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As FDA resumes domestic inspections while keeping foreign inspections on hold, questions remain about the agency's ability to keep tabs on the global supply chain

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On July 10, 2020, the Food and Drug Administration (FDA or the Agency) announced plans to resume domestic facility inspections following the March 2020 suspension of most foreign and domestic facility inspections during the COVID-19 pandemic.[1]

FDA resumed domestic on-site inspections the week of July 20, 2020, and indicated that it would preannounce such inspections to regulated businesses. (Retail tobacco inspections will continue to be unannounced.)

FDA is scheduling domestic inspections and other regulatory activity using its newly developed Advisory Rating system, which assesses the phase of reopening and the current intensity and risk of COVID-19 infections in geographical areas where facilities are located.

The Agency also continues to clarify its approach to inspections periodically, most recently through new guidance issued on August 19, 2020. Despite resuming domestic inspections, however, FDA has yet to resume most foreign inspections.

Until all foreign inspections resume, disparities in the regulatory oversight of domestic and foreign facilities will continue to persist, deepening the competitive advantage foreign facilities enjoy over domestic facilities.

KEY TAKEAWAYS

- Domestic on-site inspections resumed the week of July 20, 2020, with FDA preannouncing all but retail tobacco inspections.
- Most foreign inspections remain on hold, deepening the gap in regulatory oversight between domestic and foreign facilities. Because nearly three out of every four API facilities and more than half of finished dosage manufacturing facilities are located outside of the US, this disparity in inspections has subjected FDA to congressional scrutiny.
- FDA developed an Advisory Rating system to determine where and when it is safest to conduct domestic inspections during the COVID-19 pandemic.
- FDA is prioritizing inspections it considers "mission-critical" (i.e., highest priority during the pandemic) based on many public health factors, including if the product has received breakthrough therapy designation or regenerative medicine advanced therapy designation, or if the product is used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute. The prioritized domestic inspections generally include pre-approval and surveillance inspections.

SUMMARY OF ANNOUNCEMENT

FDA paused facility inspections in March 2020 because of the COVID-19 pandemic. In connection with its goal to resume domestic on-site surveillance inspections of regulated facilities on or after July 20, 2020, FDA announced an approach to conducting domestic inspections that is intended to carry out FDA's regulatory mission while protecting the health, safety and well-being of its investigators and the public.

This approach includes the preannouncement of inspections, the use of an Advisory Rating system to determine when and where inspections safely can be carried out, and the identification of categories of regulatory activities that may occur in a geographic region.

In view of the risks presented by the current pandemic, FDA's July 20 announcement indicated the Agency would preannounce domestic on-site inspections, with the exception of retail tobacco inspections, for the foreseeable future. FDA declined to preannounce retail tobacco inspections because they are typically performed undercover.

In addition, FDA developed a COVID-19 Advisory Rating system to help determine the best time and place to conduct prioritized domestic on-site inspections.

This rating system relies on real-time data at the national and state level to qualitatively assess the number of COVID-19 cases in a specified region, termed an Advisory Level.

The Advisory Level is based on three metrics, including the "phase of the state," as defined by White House guidelines, and county-level statistics gauging the current trend and intensity of infection. FDA will make this data available to state partners that conduct inspections on the Agency's behalf.

As of May 2020, approximately three out of every four facilities that manufacture active pharmaceutical ingredients for the U.S. market were located outside the U.S.

FDA is using the Advisory Level to determine the level of regulatory activity that it can carry out within a specified region. There are three main categories of regulatory activity:

(1) only mission-critical inspections,

(2) all inspections with caveats to protect staff who self-identify as being in a vulnerable population, and

(3) all regulatory activities.

FDA investigators will be outfitted with personal protective equipment and other necessary equipment to carry out their work while they are on-site, to adhere to guidance from the Centers of Disease Control and Prevention as well as from state and local governments.

FDA acknowledged that the resumption of on-site inspections is dependent on data reflecting the trajectory of the COVID-19 virus in a specified state and locality, along with the rules and guidelines put in place by state and local governments.

FDA will look for a downward trend in the rate of new COVID-19 cases and hospitalizations in a given area before on-site inspections can resume. The agency also noted that its ability to resume will depend upon the availability of certain services impacted by the pandemic, such as public transportation.

The inspections prioritized by FDA generally include pre-approval and surveillance inspections. FDA has also prioritized inspections it deems "mission-critical" on a case-by-case basis. On August 19, 2020, FDA released new guidance explaining its inspection policy in hopes of answering questions raised by the industry.[2]

In particular, the agency clarified its approach to determining which inspections were "mission-critical." FDA will consider many public health related factors when making this determination, including whether the products have received breakthrough therapy designation or regenerative medicine advanced therapy designation, or whether the products were used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other appropriate substitute.

When determining whether to conduct a mission-critical inspection, the agency stated it would take into account concerns about the safety of its investigators, employees at a site or facility, and where applicable, clinical trial participants and other patients at investigator sites.

The mission-critical determination would be used in the assessment of both domestic and foreign inspections. Foreign pre-approval and for-cause inspections which are not deemed mission-critical will remain postponed. However, foreign inspections that are deemed mission-critical will be considered for inspection on a case-by-case basis.

Given FDA's limited ability to conduct foreign inspections, the agency has adopted several alternative approaches to inspections in its recent guidance.

These alternative measures include denying entry of dangerous products into the U.S., conducting product examinations at the borders, using information shared from foreign governments as part of mutual recognition and confidentiality agreements, and requesting records in advance of or in lieu of on-site drug inspections.[3]

The agency also is targeting products through its Predictive Risk-based Evaluation for Dynamic Import Compliance Targeting (PREDICT) import screening tool to focus its examinations and sample collections based on heightened concerns of specific products being entered into U.S. commerce.

IMPLICATIONS FOR THE INDUSTRY

The resumption of domestic inspections ahead of foreign inspections gives a continued reprieve to a large segment of FDA-regulated industry. As of May 2020, approximately three out of every four facilities that manufacture active pharmaceutical ingredients for the U.S. market were located outside the U.S.[4]

Similarly, more than half of the facilities that manufacture finished dosage forms for the U.S. market were also located outside the U.S.[5] FDA has been focused in the past decade on increasing the number of foreign inspections it conducts, as well as working to expand partnerships with foreign governments and leveraging their inspectional findings, to address the increasingly global nature of the pharmaceutical supply chain.

Despite this, the total number of foreign and domestic inspections decreased by about 10 and 13 percent, respectively, from 2016 to 2018. This decrease in total number of inspections will likely continue as a result of COVID-19.

In 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act ("FDASIA") and the Generic Drug User Fee Amendments, which, among other things, required FDA to institute a risk-based approach in both foreign and domestic inspections to

better achieve parity in their regulation. FDASIA also imposed higher inspection fees on foreign facilities.

The U.S. Senate Committee on Finance held a hearing on June 2, 2020, to address FDA's oversight of the global pharmaceutical supply chain. At the hearing, FDA reiterated its commitment to balancing its focus on both foreign and domestic facilities.[6]

The Agency cited the increasingly growing number of inspections it conducts overseas and pointed out that starting in 2015, the annual number of foreign inspections have consistently surpassed domestic inspections.[7]

FDA issues Warning Letters in disproportionately higher amounts to companies located outside the U.S., particularly India and China.

Despite this, Sen. Chuck Grassley, R-Iowa, expressed concern about the reliability of a global supply chain dependent on overseas manufacturing, especially given the unique vulnerabilities exposed by the COVID-19 pandemic.

Such concerns are not without merit, as FDA faces persistent criticism for the gap in oversight between its regulation of foreign and domestic facilities.

This gap is attributable to many causes, including a significant number of job vacancies among inspectors who carry out foreign inspections, an increase in the number of foreign drug manufacturing facilities over time, and challenges in conducting unannounced inspections abroad.

With regard to vacancies, FDA identified 190 filled positions among U.S. inspectors who conduct foreign inspections but 58 vacant positions.[8] Of these 58, only 26 were in the process of being filled. FDA further cited "persistent" vacancies among investigators in foreign offices.[9]

An increase in the number of foreign drug manufacturing facilities also constitutes a growing burden on FDA resources. From 2011 to 2016, the number of drug manufacturing facilities increased by 28% in the EU, 66% in India, and 66% in China.[10]

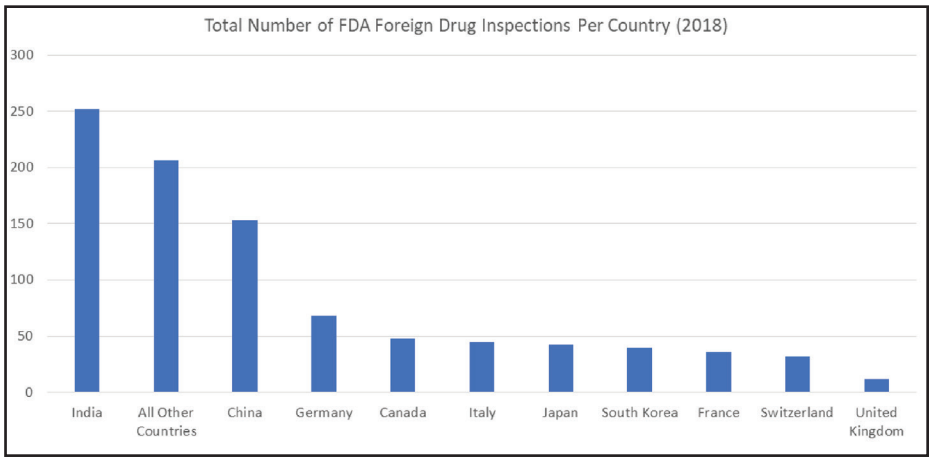
In addition to position vacancies and the increased number of facilities, FDA faces additional challenges in its ability to conduct inspections abroad without providing notice. According to a June 2020 report by the United States Government Accountability Office ("GAO"), FDA preannounces the majority of inspections in foreign countries and may even provide facilities with up to 12 weeks' notice.[11]

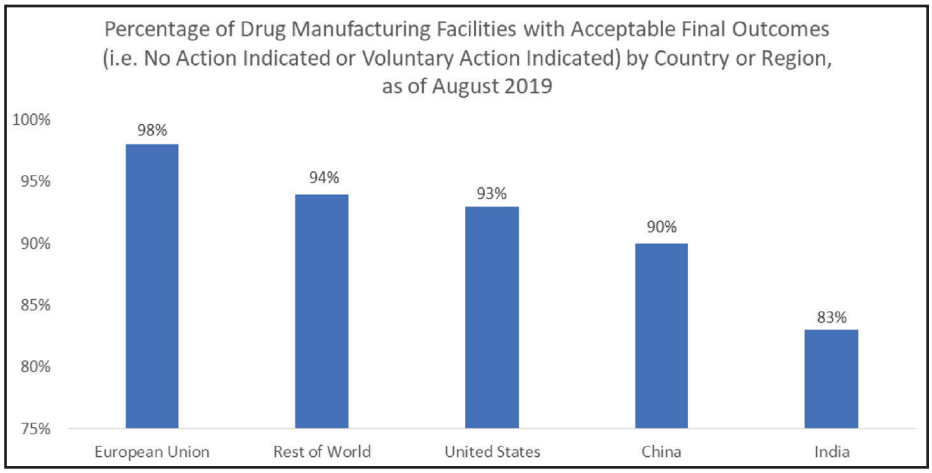
Investigators in China and India, particularly, perform only a limited number of unannounced inspections: as of December 2019, investigators in China were only able to conduct unannounced inspections in roughly one time out of four, while investigators in India are only to conduct unannounced inspections one time out of ten.[12]

In these countries, even inspections that FDA refers to as "unannounced" may still result in the facilities receiving some amount of notice. The low rate of unannounced inspections abroad is in stark contrast to domestic inspections, which are "almost always" unannounced.[13]

This gap in oversight is thought to contribute to a lesser quality of manufactured drugs imported into the United States.

For example, while India and China are the two foreign countries with the highest total number of inspections conducted in 2018 (27% and 16%, respectively),[14] they had the lowest number of acceptable outcomes when compared to other regions of the world in August 2019 (83% and 90%, respectively).[15]





Disparities in the quality of foreign manufactured drugs may also be evidenced by the increase in Warning Letters in recent years and by the comparatively lower site inspection scores for foreign facilities.

FDA issues Warning Letters in disproportionately higher amounts to companies located outside the U.S., particularly India and China.[16] The number of total Warning Letters FDA issued has increased over time: while FDA issued 19 letters to global drug manufacturers in 2015, the agency issued 98 letters in 2019 — an increase of 415%.[17]

> The indefinite halting of most foreign inspections amidst the COVID-19 pandemic raises new resource and prioritization dilemmas for FDA.

Facilities in certain foreign countries also score lower than the U.S. on compliance with cGMP regulations, as measured by FDA's "site inspection scores." Though all the countries' scores indicate an acceptable level of compliance to cGMPs, the average scores for sites in the EU (7.7) and U.S. (7.6) are statistically higher than the global average (7.4), while the average scores for sites in China (7.0), India (6.8), and Latin America (6.8) fall below the global average.[18]

FUTURE OUTLOOK

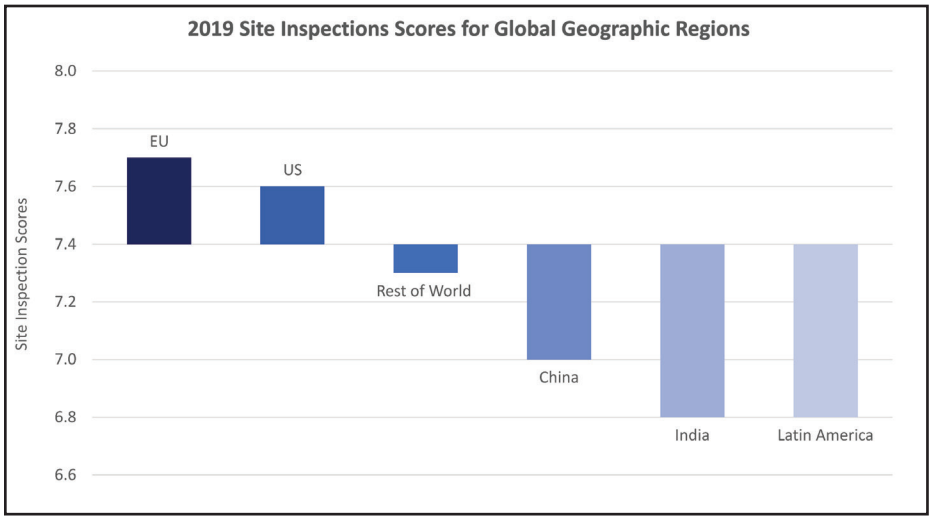
The indefinite halting of most foreign inspections amidst the COVID-19 pandemic raises new resource and prioritization dilemmas for FDA. Though the agency purports to have other mechanisms to ensure the safety of the U.S. drug supply, the pausing of foreign inspections nonetheless "removes a critical source of information about the quality of drugs manufactured for the U.S. market."[19]

In light of the uneven nature of FDA's inspection regime during the global pandemic, domestic and foreign companies are well-advised to train additional focus and resources on their internal and third-party audit programs to ensure that their facilities are keeping pace with expectations.

In parallel, it would be wise for domestic facilities to increase their readiness preparations to anticipate FDA's resumption of on-site inspections, especially in regions where the severity of the COVID-19 risk is decreasing and where state and local governments are transitioning to subsequent phases of reopening.

Non-U.S. facilities might well use this window of time to evaluate and strengthen inspection readiness capabilities and to continue to improve systems and processes. These entities should also be mindful of FDA's increased coordination with certain foreign governments during this period.

While FDA is working to ensure the health and safety of its investigators, it remains keenly focused on protecting the public health by assuring the safety, effectiveness and security of FDA-regulated products.



Notes

[1] FDA Statement, "Coronavirus (COVID-19) Update: FDA Prepares for Resumption of Domestic Inspections With New Risk Assessment System" (July 10, 2020).

[2] FDA Guidance, "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers" (August 2020).

[3] FDA Guidance, "Manufacturing, Supply Chain, and Drug and Biological Product Inspections During COVID-19 Public Health Emergency Questions and Answers" (August 2020); Statement, Food and Drug Administration, "Coronavirus Disease 2019 (COVID-19) Update: Foreign Inspections" (March 2020).

[4] FDA Testimony, "COVID-19 and Beyond: Oversight of the FDA's Foreign Drug Manufacturing Inspection Process" (June 2, 2020).

[5] *Id.*

[6] *Id.*

[7] J. Woodcock, Testimony, "Securing The U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program" (Dec. 2019).

[8] Testimony, United States Government Accountability Office, "COVID-19 Complicates Already Challenged FDA Foreign Inspection Program" (June 2020).

[9] *Id.*

[10] E. Stevulak, Food and Drug Law Institute, "FDA Inspections: The Changing Landscape" (July 2017).

[11] Testimony, United States Government Accountability Office, "COVID-19 Complicates Already Challenged FDA Foreign Inspection Program" (June 2020).

[12] *Id.*

[13] *Id.*

[14] *Id.*

[15] J. Woodcock, Testimony, "Securing The U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program" (Dec. 2019).

[16] E. Wilkinson, The Pharmaceutical Journal, "Half of all safety warnings issued to drug manufacturers in India and China" (Aug. 2019):

"The analysis of [publicly] available data by The Pharmaceutical Journal shows that from early 2018 until August 2019, the FDA's Office of Manufacturing Quality has published 75 warning letters to pharmaceutical manufacturers that have violated its safety and/or quality standards. Half of these warning letters (49%) — which could result in the regulator taking enforcement action — were sent to companies based in [China or India]."

[17] J. Woodcock, Testimony, "Securing The U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program" (Dec. 2019).

[18] FDA's CDER and OPQ, "Report On The State Of Pharmaceutical Quality: Fiscal Year 2019" (June 2020).

[19] Testimony, United States Government Accountability Office, "COVID-19 Complicates Already Challenged FDA Foreign Inspection Program" (June 2020).

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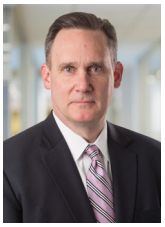
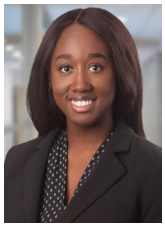

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