



TESTIMONY

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

BEFORE THE

SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS

COMMITTEE ON ENERGY AND COMMERCE

U.S. HOUSE OF REPRESENTATIVES

**“SECURING THE U.S. DRUG SUPPLY CHAIN: OVERSIGHT OF FDA’S FOREIGN
INSPECTION PROGRAM”**

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RELEASE ONLY UPON DELIVERY

Chair DeGette, Ranking Member Guthrie, and Members of the Subcommittee, I am Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency), which is part of the Department of Health and Human Services (HHS).

Today I will provide the Committee with an overview of the history of FDA's foreign drug inspection program, and the ways it has evolved in response to the industry's globalization and changes in law and regulation. I will also explain our approach when our inspections indicate that a facility does not operate in keeping with established quality standards. These standards are known as current good manufacturing practices (CGMPs). I will also describe some potential enhancements that would enable FDA to complement our foreign drug inspection program. The Agency believes that over the longer term, we should encourage investment in advanced manufacturing technology and in strengthening the approach by which manufacturers assure the quality of their products. This approach, which we call quality management maturity, would provide a safer and more secure drug supply because it can help prevent many quality problems from occurring in the first place. Advanced technology, which can be more cost-effective and environmentally friendly than traditional manufacturing technology, may also enable the United States to play a larger role in pharmaceutical manufacturing.

The Globalization of Pharmaceutical Manufacturing

Over the past 30 years, pharmaceutical manufacturing has become an increasingly global enterprise. Beginning in the 1970s, industry moved away from the mainland United States, first to Puerto Rico in response to tax incentives, and then to Europe and developing nations such as China and India. Developing nations can provide significant cost savings to pharmaceutical companies because of their lower labor, energy, and transportation costs. In addition, they often have weaker environmental regulations than more developed countries. A World Bank study estimated that in 2004, China and India held a cost advantage of

about 40 percent when compared with the United States and Europe.¹ FDA’s 2011 report, “Pathway to Global Product Safety and Quality,” also noted that both China and India enjoy a labor cost advantage and that manufacturing active pharmaceutical ingredients (APIs) in India can reduce costs for U.S. and European companies by an estimated 30 percent to 40 percent.²

As the U.S. drug market shifted toward lower-priced generic drugs, manufacturers came under increasing cost pressure and found these efficiencies compelling reasons to locate more of their facilities overseas, particularly in developing parts of the world. This shift is reflected in the CDER’s Site Catalog (“Catalog”), which lists all drug manufacturing facilities worldwide that are subject to routine FDA inspections.³ As of August 2019, 28 percent of facilities manufacturing APIs and 47 percent of the facilities producing finished dosage forms (FDFs) of human drugs for the U.S. market were located in the United States. **(See Figures 1 and 2)**

¹ Bumpas, Janet; Betsch, Ekkehard. *Exploratory study on active pharmaceutical ingredient manufacturing for essential medicines (English)*. Health, Nutrition and Population (HNP) discussion paper. Washington, DC: World Bank: 12 – 13, Figure 2. <http://documents.worldbank.org/curated/en/848191468149087035/Exploratory-study-on-active-pharmaceutical-ingredient-manufacturing-for-essential-medicines>. Accessed September 30, 2019.

² U.S. Food and Drug Administration, “Pathway to Global Product Safety and Quality,” A Special Report, p. 20. Accessed October 4, 2019 at <https://www.hsdl.org/?view&did=4123>.

³ The Agency updates the Catalog continually, so the information it provides is a snapshot in time.

Percentage of Active Pharmaceutical Ingredient Manufacturing Facilities for All Drugs by Country or Region, August 2019

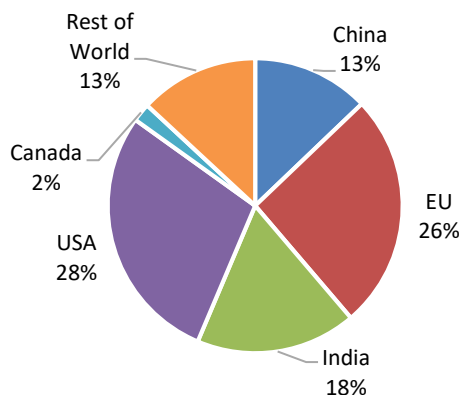


Figure 1: For all FDA-regulated drugs, 28 percent of manufacturing facilities producing active pharmaceutical ingredients (APIs) are located in the United States.

Percentage of Finished Dosage Form Manufacturing Facilities for All Drugs by Country or Region, August 2019

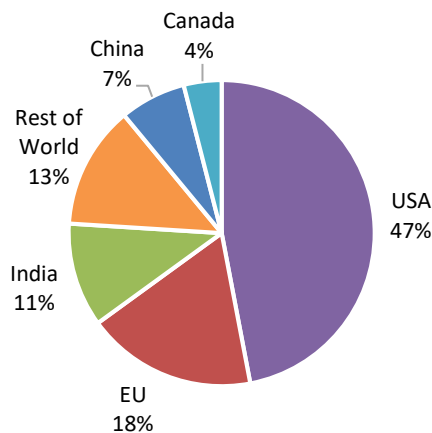


Figure 2: For all FDA-regulated drugs, 47 percent of manufacturing facilities producing finished dosage forms (FDFs) are located in the United States.

This movement accelerated in the 2000s, but due to mandates for domestic inspections and limited staffing, FDA’s inspectorate remained focused on domestic manufacturing. Until passage of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012 (P.L.112-144), the Agency was legally required to inspect manufacturing facilities in the United States every two years but had no similar mandate for the inspection frequency of foreign facilities. This resulted in more frequent inspections for domestic facilities and created an unequal playing field that was exacerbated by resource constraints.

The Globalization of FDA's Drug Inspection Program

In response to the move from domestic to global manufacturing and the passage of FDASIA, FDA's drug inspection program shifted from one focused heavily on U.S.-based facilities through the early 2000s to a program that, since 2015, has conducted more foreign than domestic drug inspections. (See Figure 3)

FDA's drug inspection program is now risk-based. FDA prioritizes for inspection facilities deemed higher-risk based on specific, defined criteria.

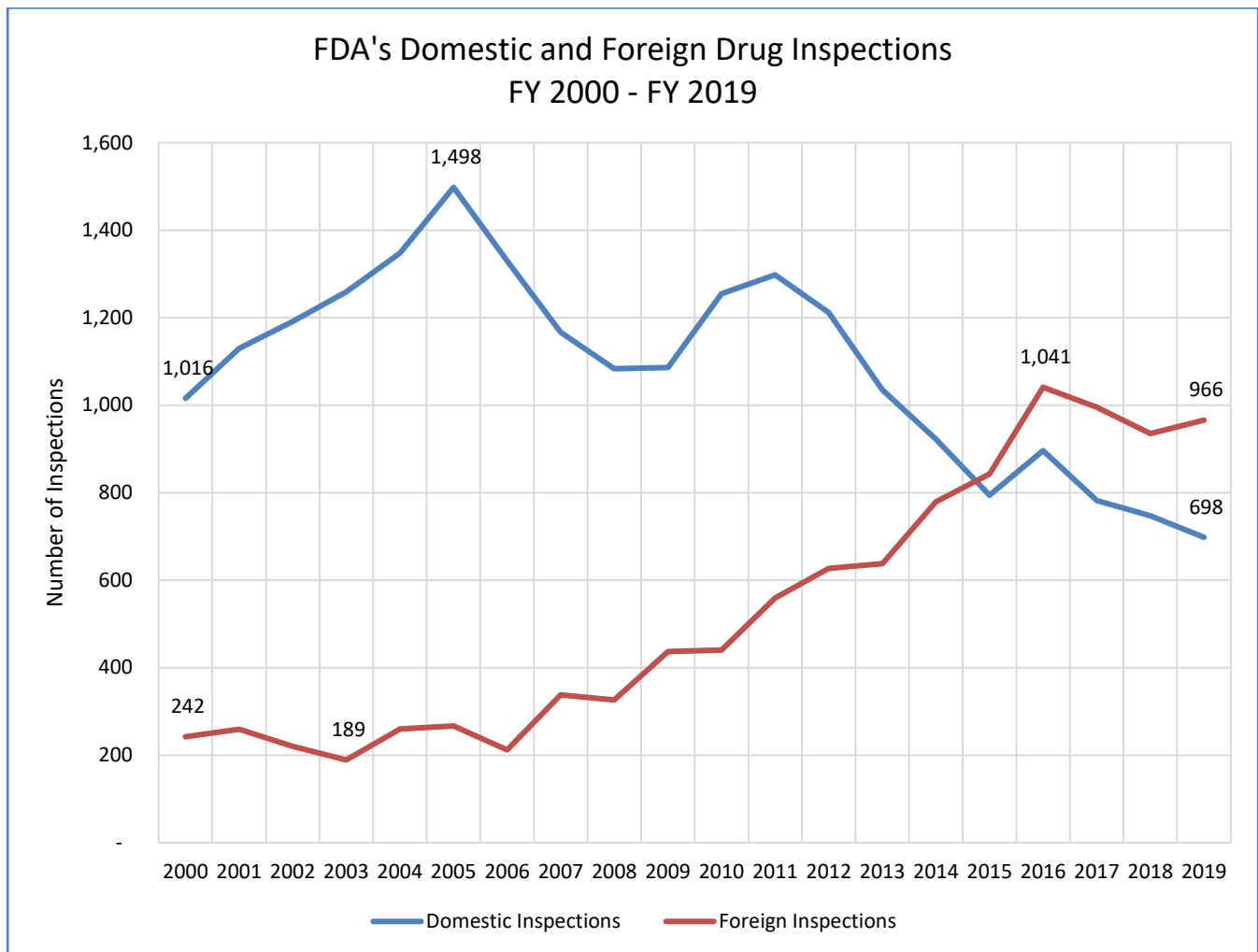


Figure 3: FDA's Inspections of Foreign Drug Manufacturing Facilities Increased Sharply After 2006 and Have Exceeded Inspections of Domestic Drug Facilities Since 2015

Types of Inspections

The types of inspections performed in both domestic and foreign facilities include *pre-approval*, *surveillance*, and *for-cause inspections*.

- *Pre-approval inspections*: conducted as part of the review of an application to market a new brand or generic drug.
- *Surveillance inspections*: Used to monitor the manufacturing process and, periodically, the quality of distributed drugs. FDA uses the findings to evaluate whether a manufacturer is complying with CGMPs. In general, the Agency does not announce domestic surveillance inspections to the company in advance but announces international surveillance inspections.⁴ Whether inspections are announced often depends on particular cases and the history of specific facilities.
- *For-cause inspections*: Triggered when FDA has reason to believe that a facility has serious manufacturing quality problems or when FDA wants to evaluate corrections that have been made to address previous violations. For-cause inspections can be announced or unannounced, whether domestic or international, depending on the specific situation.

The Site Selection Model

To address the need to prioritize use of limited resources, in 2005 FDA implemented a risk-based approach to drug facility surveillance inspections. A mathematical model, the Site Selection Model (SSM), was designed to select facilities with the greatest potential for public health risk should they not comply with established manufacturing quality standards. FDA uses results of the model to prepare a prioritized list of facilities for inspection.

⁴ FDA usually announces international surveillance inspections in advance, partly due to logistics such as arranging travel and access to facilities, and securing visas, and partly because of the high costs of conducting foreign inspections. When a surveillance inspection is announced, some manufacturers conduct a self-inspection or hire an independent inspector to ensure that manufacturing processes meet requirements.

The passage of FDASIA ratified our risk-based approach and removed the requirement to inspect domestic facilities on a fixed biennial schedule. FDASIA also enhanced our inspectional authority by requiring facilities to provide, upon request, records or other information in lieu of or in advance of an inspection. Additionally, under another provision added by FDASIA, if the owner or operator of a foreign facility delays, denies, or refuses to permit inspection, all drugs manufactured at that facility would be deemed “adulterated.”⁵ The Agency thanks this committee and Congress for your support in enacting this law.

In 2007, FDA began to shift its investigator workforce to cover foreign facilities and to rebalance allocation between domestic and foreign inspections. Still, the Agency did not have adequate staffing and financial resources for foreign inspection coverage. Both the Generic Drug User Fee Amendments (GDUFA) of 2012 and its reauthorization in 2017 provided new resources to FDA for inspecting foreign facilities, which are often the source for APIs and FDFs of generic drugs.

With new resources, FDA has been able to inspect some facilities that previously had not been inspected. CDER’s Catalog showed that as of July 2016, there were 965 foreign manufacturing facilities that had never been inspected by FDA. By the end of FY 2019, FDA had inspected 495 or 51 percent of these previously uninspected facilities (**See Figure 4**). An additional 359 facilities (37 percent) were removed from the Catalog because they were no longer part of FDA’s inspection obligations for a number of reasons: e.g., they had gone out of business, were not serving the U.S. market, or had been registered with FDA erroneously. In addition, 52 or six percent of the facilities had refused inspection;⁶ 37 or four percent of the facilities were inaccessible to FDA investigators because they were unable to travel to them (e.g., as

⁵ The Federal Food, Drug, and Cosmetic Act (FD&C Act) describes different circumstances in which a drug may be considered adulterated. For example, a drug might be adulterated where it is contaminated with filth, where its purity departs from certain compendial standards, or where the conditions of its manufacturing are not consistent with current good manufacturing practice (CGMP).

⁶ Under the FD&C Act, as amended by FDASIA, a drug product will be deemed adulterated if a drug has been manufactured, processed, packed, or held in any factory, warehouse, or establishment which delays, denies, or limits an inspection, or refuses to permit entry or inspection. In such a case, FDA typically will place the firm on import alert.

a result of travel warnings); and 22 or two percent had no drug shipments.

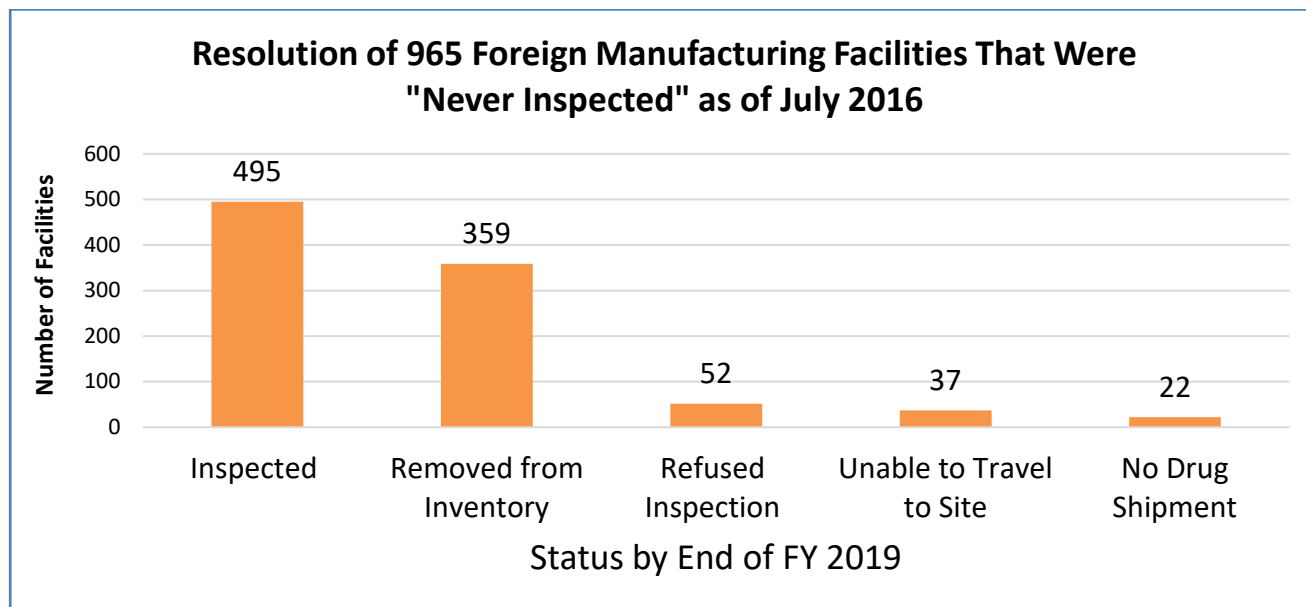


Figure 4. FDA has now inspected 495 (51%) of the 965 foreign manufacturing facilities that had never been inspected, as of July 2016.

The SSM is at the core of FDA’s surveillance inspection prioritization program and ensures a uniform approach for domestic and foreign facility inspections. The Agency uses the model to calculate a score for every facility in its Catalog using risk-based factors. Factors in the SSM include:

- **Inherent product risk.** Different types of products carry different levels of risk based on characteristics such as dosage form, route of administration, or whether the product is intended to be sterile. For example, a manufacturing facility that makes sterile injectable drug products will have a higher inherent product risk than a facility that makes oral capsules.
- **Facility type.** Risk levels can vary depending on the operations that a facility performs. A facility that manufactures drug product or active ingredients is higher in risk than a facility that only packages drug product.
- **Patient exposure.** The more products a facility manufactures, the more likely a patient is to encounter products made at that facility. This refers to both number and types of products

manufactured. A facility that manufactures many products will have a higher exposure factor than a facility that makes few products.

- **Inspection history.** A facility that has not met established quality standards when previously inspected is considered higher risk than those that have met standards in the past.
- **Time since last inspection.** As the time since a facility was last inspected increases, the risk that it may not meet established quality standards increases, as does the need for re-inspection.
- **Hazard signals.** Events such as product recalls or manufacturers' or patients' reports of quality problems associated with a facility increase the risk score when compared with facilities that have fewer or no major hazard signals.

FDA compares a facility's score to others in the Catalog and ranks them by risk, with the highest risk assigned for inspection regardless of location.

If the three factors that are fairly static for a facility (inherent product risk, facility type and patient exposure) are used to risk rank facilities, for inspections conducted from December 2011 to June 2019, the median time between inspections was 2.1 years for high-risk facilities. In general, all high-risk facilities were inspected with about the same frequency regardless of location. **(See Figure 5)**

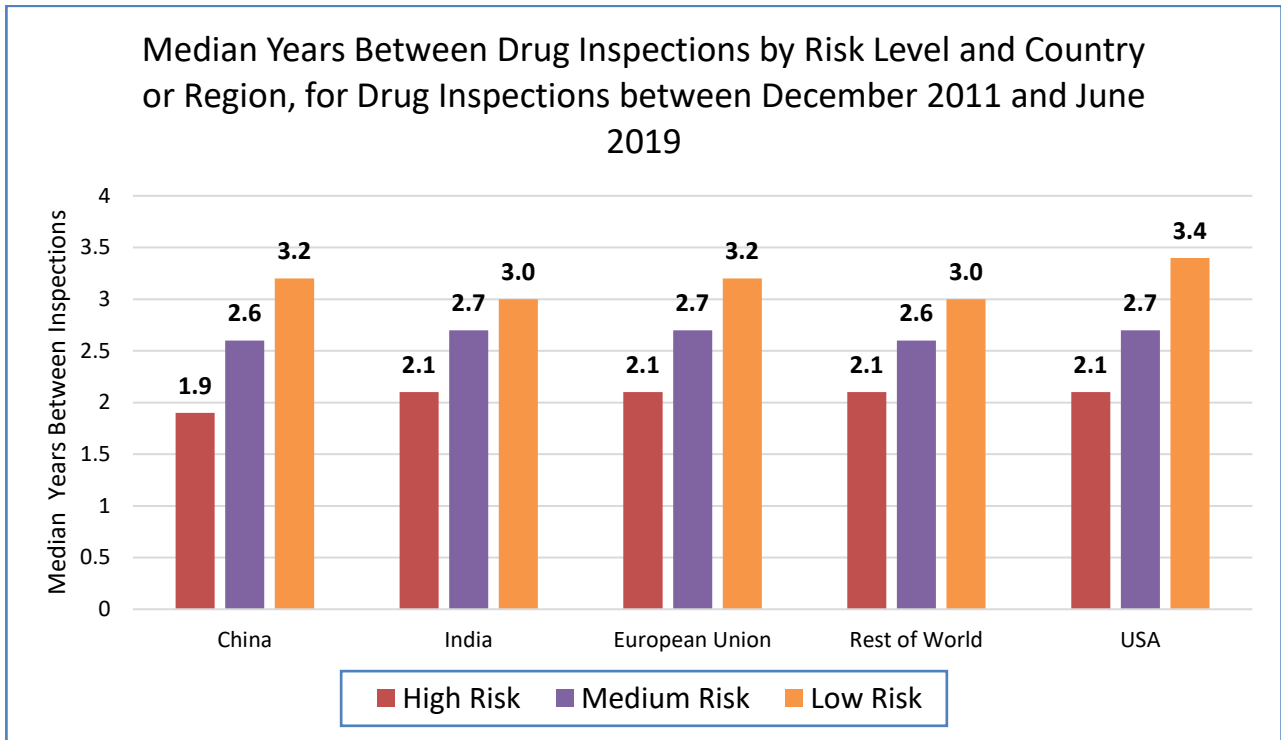


Figure 5. FDA inspected high-risk manufacturing facilities more frequently than medium- or low-risk facilities, and medium-risk facilities more frequently than low-risk facilities, across all countries or regions. In general, all facilities in a risk category were inspected with about the same frequency, regardless of location.

Inspection Outcomes

Following inspection of a manufacturing facility, FDA classifies the inspection as “no action indicated” (NAI), “voluntary action indicated” (VAI), or “official action indicated” (OAI).

- *No Action Indicated (NAI)* means that no objectionable conditions or practices (e.g., quality problems) were found during the inspection (or they were minor problems that do not justify further regulatory action).
- *Voluntary Action Indicated (VAI)* means objectionable conditions or practices were found but the Agency is not prepared to take or recommend any administrative or regulatory action.

- *Official Action Indicated (OAI)* means regulatory and/or administrative actions will be recommended.⁷

Not surprisingly, with more frequent inspections directed to higher-risk facilities since 2012, FDA uncovered some deficiencies, particularly in foreign facilities that had not been inspected as frequently as domestic ones prior to the inception of FDASIA and GDUFA. Nevertheless, 90 percent or more of the final outcomes of inspections were acceptable (NAI or VAI) in all countries or regions except India (See **Figure 6**).

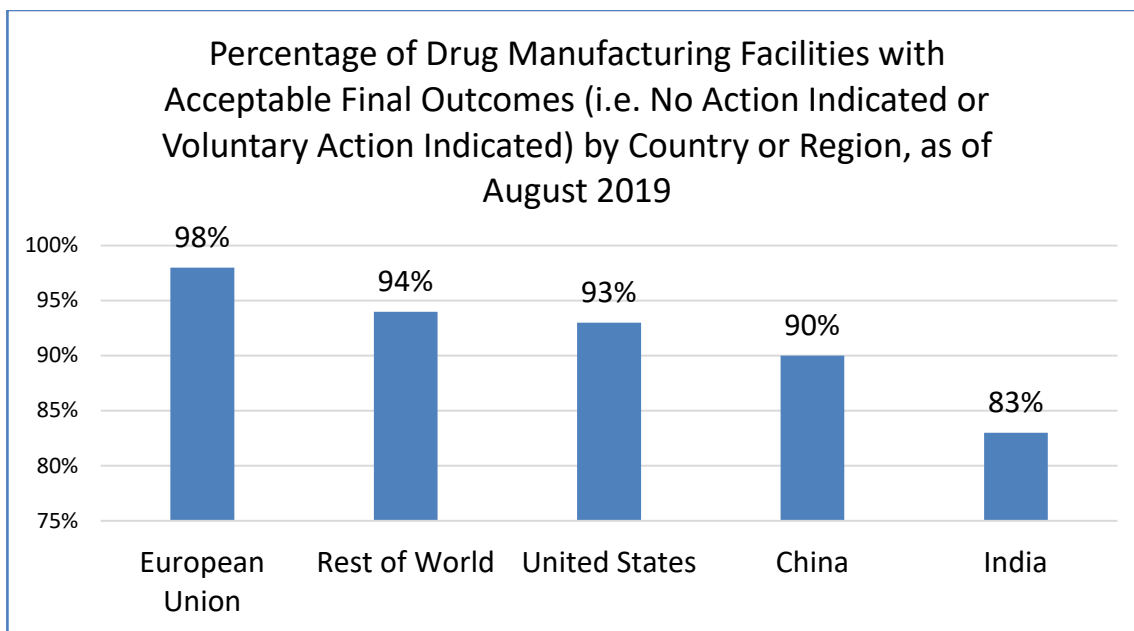


Figure 6. The majority of final inspection outcomes for manufacturing facilities making human drugs were acceptable, meaning that they were classified as having No Action Indicated or Voluntary Action Indicated. However, India had a lower percentage of acceptable outcomes than other countries and regions. (These were outcomes as of August 2019 for the most recent inspection of facilities that were in the Catalog as of July 2019.)

Both foreign and domestic drug manufacturers must meet the same regulatory requirements in terms of complying with established quality standards (CGMPs). If a facility doesn't meet CGMP standards upon inspection, FDA has an array of regulatory tools it can use to encourage a company to remediate their

⁷ See "What Is A Classification?" at <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-references/inspections-database-frequently-asked-questions>.

manufacturing processes and achieve compliance. These tools include warning letters, import alerts, injunctions, and seizures.⁸ If the Agency observes on a follow-up inspection that a facility still does not meet CGMP standards, it can escalate the matter as appropriate.

If a foreign facility is found to have quality problems serious enough for FDA to classify it as OAI, the Agency can place a facility on Import Alert to prevent drugs from the facility from legally entering the United States. Generally FDA will remove a facility from a CGMP-related Import Alert after an onsite re-inspection demonstrates that the problems have been remediated and the firm is in compliance with CGMP.

Despite the tools at FDA's disposal, we still face some challenges in ensuring the safety of imported drugs entering our drug supply. Under our current authorities, foreign-based manufacturers of certain drugs can legally ship drugs to the United States without ever having been inspected by FDA. Drugs in this category typically include OTC monograph drugs and APIs used in pharmacy compounding. This increases the risk of exposing American patients to unsafe or ineffective drugs and requires resource-intensive efforts on FDA's part to identify and respond to any problems that arise subsequently. For example, last month, we issued a warning letter to a discount retailer for receiving OTC drugs produced by foreign manufacturers with serious violations of CGMPs. The majority of the foreign facilities involved had distributed drugs to the United States prior to FDA inspections.⁹

FDA's Program Alignment Initiative and Concept of Operations Agreement

The inspection of drug manufacturing facilities relies on the collaboration of two organizations within FDA: the Office of Regulatory Affairs (ORA), which contains the field force of investigators who conduct

⁸ Import Alert: Import alerts inform the FDA's field staff and the public that the agency has enough evidence to allow for Detention Without Physical Examination (DWPE) of products that appear to be in violation of the FDA's laws and regulations. These violations could be related to the product, manufacturer, shipper and/or other information.

⁹ <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/greenbrier-international-inc-dba-dollar-tree-574706-11062019>.

the inspections, and CDER, which includes compliance officers who review inspection reports that are initially recommended as OAI and for-cause inspections to determine the final classification and whether appropriate regulatory action is required. CDER also includes reviewers who evaluate applications for marketing approval and post-marketing changes. ORA has recently completed a multi-year effort to implement a specialized inspectorate focused on human drugs.

On June 6, 2017, CDER and FDA's Office of Regulatory Affairs (ORA) entered into a Concept of Operations¹⁰ (ConOps) agreement to better integrate facility evaluations and inspections for human drugs. The planning for this integration began in 2013 in a Program Alignment initiative.¹¹ The ConOps is designed to improve the collaboration between ORA and CDER and enhance the efficiency and effectiveness of FDA's oversight of drug manufacturing facilities. As part of this effort, FDA redesigned processes to enhance the efficiency and effectiveness of classifications of inspection classifications (**See Figure 7**). If ORA initially recommends classifying the inspection report as OAI, CDER's Office of Compliance then reviews the report and the manufacturing facility may submit a remediation plan to rectify any quality problems that were noted. CDER evaluates the evidence supporting inspection observations, impacts to patient safety, the company's responses to the observations, and the adequacy of proposed corrective actions. Depending on the particular circumstances, including remediation efforts made at the facility, CDER may reclassify the inspection.

¹⁰ See <https://www.fda.gov/media/107225/download>.

¹¹ See <https://www.fda.gov/about-fda/office-regulatory-affairs/program-alignment-and-ora>.

Concept of Operations CGMP Surveillance Inspection Process

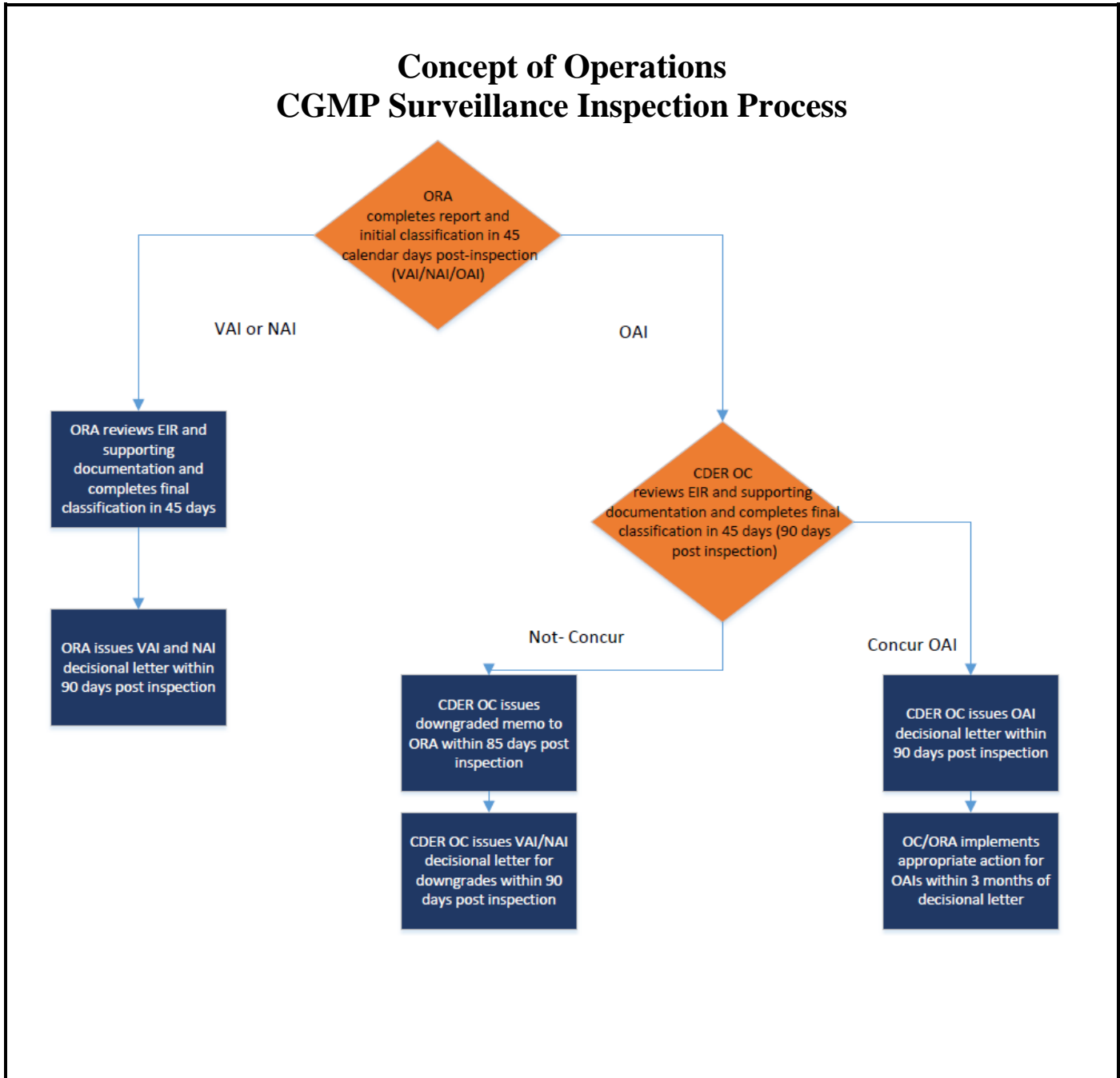


Figure 7. Process for classifying surveillance inspection outcomes after implementation of the ConOps.

Implementation of the ConOps has helped improve consistency in evaluation of inspection observations, classification of the inspection, and has reduced the time frames for taking enforcement action. The percentage of cases in which CDER concurs with ORA’s initial recommendation is known as the “concurrence rate” (See **Figure 8**). In 2019, the concurrence rate had risen to 73 percent.

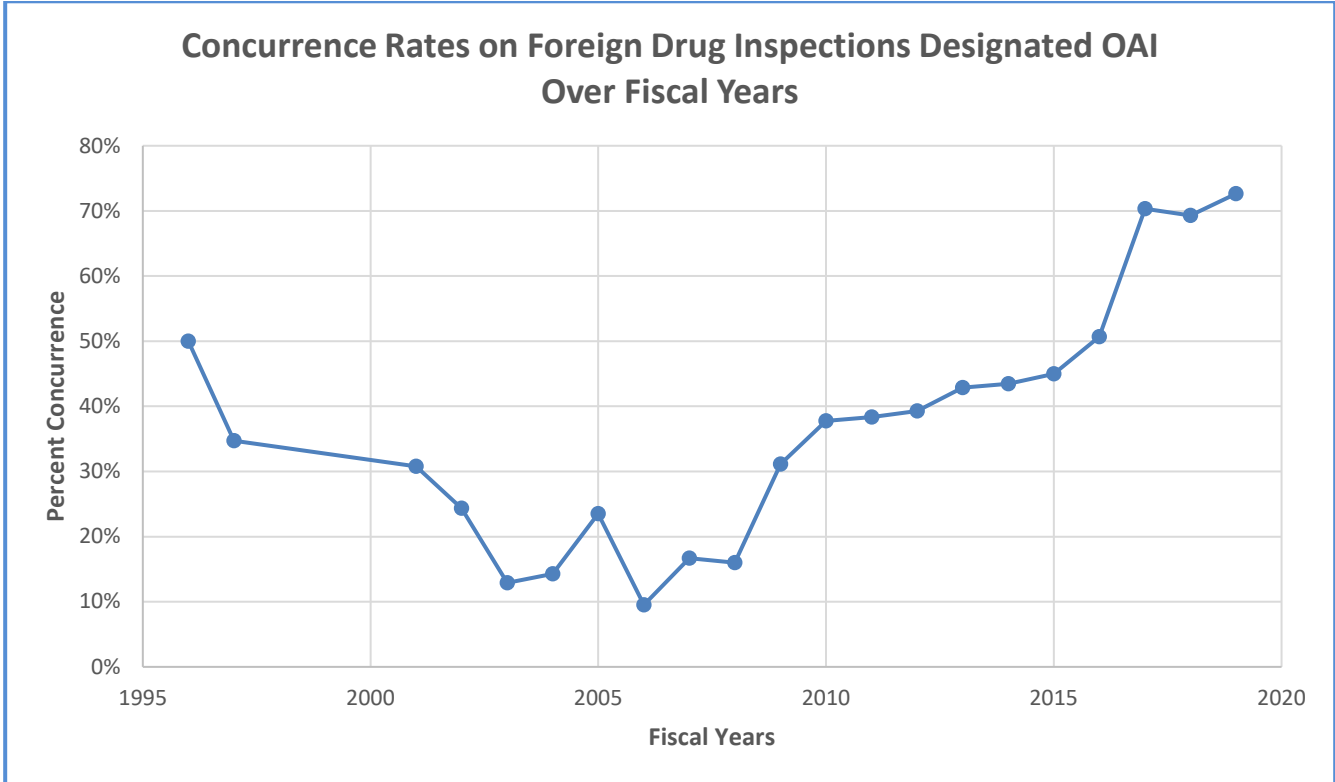


Figure 8. Concurrence rates on foreign drug inspections designated OAI were 50% in 1996 and rose to 73% in 2019. (FY 1996-1997 based on GAO data, all other data from FDA compliance database.)

The median time for FDA to issue a warning letter for drug manufacturing issues has decreased since ConOps was implemented, even though the number of warning letters FDA has issued has increased during that same time period (See **Figure 9**).

Agency Progress Toward Six-Month Compliance Actions

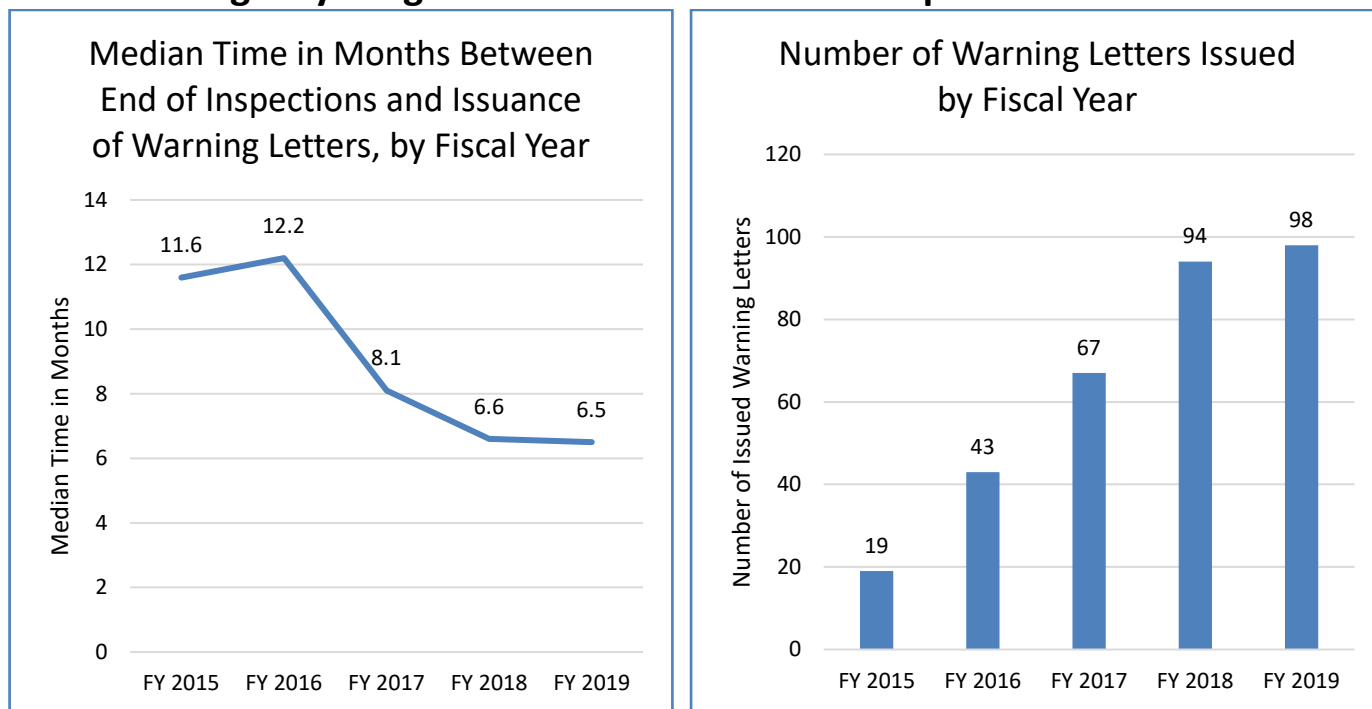


Figure 9. From FY 2015 to FY 2019 there has been an overall median 44% improvement in median time between the end of an inspection and issuance of a warning letter. During the same time, the number of warning letters increased.

Building an Investigator Work Force

FDA has performed more foreign than domestic inspections since 2015. The Agency utilizes a risk-based site selection model to identify firms for inspection. FDA has achieved this level of foreign coverage by using a mixed investigator work force consisting of (1) U.S.-based investigators who perform both domestic and foreign inspections; (2) a dedicated foreign cadre of U.S.-based drug investigators who conduct foreign inspections exclusively; and (3) foreign office-based investigators who inspect facilities manufacturing human drugs (See **Table 1**). The majority of foreign inspections are performed by domestically based staff in the first two categories.

Type of Investigator	Number of Qualified Foreign Drug Investigators in FY 2019	Number of Foreign Inspections Each Investigator is Expected to Perform Each Year	Estimated Percentage of All Foreign Inspections Performed in FY 2019
U.S.-Based Investigators Performing Foreign and Domestic Inspections	188	3-6 Foreign inspections per year	90%
Dedicated Foreign Drug Cadre	12 (included in the 188 listed above)	16 -18 inspections per year	16% (part of the 90% above)
Foreign Office-Based Investigators	12	15 inspections per year	10%

Table 1. FDA’s Investigator Work Force for Inspections of Foreign Facilities Producing Human Drugs, FY 2019

By the end of this calendar year we expect 20 pharmaceutical investigators will be onboarding, and with our new direct hire authority we anticipate filling all our pharmaceutical investigator vacancies in 2020. In recent years, FDA has made progress in developing the foreign office-based inspectorate. At the same time, FDA’s participation in the Mutual Recognition Agreement with the European Union has enabled us to focus more of our investigator work force on higher-risk facilities around the world.

However, the Agency continues to face challenges in developing the investigator work force due to the rigorous nature of the job (e.g., foreign travel restrictions and hardship). Competition for qualified candidates in a low-unemployment economy adds to our challenge in hiring. Even if the Agency succeeds in hiring a new investigator, it can take 1.5 to 2 years of training to bring them to a fully proficient level. Beyond these general issues, FDA faces specific challenges to achieving optimum staffing levels, such as negotiated agreements with host countries that affect the number of investigators who can be permanently attached to a foreign office.

FDA's Sampling and Testing Program

Although application assessments and inspections are a foundation of FDA's efforts to maintain a safe, reliable drug supply, the safety and effectiveness of drugs depends on a multipronged approach, of which quality checks by FDA and manufacturers are a part. To help ensure that safe and effective drugs are sold in the United States, we test selected drugs in state-of-the-art FDA laboratories and through research contracts and grants. This testing program includes APIs and finished drug products. We test using the same standards that are part of the drug approval process for identity, strength, and purity.

Some have raised the question of why we do not test every drug product before it enters the United States. FDA performs thousands of tests a year pre- and post-market. Only a small percentage (about one percent) of drugs that are tested fail to meet the established quality specifications.¹² Testing by FDA or third parties of each batch of drug product in U.S. commerce, which amounts to millions of batches and trillions of individual tablets, capsules, and other dosage forms, before they enter the U.S. market would not be feasible at a practical level (in 2018, there were almost 186 trillion tablets and capsules on the U.S. market¹³) and the current approach is effective and efficient.

FDA Encourages Industry to Invest in Mature Quality Management Systems and Advanced Manufacturing Technology

FDA inspects manufacturing facilities and takes action, if needed, to enforce CGMP quality standards and applicable regulations. The Agency's investigators look for deficiencies in meeting CGMP standards, but these assessments do not measure how far the facility is above the minimum CGMP. Simple adherence to CGMP standards does not indicate that a firm is investing in improvements or planning or deploying advanced quality control techniques that could better enable it to prevent quality problems leading to

¹² These are established by USP, see <https://qualitymatters.usp.org/what-usp-standard>.

¹³ IQVIA. National Sales Perspective. 2014-2018. Extracted: August 2019.

supply disruptions.

Even when a firm does invest in such improvements, it may be difficult to identify measures of quality that could be used to predict major quality issues that can lead to shutdowns of manufacturing lines resulting in supply disruptions. Even if these measures were readily available, FDA might not have access to the needed data regarding the performance of the manufacturing facility.

This is why it is critical that industry evolve from meeting the minimum manufacturing quality threshold to achieving quality management maturity. Some pharmaceutical firms have been slow to implement robust, mature quality systems and the accompanying quantitative measures of quality that have been the foundation of success in other industries, such as automotive and aerospace.¹⁴ These industries exercise quality oversight by continuously monitoring quality in real time during manufacturing of their products, and promptly correcting operations when needed. Numerous organizations and quality experts have worked to develop conceptual models and standards for advancing the maturity of industrial quality management systems. These models could be used more broadly in the pharmaceutical industry to improve the quality and reliability of the drug supply.

Many pharmaceutical manufacturers, whether domestic or foreign, have been slow to invest in these mature quality management systems because the market currently has no visibility into manufacturing facilities' quality. This lack of transparency reinforces competition based solely on price and disincentivizes companies from making investments in upgrading their facilities and quality practices until problems become frequent and severe enough to result in supply disruptions and drug shortages. As we have stated in our recent report, "Drug Shortages: Root Causes and Potential Solutions",¹⁵ a way to create incentives for manufacturers to invest in product quality is to develop and implement a rating system for quality

¹⁴ Fuhr, Ted, et al., 2015, Flawless-from Measuring Failure to Building Quality Robustness in Pharma, McKinsey & Company.

¹⁵ <https://www.fda.gov/drugs/drug-shortages/agency-drug-shortages-task-force>.

management maturity that is based on objective criteria. Such a rating system could enable purchasers to compare differences in quality and choose whether to reward more reliable manufacturers financially and with increased market share.

In addition to quality management maturity, the Agency encourages pharmaceutical manufacturers to invest in advanced manufacturing technology to improve their products and processes. Although widely used in some other industries, such as automotive, aerospace, and semiconductors, advanced manufacturing is now just beginning to be used by pharmaceutical companies. New technologies include “continuous manufacturing” (CM), wherein the finished drug product or active pharmaceutical ingredient is produced as a continuous stream, as opposed to traditional batch manufacturing where breaks or stops exist between different processing steps. In some examples of advanced pharmaceutical manufacturing, production can be continuous from chemical synthesis of the active ingredient through production of the tablets or other dosage forms. Product quality can be precisely controlled with modern automation and control systems and can be closely monitored during production by using highly sensitive analytical tools.

Conclusion

Over the past 20 years, the pharmaceutical industry that supplies American patients with drugs has, to a significant degree, moved offshore, so that today the majority of API and FDF manufacturing facilities are located outside the United States. In response, FDA has developed a risk-based approach to surveillance inspections that ensures equal treatment of foreign and domestic facilities. We believe that this is an effective and efficient approach for ensuring that American patients have access to a supply of safe and effective drugs. We thank the committee for the legislation that has made this transition possible. At the same time, the reliability of our drug supply chain could be further strengthened by investment in modern manufacturing technology and in establishing mature quality management systems in manufacturing facilities.