Indian Pharma: Congress and FDA Continue Scrutiny of Foreign Drug Companies with Heightened Focus on Companies Located in India

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India is an increasingly important supplier of drugs to the U.S. market.[1] In 2018, 12% of drug manufacturing sites for the U.S. market were located in India, surpassing any other foreign country including China.[2] As of August 2019, 72% of the active pharmaceutical ingredient (API) manufacturers supplying the U.S. market were located outside the United States, with 18% of them located in India.[3] India is also the world's largest producer of generic drugs. These numbers are expected to increase as India's pharmaceutical industry grows: at $20.49 billion in 2018, the industry is estimated to reach $52.61 billion by the end of 2028.[4]

As India has taken on an essential role in the U.S. pharmaceutical supply chain, Indian companies exporting drugs to the United States are experiencing greater scrutiny from Congress and U.S. regulators including the Food and Drug Administration (FDA). For example, Congress has held multiple hearings to address the safety of imported drugs in response to the recalls of angiotensin II receptor blockers (ARBs) (i.e., valsartan, losartan, and irbesartan) and the heartburn drug ranitidine, all due to potentially dangerous impurities. In particular, Congress has focused on India and China as manufacturers in both countries were implicated in the recalls.

Congressional scrutiny is likely to continue due to the recent outbreak of the novel coronavirus originating in Wuhan City, China, which has the potential to disrupt

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1 This article is part of a series of Debevoise publications addressing legal developments impacting companies located in, or doing business in, India. *See, e.g.*, *Indian Supreme Court Takes Another Step to Strengthen Arbitration*, DEBEVOISE & PLIMPTON (Dec. 17, 2019), https://www.debevoise.com/insights/publications/2019/12/indian-supreme-court-takes-another-step-to.

2 FDA Ctr. for Drug Evaluation and Research, *Report on the State of Pharmaceutical Quality* 3 (2018), https://www.fda.gov/media/125001/download.

3 *Hearing on Safeguarding Pharmaceutical Supply Chains in a Global Economy Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 116th Cong. 1 (2019) (statement of Janet Woodcock, M.D., Director of the Ctr. for Drug Evaluation and Research), https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Testimony-Woodcock-API_103019.pdf.

4 *Pharma Analytics*, DELOITTE 1 (June 2019), https://www2.deloitte.com/content/dam/Deloitte/in/Documents/risk/Pharma%20Analytics_Final%20Single%20page.pdf.

pharmaceutical supply chains in China, India, and the United States. Indian pharmaceutical companies are estimated to source 80% of their APIs from China, further exemplifying the global nature of the pharmaceutical supply chain.[5] FDA Commissioner Stephen Hahn has stated there are no reports of drug or device shortages in the United States due to supply chain disruptions caused by the coronavirus but that "the situation is fluid."[6]

Below, we summarize Congressional and regulatory developments related to the pharmaceutical supply chain, background on FDA inspections of pharmaceutical companies located in India and how Indian pharmaceutical companies and potential acquirers can best position themselves in 2020 and beyond.

Pharmaceutical Supply Chain Scrutiny

Foreign manufacturers of APIs and finished prescription and generic drugs are expected to confront additional scrutiny from Congress and FDA in the coming years. In remarks at an oversight hearing on FDA foreign inspections on December 10, 2019, House Energy and Commerce Committee Chairman Frank Pallone indicated that the committee will be focusing on foreign manufacturers, stating that "manufacturers have the first responsibility to guarantee their products are safe and effective," and "FDA must ensure that any company, whether brand or generic, that wishes to market drug products in the United States adheres to the same quality standards."[7]

Congressman Pallone's statement is not surprising, as certain members of Congress now consider the United States' reliance on foreign manufacturers—particularly China—to be a national security issue. In a recent Congressional hearing, Dr. Janet Woodcock, Director of FDA's Center for Drug Evaluation and Research, acknowledged

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5 Deepak Patel, *Pharma Sector: 80 Percent APIs via Chinese Imports Despite Similar Making Costs*, THE INDIAN EXPRESS (June 19, 2018), https://indianexpress.com/article/business/business-others/pharma-sector-80-per-cent-apis-via-chinese-imports-despite-similar-making-costs-5222951/.

6 Sarah Karlin-Smith, *FDA: No Drug Shortages Reported Because of Coronavirus but Situation "Fluid,"* POLITICO (Feb. 7, 2020), https://www.politico.com/news/2020/02/07/chinese-drugs-shortage-coronavirus-112049. Senators Marco Rubio and Chris Murphy sent a letter to Commissioner Hahn requesting information on FDA's efforts to guarantee the safety and supply of drugs, foods, and medical supplies from China in light of the epidemic. Letter from U.S. Senators Marco Rubio and Christopher S. Murphy to FDA Commissioner Stephen Hahn (Feb. 6, 2020), https://www.murphy.senate.gov/download/rubio-coronavirus-letter.

7 *Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program, Hearing Before the Subcomm. on Health of the Comm. on Energy and Commerce*, 116th Cong. 2 (Dec. 10, 2019) (statement of Frank Pallone, Jr., Chairman, House Energy and Commerce Committee), https://docs.house.gov/meetings/IF/IF02/20191210/110317/HHRG-116-IF02-MState-P000034-20191210.pdf.

the U.S. pharmaceutical sector's heavy reliance on foreign production due to cost advantages and the potential national security implications of that reliance.[8]

Lawmakers are primarily concerned with China's significance in the pharmaceutical supply chain, but Indian companies have also been implicated due to their reliance on Chinese-produced APIs. As noted above, Indian drug manufacturers reportedly source 80% of their APIs from China, which are then used in drugs destined for the U.S. market.[9]

The United States' reliance on foreign pharmaceutical manufacturers is not a new issue. In 2009, for example, the U.S. Government Accountability Office (GAO) identified "Protecting Public Health through Enhanced Oversight of Medical Products" as an area of high risk due in part to "globalization as more products are manufactured abroad."[10] More recently, in June 2019, following the high-profile recalls of ARBs and ranitidine produced outside the United States, the House Energy and Commerce Committee requested that the GAO review FDA's drug inspection programs, with a focus on FDA's efforts to oversee the drug product supply chain (including APIs) and to assess foreign inspection programs.[11] In a report issued December 10, 2019, the GAO found that continuing vacancies in FDA's foreign inspection workforce has contributed to declining total foreign inspections but that a growing percentage of FDA's foreign inspections (43% in 2018) were conducted in China and India.[12]

Increased interest in drug importation is also expected to result in greater scrutiny of the pharmaceutical supply chain. In July 2019, the Department of Health and Human Services (HHS) and FDA published the Safe Importation Action Plan, describing regulatory developments that would permit the importation of certain drugs originally intended for foreign markets.[13] In response, Senator Chuck Grassley wrote to HHS Secretary Alex Azar and then FDA Acting Commissioner Ned Sharpless in August 2019, noting that though he "believe[s] that drug importation will help to reduce drug costs

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8 *Safeguarding Pharmaceutical Supply Chains in a Global Economy* (statement of Janet Woodcock), *supra* note 3, at 6-8.

9 Deepak Patel, *supra* note 5.

10 U.S. Gov't Accountability Office, *High-Risk Series: Substantial Efforts Needed to Achieve Greater Progress on High-Risk Areas* 198 (Mar. 2019), https://www.gao.gov/assets/700/697245.pdf. While the GAO acknowledges in its 2019 report that FDA has made progress, it concluded that FDA still needs to "continue to take actions to monitor foreign establishments." *Id.*

11 Letter from the House Energy and Commerce Committee to Gene L. Dodaro, Comptroller General of the United States (June 28, 2019), https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/GAO.2019.6.28..pdf.

12 U.S. Gov't Accountability Office, *Drug Safety: Preliminary Findings Indicate Persistent Challenges with FDA Foreign Inspections* (Dec. 10, 2019), https://www.gao.gov/assets/710/703078.pdf.

13 U.S. Dep't of Health & Human Servs. and U.S. Food & Drug Admin., *Safe Importation Action Plan* https://www.hhs.gov/sites/default/files/safe-importation-action-plan.pdf.

for American consumers and patients . . . [his] position is predicated on the FDA ensuring the safety and efficacy of those drugs."[14] The letter identified a number of safety concerns associated with importation and noted the low numbers of foreign manufacturing facility inspections given the high percentage of APIs produced outside the United States. More recently, on December 18, 2019, FDA published a proposed rule that would allow for the importation of certain prescription drugs from Canada "under specific conditions that ensure the importation poses no additional risk to the public's health and safety."[15] Although importation from Canada may not directly impact Indian pharmaceutical manufacturers, it may have an indirect impact by increasing the focus on foreign supply chains more generally.

In sum, based upon Congressional and FDA concerns associated with the pharmaceutical supply chain and increased interest in drug importation, the quality of foreign-produced drugs and APIs will remain a key issue in the near future. For noncompliant companies, this could lead to unacceptable inspection results, import detentions, recalls, or more significant FDA enforcement.

FDA Inspections of Indian Pharmaceutical Manufacturers: Summary Data

Although the overall number of FDA foreign drug inspections has been decreasing since 2016 due to a number of factors, the number of inspections in India continues to increase. FDA has stated that, "[a]mong other things, the number of inspections in any given country reflects our risk-based prioritization of our inspections and improvements in our targeting; our increasing ability to leverage inspectional work done by trusted partners, especially in Europe; and a higher number of pre-approval inspections."[16] In 2018, 27% of all foreign drug inspections and 15% of all drug inspections took place in India.[17]

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[14] Letter from Charles E. Grassley, Chairman of the Committee on Finance, to Alex Azar, Secretary of the Department of Health and Human Services, and Dr. Norman Sharpless, Acting Commissioner of the Food and Drug Administration 1 (Aug. 6, 2019), https://www.finance.senate.gov/imo/media/doc/2019-08-06%20CEG%20to%20HHS%20FDA%20(Importation%20Plan).pdf.

[15] U.S. Dep't of Health & Human Servs., *Trump Administration Takes Historic Steps to Lower U.S. Prescription Drug Prices* (Dec. 18, 2019), https://www.hhs.gov/about/news/2019/12/18/trump-administration-takes-historic-steps-to-lower-us-prescription-drug-prices.html; *see* Importation of Prescription Drugs, 84 Fed. Reg. 70796 (proposed Dec. 23, 2019).

[16] Scott Gottlieb and Janet Woodcock, *Statement from FDA Commissioner Scott Gottlieb, M.D., and Director of FDA's Center for Drug Evaluation and Research Janet Woodcock, M.D., on the FDA's Continuing Efforts to Maintain Its Strong Oversight of Generic Drug Quality Issues Domestically and Abroad* (Feb. 22, 2019), https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-director-fdas-center-drug-evaluation-and-research-0.

[17] U.S. Gov't Accountability Office, *supra* note 12, at 13.

India's drug manufacturing sites have historically received slightly lower-than-average inspection scores; in 2018, India's average site inspection score was 7.0, lower than the average score of 7.5.[18] Additionally, 15% of all import refusals issued by FDA for drugs and biologics in 2018 were to firms based in India.[19] Notably, the majority of FDA's inspections in India have resulted in acceptable findings (either No Action Indicated or Voluntary Action Indicated); however, while the percentage of facilities with acceptable findings was 93% in the United States and 98% in the European Union, it was 90% in China and 83% in India as of August 2019.[20] In general, the number of unacceptable findings (Official Action Indicated (OAI)) has decreased for U.S. facilities over the last five years, but India's share of OAI classifications has remained relatively constant.[21] Although some have questioned whether Indian manufacturers are being treated on a level playing field with those in the United States or elsewhere, FDA insists that its inspectors are applying the same standards to all manufacturers regardless of location. Further research and additional data points are necessary to assess the validity of FDA's position.

Congressional pressure could lead to future changes in FDA inspection protocols. In its recent report on foreign inspections, the GAO identified pre-announced inspections as another challenge to FDA's inspectional authority outside the United States, as advance notice may impact the agency's ability to identify the full range of potential quality problems and drug Good Manufacturing Practices (GMPs) violations.[22] While investigators based in FDA's India office generally announce inspections with only three to five days' notice and are able to conduct "short-notice inspections," which are announced 30 minutes beforehand, only 10% of all inspections in India are conducted by investigators based in FDA's India office.[23] FDA inspections conducted by investigators located outside the agency's India office require additional advance notice (averaging 12 weeks). In his August 2019 letter, Senator Grassley suggested that FDA resume

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[18] FDA Ctr. for Drug Evaluation and Research, *supra* note 2, at 4. A site inspection score is a score, on a scale of 1 to 10, that is intended as a "measure of a site's compliance to Current Good Manufacturing Practice (CGMP) regulations based on the classification of FDA Drug Quality Inspections conducted over the last 10 years." *Id.* at 2.

[19] FDA DATA DASHBOARD: IMPORT REFUSALS, https://datadashboard.fda.gov/ora/cd/imprefusals.htm.

[20] *Securing the U.S. Drug Supply Chain: Oversight of FDA's Foreign Inspection Program, Hearing Before the Subcomm. on Oversight and Investigations of the Comm. on Energy and Commerce*, 116th Cong. 1 (2019) (statement of Janet Woodcock, M.D., Director of the Ctr. for Drug Evaluation and Research), https://energycommerce.house.gov/sites/democrats.energycommerce.house.gov/files/documents/Updated%20Testimony%20-%20Woodcock%20%28FDA%29%2020191210.pdf.

[21] FDA Inspection Classification Database, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/inspection-classification-database.

[22] U.S. Gov't Accountability Office, *supra* note 12, at 21-23.

[23] *Id.* at 22.

unannounced inspections of foreign manufacturing facilities as it had done in India between 2013 and 2015.[24]

Looking Ahead: Considerations for Pharmaceutical Companies and Potential Acquirers

The future is bright for Indian pharmaceutical manufacturers, provided they successfully comply with FDA drug GMPs. Ongoing U.S. political pressure in support of more affordable medications may open up new avenues for Indian manufacturers to increase exports of APIs as well as generic and prescription drugs due to the lower cost (on average) of products manufactured in India. Indian companies are also well positioned to expand market share in the United States as scrutiny of Chinese companies increases due to trade tensions, national security concerns, and potential fallout from the novel coronavirus (which may have a larger impact on companies located in China compared to Indian companies using Chinese APIs).

Due to the Congressional and FDA scrutiny surrounding the pharmaceutical industry, it will be increasingly important in corporate transactions for potential acquirers to conduct FDA drug GMP diligence on companies manufacturing APIs as well as the finished product, particularly when these facilities are located outside the United States. Potential acquirers should ordinarily expect to evaluate FDA inspection results along with third-party audit reports and certain quality processes and standard operating procedures (SOPs). In addition, in certain diligence scenarios, it may be prudent to retain a GMP consultant to conduct a GMP audit, particularly if a facility has never been inspected by FDA or was recently subject to an adverse inspection, or if significant time has passed since the last inspection.[25]

In sum, pharmaceutical companies located in India are well positioned to expand market share in the United States. Those compliant companies that successfully navigate Congressional concerns and FDA regulatory requirements will be well positioned for

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[24] Letter from Charles E. Grassley, *supra* note 14.

[25] Failure to adhere to FDA drug GMP regulatory requirements can have significant adverse consequences in the deal context. For example, Daiichi Sankyo paid $4.6 billion for a 63% share of Indian generic manufacturer Ranbaxy Laboratories Limited ("Ranbaxy") in 2008, but the value of the company significantly decreased due to issues associated with Ranbaxy's GMP compliance. Daiichi Sankyo took a $3.84 billion loss on its investment approximately six months later in 2009. Michiyo Nakamoto, Daiichi to Book $3.9bn Loss on Ranbaxy, FINANCIAL TIMES (Jan. 5, 2009), https://www.ft.com/content/c8fb926e-db02-11dd-be53-000077b07658. In 2013, Ranbaxy's subsidiary Ranbaxy USA Inc. pled guilty to felony charges related to producing and distributing adulterated drugs. *Generic Drug Manufacturer Ranbaxy Pleads Guilty and Agrees to Pay $500 Million to Resolve False Claims Allegations, cGMP Violations and False Statements to the FDA*, U.S. DEP'T OF JUSTICE (May 13, 2013), https://www.justice.gov/opa/pr/generic-drug-manufacturer-ranbaxy-pleads-guilty-and-agrees-pay-500-million-resolve-false.

success as competitors without sophisticated compliance programs may be subject to additional scrutiny and declining market share.

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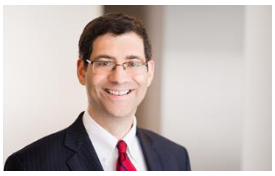

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