQ's efforts to enhance the flexibility, agility, efficiency, and effectiveness of the BLA PLI/PAI compliance program while maintaining its approvability standards and promoting quality.

Using MRA partner inspections and §704(a)(4) records request reviews appropriately as part of the pre-approval and pre-license process enables efficient assessment of manufacturing (process and facility) and product risks prior to application approval. In FY2025, FDA utilized the highest combined number of MRA partner inspections and §704(a)(4) records request reviews to support application assessment. Employing multiple evaluation methods allows FDA to assess application sites with greater flexibility and efficiency.

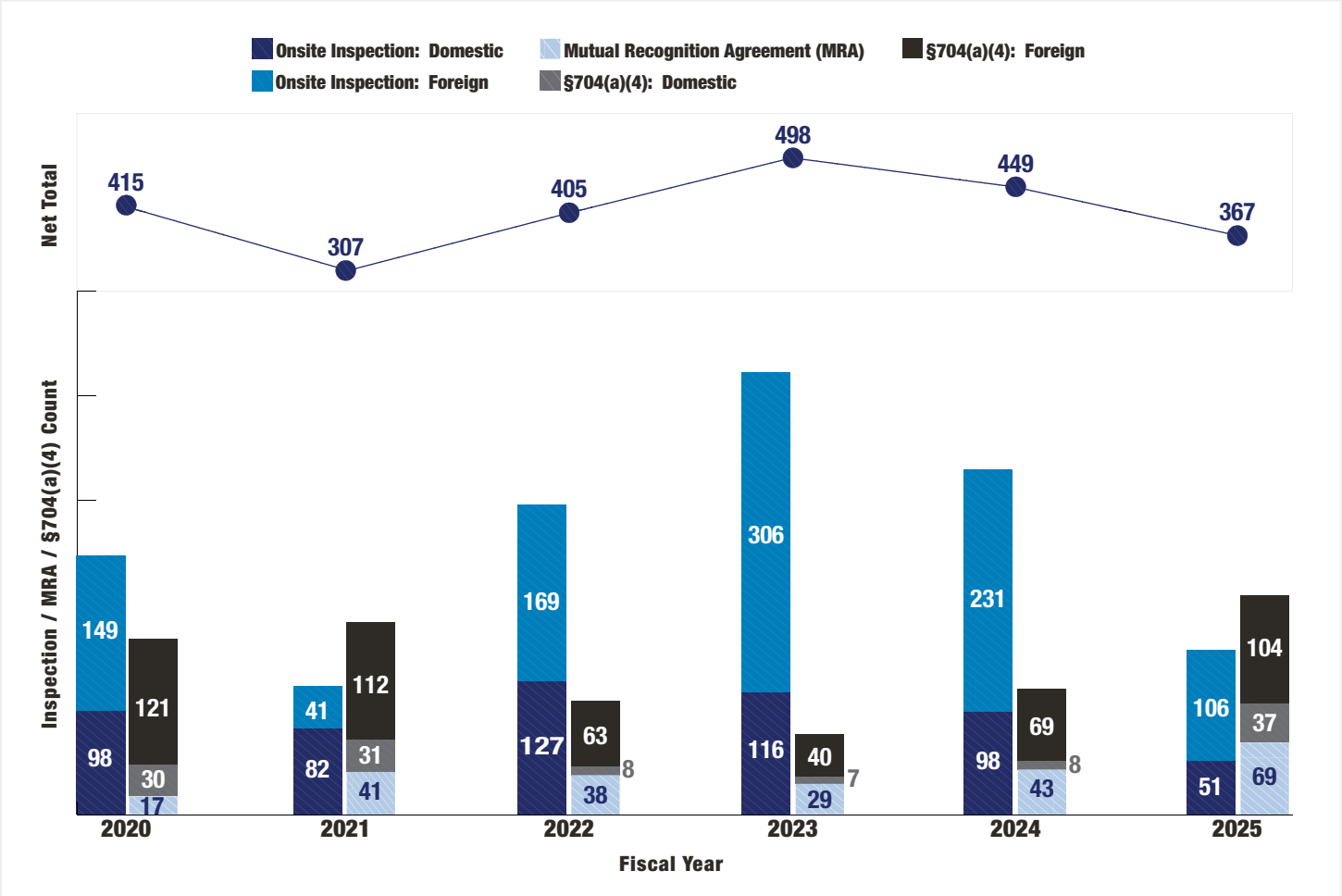

Figure 6. Application Evaluation Tools for FY2020-2025: FDA Pre-Approval Inspections, Pre-License Inspections, FD&C Act §704(a)(4) Records Request Reviews, and MRA Partner Inspections



Sampling and Testing

Key Takeaways

A study of benzene in certain OTC products found the average benzene level was well below 2 ppm[19] and demonstrated that some manufacturers can consistently meet lower limits.

A study of diethylene glycol (DEG) and ethylene glycol (EG) in OTC drug products provided assurance to U.S. consumers about the quality of the tested products.

Surveillance of Aerosol OTC Medications for Benzene Contamination

Concern for the safety of aerosol OTC drug products such as sunscreens and antiperspirants arose when several of these products were found to have benzene levels exceeding recommended limits. The agency issued multiple press releases on the topic, alerting the public and prompting manufacturers to test at-risk products, with voluntary recalls[20] subsequently initiated by drug manufacturers.

During FY2023-2024,[21] FDA funded two contracts focusing on method development and testing of aerosol sunscreens, antiperspirants, antifungals (powder and liquid), and anesthetics using gas chromatography-mass spectrometry to determine baseline benzene levels in these OTC drug products.

[19] If the presence of benzene is unavoidable in a finished drug product, benzene levels should be limited so that consumers are not exposed to more than 20 micrograms (mcg) per day of benzene from the product. For products with a 10 g per day dose, this 20 mcg per day exposure limit is reached through a product concentration limit of 2ppm. The 20 mcg per day exposure is associated with a lifetime excess cancer risk of 1-in-100,000. Benzene concentration limits may vary among consumer products based on their characteristics and intended use.

[20] Multiple recalls since 2021 can be found by searching for “benzene.”

[21] Research was funded by FDA and supported through contracts 75F40122P00501 and 75F40123P00423.

The lower limit of detection established was 0.1 ppm, with any results below this limit described as “not detected.”

In total, 189 unique drug products (defined by NDC) across 44 brands were tested (several with multiple aliquots), with the following results (**Figure 7**):

- 63 aerosol sunscreen samples were analyzed. Their average benzene level was 0.06 ppm, with a range of “not detected” to 0.32 ppm.
- 72 aerosol antiperspirant samples were analyzed. Their average benzene level was 0.09 ppm, with a range of “not detected” to 1.0 ppm.
- 54 aerosol antifungal and anesthetic samples were analyzed. Their average benzene level was 0.04 ppm, with a range of “not detected” to 0.22 ppm.

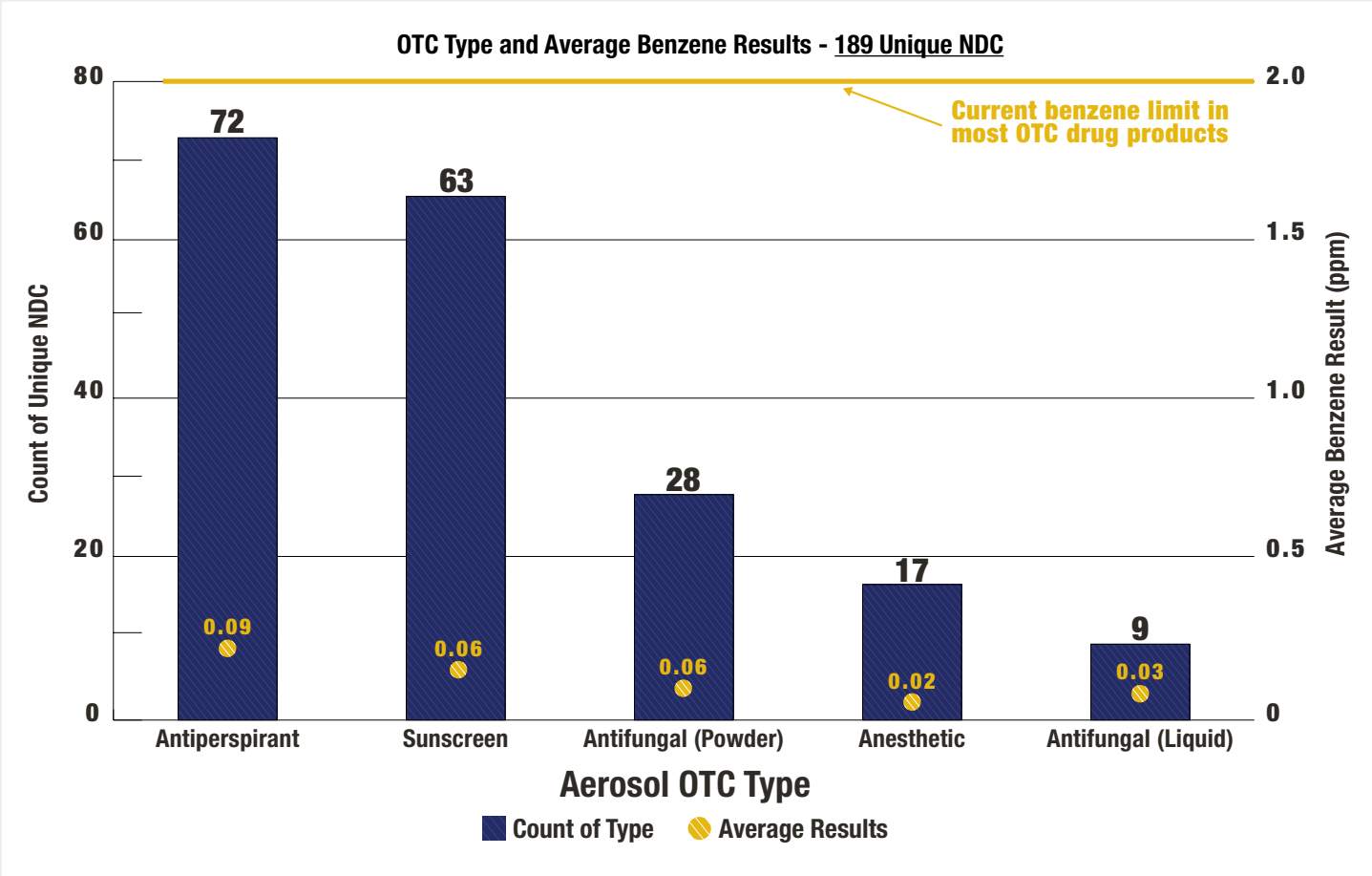

Figure 7. Benzene Levels Detected in Various Aerosol OTC Products

This study demonstrates that these OTC products typically contain concentrations of benzene below 2 ppm. In addition, it demonstrated that some manufacturers can consistently meet lower limits, even below the 0.1 ppm lower limit of detection. This research highlights that robust processes can be established to meet quality standards and protect U.S. patients and consumers. These outcomes will inform the agency’s understanding of benzene levels in drug products.

Surveillance of OTC Medications for Diethylene Glycol (DEG) and Ethylene Glycol (EG) Contamination[22]

DEG and EG contaminations pose a persistent threat to global public health, primarily involving OTC children's cough syrups that have caused deaths in developing countries. These toxic industrial solvents are often illegally or mistakenly used as cheaper substitutes for safe pharmaceutical-grade solvents like propylene glycol or glycerin.

Deaths due to DEG and EG contamination in The Gambia, Indonesia, and Uzbekistan in 2022 and 2023 reaffirmed the need for pharmaceutical companies to test every container of high-risk ingredients rather than simply relying on supplier certificates of analysis. In May 2023, the agency addressed this urgent public health need by issuing revised guidance that provides updated recommendations on DEG and EG testing and other activities that will help prevent the use of contaminated high-risk drug components.

To advance the state of pharmaceutical quality surveillance, FDA developed and validated an analytical test method for detecting DEG and EG contamination in finished OTC pediatric cough, cold, and allergy medications in March 2025. FDA applied this new test method in a targeted surveillance study of over 160 products from 120 sites, including both adult and pediatric OTC cough, cold, and allergy products as well as kits, from the U.S. market. This study confirmed that none of the samples tested contained DEG or EG at concentrations exceeding the relevant safety limit of not more than 0.10% as recognized by the applicable United States Pharmacopeia or National Formulary (USP-NF) monograph. These results demonstrate that the tested samples are free from DEG and EG contamination and are safe for U.S. consumers. More significantly, ongoing surveillance activities, including future testing for DEG and EG in finished dosage form OTC products, can identify noncompliant products. This can strengthen the safety and integrity of the U.S. pharmaceutical supply chain.

[22] This research was funded by FDA and supported through contract 75F40123P00405.



Commitment to Quality

Key Takeaway

A two-year review of original applications and supplements requiring facility assessments found that most facility withholds occurred at facilities with pre-existing OAI status.

Complete Response Letters Due to Pre-Existing Facility Noncompliance

FDA's drug application review process is intended to assure the quality, safety, and effectiveness of marketed products while providing therapies to the American public. All submissions for NDAs, ANDAs, and BLAs that require a facility assessment can result in a Complete Response Letter (CRL) that identifies deficiencies precluding approval. FDA issues a CRL after determining that a submission cannot be approved in its present form and can cite deficiencies across several categories. Chemistry, Manufacturing, and Controls deficiencies are a major category that encompasses inadequate manufacturing process controls, unacceptable impurity profiles, insufficient stability data, and quality concerns raised by facility assessments. To support its desk review of the application to make decisions, FDA may inspect facilities through PAIs (for NDAs and ANDAs) and PLIs (for new BLAs) or rely on the established FDA or MRA inspection history and other quality intelligence.

To better understand the reasons for CRLs, FDA analyzed nearly 10,000 original applications and supplements that required a facility assessment and were received during FY2024-2025. As of May 2026, 28% of these submissions had received a CRL. Of those, 43% (12% of all submissions) were due to "facility

withholds."[23] Greater than 50% of facility withholds resulted from facilities with pre-existing OAI or potential OAI (pOAI[24]) status. The remaining facility withholds resulted primarily from OAI/pOAI outcomes from inspections that were conducted during the review cycle. The high occurrence of pre-existing OAI/pOAI status in submissions made it more likely that these submissions would receive CRLs due to facility status. Many of these CRLs could have been prevented had the submission included only facilities with a compliant status. Assuring that facilities have a compliant status is one factor that can support successful submissions.

In addition, there were three citations among the top inspection citations[25] that resulted in facility withholds. These common citations provide specific areas for sponsors and manufacturers to assess prior to submissions.

- Failure to thoroughly review discrepancies or batch failures within production record review (i.e., inadequate investigations)
- Quality control unit (QCU) responsibilities or procedures not written or followed (e.g., insufficient documentation of QCU decisions, lacking QCU approval for changes, inadequate QCU oversight of deviations)
- Inadequate control of microbiological contamination (e.g., inadequate procedures established and/or followed to prevent microbiological contamination of sterile drug products, inadequate validation of aseptic or sterilization processes)

[23] A "facility withhold" is an FDA administrative action that places a hold on the approval of a submission due to concerns about the facility that will manufacture the drug product.

[24] FDA uses an initial pOAI classification and alert when an advisory action (e.g., warning letter or regulatory meeting) may be indicated based on significant CGMP violations. After receiving and evaluating the manufacturer's response, FDA will finalize the inspection classification as OAI, VAI, or NAI.

[25] These top citations were obtained electronically from Form FDA 483 observations (for, or based on, surveillance and preapproval inspections) mapped to the Current Good Manufacturing Practice regulations in 21 CFR 211.



Continuing to Assure Quality

OPQ is committed to communicating the state of pharmaceutical quality through comprehensive data, findings, and analyses. By providing data-driven insights that can improve pharmaceutical quality, this report advances OPQ's mission to assure that quality medicines are available to the American public. This valuable information contextualizes FDA's actions and strengthens our partnership with the public. OPQ remains poised to address emerging quality challenges. Our proactive approach to quality management encourages a strong quality culture and supply chain reliability (for example, see CDER's Quality Management Maturity webpage). FDA is actively expanding its data sources and developing predictive tools to enhance decision making and optimize resource allocation (for example, see CDER's Risk-Based Site Selection Model). FDA's ongoing commitment to monitor sites and products through rigorous inspections, product testing, and postmarket data assessment remains unwavering (for example, see Drug Quality Sampling and Testing Programs). Continually improving these practices is part of the forward-thinking strategy to safeguard public health by effectively and efficiently regulating the pharmaceutical industry.





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