May 9, 2023

The Honorable Cathy McMorris Rodgers
Chair
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chair McMorris Rodgers:

Thank you for your letter of March 27, 2023, cosigned by two of your colleagues, regarding the Food and Drug Administration (FDA or the Agency) and certain drug shortages. FDA responds to potential drug shortages by working to help identify, prevent, and, when necessary, mitigate shortages using a variety of strategies and authorities.[1] It is important to note that not all shortages are the same: some are due to manufacturing issues, while others may be due to lack of redundancy in manufacturing or significant increase in demand. Regardless of the root cause, FDA is committed to continuing to prioritize our efforts to prevent and mitigate shortages and to ensure the availability of necessary drug products for the American people.

The authorities provided under section 3112(e) of the Coronavirus Aid, Relief, and Economic Security Act (CARES Act, P.L. 116-136) enhanced FDA's visibility into drug and medical product supply chains and the tools available to the Agency to help identify, prevent, and mitigate drug shortages. For example, the drug amounts that manufacturers must report under section 510(j)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as added by the CARES Act, may provide insights into supply chains that could identify products at greater risk of shortage. Section 510(j)(3) of the FD&C Act requires registrants of drug establishments to report annually the amounts of each listed drug manufactured, prepared, propagated, compounded, or processed for commercial distribution. However, as discussed in more detail below, the lack of linkage between the active pharmaceutical ingredient (API) production amount and allocation to specific finished dosage form (FDF) manufacturers and the requirement that this data be submitted annually limits the utility of these reports.

The Agency has taken several steps to implement section 510(j)(3) of the FD&C Act. First, FDA released two guidance documents: *"Reporting Amount of Listed Drugs and Biological Products Under Section 510(j)(3) of the FD&C Act; Draft Guidance for Industry"* [2] and "*Reporting Amount of Listed Drugs and Biological Products Technical Conformance Guide."*[3] Second, the Agency expanded our electronic portal to accept drug amount reporting information from

[1] The Federal Food, Drug, and Cosmetic Act (FD&C Act) defines a "drug shortage" as "a period of time when the demand or projected demand for the drug within the United States exceeds the supply of the drug." *See* 21 U.S.C. 356c(h)(2).

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-amount-listed-drugs-and-biological-products-under-section-510j3-federal-food-drug-and

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-amount-listed-drugs-and-biological-products-technical-conformance-guide

registrants. Third, in September 2022, the Agency hosted a day-long webinar with multiple question and answer sessions dedicated to providing manufacturers and the public with information regarding the drug amount reporting requirements under section 510(j)(3) of the FD&C Act. [4] The Agency has also made clear that while the process is ongoing to finalize the reporting guidance as part of the Agency's implementation efforts, manufacturers are legally obligated to report amounts of each listed drug manufactured, prepared, propagated, compounded, or processed for commercial distribution as required by section 510(j)(3).[5] The Agency has communicated to industry that it expects manufacturers to fulfill their obligations under this law to report the appropriate data.

The information that Congress required industry to report under section 510(j)(3) of the FD&C Act is not capable of being used to directly prevent or mitigate a shortage. Specifically, such data provide only information on the amount of drug that is manufactured, prepared, propagated, compounded, or processed for commercial distribution by each registrant. These data are insufficient to allow FDA to understand which suppliers registrants are relying upon and the extent to which they are reliant on them. Instead, these data are used as part of the Agency's efforts to understand the drug supply chain with the goal of identifying potential vulnerabilities that can lead to a shortage in the future. Once identified, the Agency can work with the manufacturer and our federal partners to find ways to address these potential vulnerabilities. Further, section 510(j)(3) of the FD&C Act requires industry to report to the Agency only annually. As a result, there may be a significant lag between when a change in manufacturing occurs that could potentially be a signal of a shortage and when the data reflecting such change is reported to the Agency.

FDA's requested authorities in the President's fiscal year (FY) 2024 budget reflect our effort to address concerns regarding potential gaps in our drug shortage authorities and feedback on how these authorities could be improved upon legislatively. If enacted, these proposals would greatly enhance the work we do to help address shortages, including by expressly requiring registrants to provide data identifying the suppliers they relied on to manufacture the listed drug and the extent of such reliance, and by increasing the frequency of such reporting.

Under section 510(j)(3) of the FD&C Act, as of March 28, 2023, the Agency has received data associated with 3,301 establishments engaged in the manufacture, preparation, propagation, compounding, or processing of human drugs for commercial distribution for combined submission years of calendar year (CY) 2020, CY2021, and CY2022. We have not yet received data from 4,119 such establishments. The Agency has received only submissions associated with 44 percent of registered establishments, and the Agency continues to use our current risk-based approach to identify and select foreign and domestic facilities for inspection.

The current aggregated data regarding submissions is included in the charts below.

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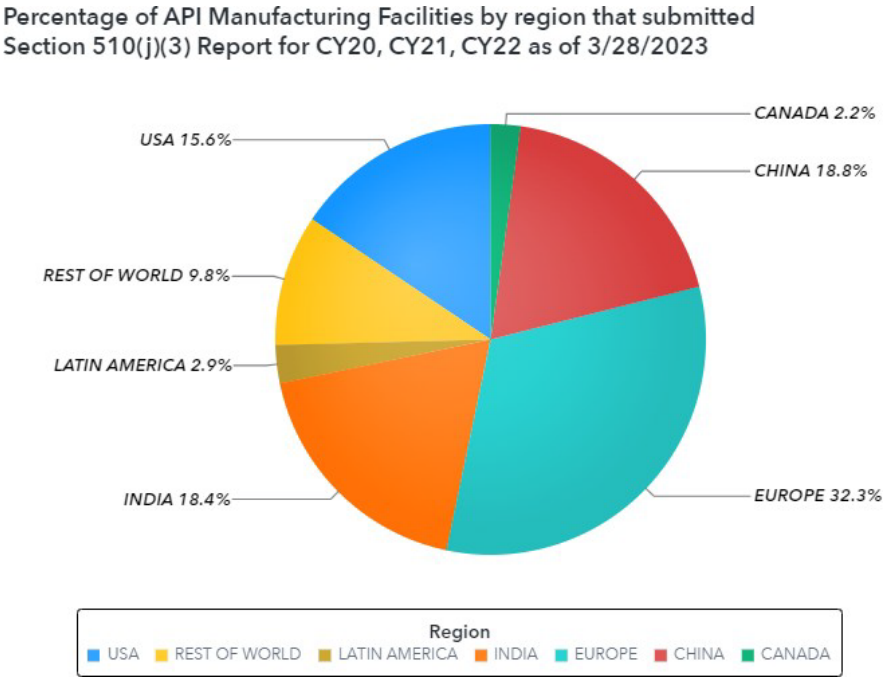
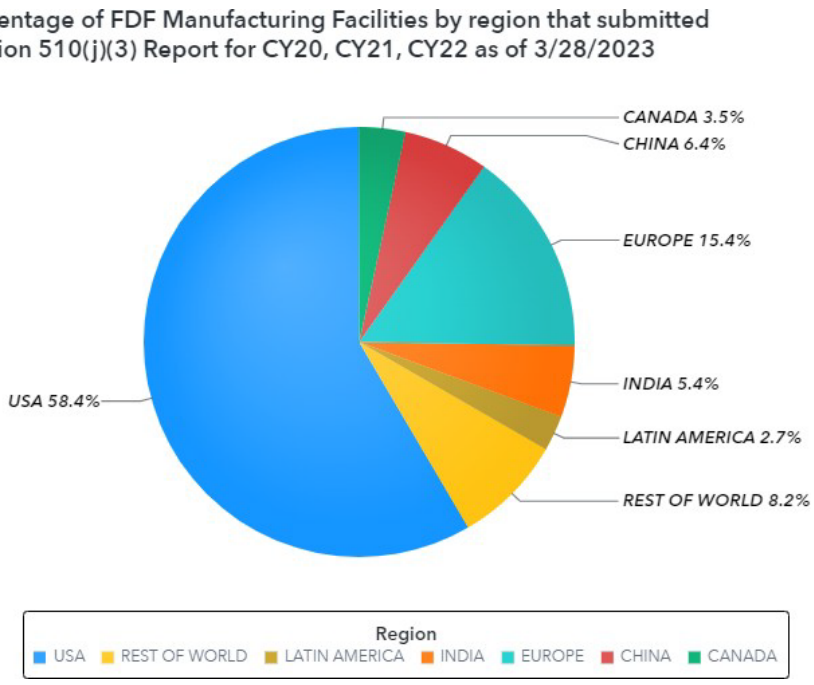
[4] https://www.fda.gov/drugs/news-events-human-drugs/reporting-drug-amount-under-section-510j3-fdc-act-09082022

[5] https://www.fda.gov/drugs/drug-shortages/coronavirus-aid-relief-and-economic-security-act-cares-act-drug-shortage-mitigation-efforts

API Reporting (NDC)	FDF Reporting (NDC)	% of FDF (NDC) on Essential Medicines (EM) List	% of FDF (NDC) Shortage
9,452	73,376	11%	3.5%





FDA works within its limited authorities to find ways to prevent and mitigate drug shortages, but there are multiple factors that can cause or contribute to drug shortages that are outside of FDA's control. FDA cannot, nor should it be in FDA's remit to, require a pharmaceutical company to make a drug or make more of a drug, and the Agency cannot control how much of a drug is distributed or which purchasers will be given priority. The Agency's core efforts on drug shortages revolve around working with drug manufacturers when we know there is a drug shortage or potential for a drug shortage to identify the cause and extent of a shortage and to determine whether other manufacturers are willing and able to fill that gap. We can also expedite inspections to bring facilities online to fill that gap and can expedite review of applications or supplements for products that could help prevent or mitigate a shortage. In 2021, through our work with manufacturers, we prevented more than 300 shortages.[6]

The Agency's ability to identify, prevent, and mitigate shortages relies on the quality of data and notification provided by industry. If the data are incomplete or notification from manufacturers of an impending shortage lags or is not submitted, the Agency's efforts are greatly constrained. In addition, at present, we receive minimal information on demand for drug products, and any information we may receive is provided on a voluntary basis, as we have no authority to require manufacturers to report increases in demand for any given drug. Having access to this information would greatly hasten and enhance our efforts to work with industry to prevent and mitigate drug shortages. For that reason, the President's FY 2024 budget includes a legislative proposal to require manufacturers to notify FDA of increased demand for certain drugs that they likely will be unable to meet.

Please find below further information related to the specific drugs raised in your letter. We hope this detailed information, which builds on the briefing on shortages of albuterol and amoxicillin

[6] https://www.fda.gov/media/159302/download

that we provided your staff in December, provides helpful insights into how the Agency is addressing these important issues.

Albuterol

The albuterol shortage began in October 2022 and involved one particular strength and bottle size of the albuterol inhalation solution used in nebulizer machines in hospitals (0.5% in 20 ml bottles). The other strengths and container sizes of albuterol inhalation solution as well as albuterol metered dose inhalers remain available as alternatives and are not in shortage. The strength and size of albuterol inhalation solution that went into shortage was a small portion of the overall albuterol inhalation solution market.

Based on information provided to FDA, our understanding is that Akorn Pharmaceuticals (Akorn), the sole manufacturer of the approved 0.5% 20 ml bottles of albuterol inhalation solution, had experienced manufacturing issues and planned to return to the market in early 2023. At that time, FDA offered assistance with any steps Akorn needed to take to return to the market that were within the Agency's regulatory authorities. However, this manufacturer recently announced bankruptcy and that it will not be returning to the market. [7] FDA is working to increase the availability of 0.5% albuterol by communicating with the other approved manufacturer of 0.5% albuterol inhalation solution which manufactures the drug in 0.5 ml containers, as well as the manufacturers of other strengths of albuterol inhalation solution that can be substituted for the 0.5% solution. At present, these products all remain available. In addition, FDA conducted outreach to outsourcing facilities that have been able to compound 0.5% 20 ml solution to meet hospital needs.

FDA is actively working with other manufacturers to increase the availability of 0.5% albuterol and has encouraged manufacturers to submit an application for this particular strength and size. FDA prioritizes and expedites review of applications that could help mitigate or resolve a shortage of an approved product such as this.

Pluvicto

Pluvicto is a radiopharmaceutical approved in March 2022 for the treatment of advanced prostate cancer. The product went into shortage in March 2023.

Based on information provided by the manufacturer, FDA's understanding is that the sole manufacturing site in Italy produces this drug in small batches, and there is a very short window of time for each dose to reach its intended patient, as is generally the case for radiopharmaceuticals. There is limited capacity at the manufacturing site that is not able to meet current patient needs. Additionally, supply interruptions caused by weather-related shipping delays and unplanned manufacturing events have resulted in lower than anticipated yields. FDA is working closely with the manufacturer on their plans to add two additional manufacturing facilities in the United States and is expediting review of all submissions related to adding these facilities. FDA has also worked with the manufacturer to maximize supply

[7] https://herald-review.com/news/local/akorn-files-for-bankruptcy-hit-with-class-action-suits/article_96b83c26-b469-11ed-a571-dbfc9638544c.html

coming out of their site in Italy by giving regulatory discretion for the firm to ship doses under quarantine to the United States while the necessary release testing is completed in Italy. The drug can then be released for patients in the United States once the testing in Italy is completed.

The company is reporting that they will be able to significantly increase supply with the two facilities that are planned to be operational in the United States over the next 12 months. FDA will continue to work closely with the manufacturer on efforts to increase supply and resolve the shortage.

Cisplatin and Fluorouracil

Fluorouracil is currently not in shortage. FDA continues to be in communication with the manufacturers on their supplies and production and will continue to monitor and offer assistance should any of the companies need assistance with steps to prevent a shortage.

Cisplatin is a chemotherapy drug used to treat various cancers. Cisplatin went into shortage in February 2023. There are five approved manufacturers and four of them are continuing full production and release of cisplatin to the U.S. market. Based on information provided by the manufacturers, FDA's understanding is that the cisplatin shortage occurred due to one of the five manufacturers deciding to halt distribution at the end of last year after identifying manufacturing quality issues, and the remaining four manufacturers were not able to keep up with demand.

FDA is continuing to work with the manufacturer that halted distribution of cisplatin to support the resumption of production, which is expected to occur in the coming weeks. FDA has also worked with the remaining four manufacturers on their efforts to increase production to meet the supply gap and has offered them assistance on steps to increase production. Depending on the manufacturer's circumstances, FDA's assistance may include expediting review of submissions related to new manufacturing lines, facilities, or suppliers. FDA is also working to identify potential alternate sources for temporary importation to address the shortage, if needed. Before temporary importation of a foreign drug is initiated, FDA evaluates the product and manufacturing facilities for quality and safety issues. A *Dear Health Care Provider* letter is generated by the importing manufacturer that points out any differences in the overseas product and is shipped with the product and posted on the FDA website. Temporary importation in such cases is not an FDA approval, but it can provide an important treatment option to patients in critical need, and in some cases, manufacturers do go on to seek FDA approval.

FDA expects resolution as the manufacturer that halted production is anticipated to return to the market in the coming weeks and the remaining manufacturers continue their efforts to increase production to meet demand. The Agency will continue efforts to resolve this shortage until the approved manufacturers are able to meet all demand.

Methotrexate

Methotrexate is an anti-metabolite most commonly used in chemotherapy and as an immunosuppressant in autoimmune diseases. Methotrexate injection went into shortage in March

2023. There are five approved manufacturers, and three of them are continuing full production and release of methotrexate injection to the U.S. market.

Based on information provided by the manufacturers, FDA's understanding is that this shortage has been caused by manufacturing delays at one manufacturer as well as another manufacturer deciding to halt distribution at the end of 2022 (this is the same manufacturer that halted distribution of cisplatin, as discussed above). The remaining three manufacturers were not able to keep up with demand.

FDA is continuing to work with the manufacturer that halted distribution of methotrexate injection to resume production, which is expected to occur in the coming weeks. FDA has also worked with the manufacturer that has experienced delays as well as the three remaining manufacturers on their efforts to increase production to meet the supply gap. FDA has offered them assistance on steps to increase production. Depending on the manufacturer's circumstances, FDA's assistance may include expediting review of submissions related to new manufacturing lines, facilities, or suppliers. FDA is also working to identify potential alternate sources for temporary importation to address the shortage, if needed. Before temporary importation is initiated, we evaluate the product and manufacturing facilities for quality and safety issues. A *Dear Health Care Provider* letter is generated by the importing manufacturer that points out any differences in the overseas product and is shipped with the product and posted on the FDA website.

FDA expects resolution as the manufacturer that halted production is anticipated to return to the market in the coming weeks and the remaining manufacturers continue their efforts to increase production to meet demand. The Agency will continue efforts to resolve this shortage until the approved manufacturers are able to meet all demand.

Bacillus Calmette-Guerin (BCG)

Bacillus Calmette–Guerin (BCG) vaccine for percutaneous use is an attenuated live culture preparation of the BCG strain of Mycobacterium bovis primarily used against tuberculosis, and can also be used to treat certain cancers. There is currently only one U.S. licensed source of BCG. In 2012, Sanofi Pasteur, Ltd. (Sanofi) announced that there would be a shortage of its BCG product due to a manufacturing problem. In November 2016, Sanofi notified FDA that it was going to permanently cease production of its BCG product at its Canadian manufacturing facility.[8] During this time period (2012-2016), FDA worked closely with Sanofi, within our authorities, to alleviate the shortage of BCG. At the time Sanofi notified FDA that there would be a shortage of its BCG product, we immediately reached out to Organon Teknika, Corporation LLC, a subsidiary of Merck & Co, Inc. (Merck), which also manufactures BCG Live (Intravesical) licensed in the United States for treatment of bladder cancer. Merck quickly took steps to increase supply of its BCG product. Since that time, Merck has largely been able to meet demand for U.S. patients who depend on this important product.

[8] https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-permanent-discontinuations

Since Merck became the only source of BCG Live (Intravesical) in the United States in 2016, it has been in ongoing communication with FDA regarding current and future supply. Although BCG Live is currently available, Merck has informed FDA that there has been an increase in demand globally. As the only source of BCG Live in many countries, Merck has indicated that it anticipates ongoing supply constraints for the foreseeable future. In order to address the imbalance between supply and increased global demand, help manage inventory, and minimize a complete disruption to patient care, the product has been placed on allocation. This means Merck is proportionally allocating the quantity of available BCG supply across countries based on historical demand.[9]

In addition, FDA has proactively engaged stakeholders including cooperative groups, pharmaceutical sponsors, and patient advocacy organizations to encourage further study and development of alternative sources of BCG. FDA also periodically reaches out to foreign regulatory counterparts to assess the global marketplace. At the onset of this shortage, FDA reached out to worldwide manufacturers of BCG products which were not approved in the United States in order to assess the ability of these foreign manufacturers to provide product for the U.S. market. Based on these efforts, the Agency developed an understanding of the global shortage situation with respect to BCG Live products and determined that foreign manufacturers were not in a position to supply product to the U.S. market to address the short-term shortage situation.

Merck announced in October 2020 it will construct a new manufacturing facility to significantly expand its production capacity for BCG Live.[10] Once this new facility is fully operational (expected in late 2025 to late 2026), Merck is expected to triple its current manufacturing capacity, which is anticipated to support the predicted demand for BCG for the foreseeable future. FDA is working closely with Merck, within our authorities, to help mitigate the supply situation for BCG. We will continue to do all we can within our authorities to address this shortage, working together with industry and other partners to promote production levels that meet the needs of patients.

Amoxicillin

Amoxicillin powder for oral suspension went into shortage in October 2022. It is made by four manufacturers, and all four are continuing full production and release of product. The capsule presentation as well as Augmentin (amoxicillin and clavulanate) in oral and intravenous presentations remain available.

Based on information provided by the manufacturers, this shortage has been caused by a significant increase in demand during an unprecedented peak in viral respiratory illnesses, including a large respiratory syncytial virus (RSV) outbreak, peak flu season, and the ongoing COVID-19 pandemic.

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[9] https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/cber-regulated-products-current-shortages

[10] https://www.merck.com/stories/facing-a-global-shortage-merck-commits-to-meeting-patient-demand-for-a-crucial-treatment-option/

As soon as FDA was made aware of the significant increase in demand, FDA offered assistance to the manufacturers on steps to increase production. Depending on the manufacturer's circumstances, FDA's assistance may include expediting review of submissions related to new manufacturing lines, facilities, or suppliers.

In November 2022, FDA published guidance on compounding of beta-lactam oral antibiotic suspension products that are in shortage (including amoxicillin powder for oral suspension) to help address unmet need. The Agency also reached out to our international regulatory contacts on supply status in their countries; all of them were experiencing increased demand as well. FDA also reached out to the manufacturers of alternate antibiotics that may be substituted for amoxicillin powder for oral suspension and offered our assistance on steps that could help increase supply. The alternate antibiotics did not end up in shortage.

The manufacturers are continuing to report improved ability to meet demand. Once inventory levels are built back up and no further supply interruptions are anticipated, we expect the shortage to be resolved.

Acetaminophen and Ibuprofen

FDA understands the temporary lack of availability of acetaminophen and ibuprofen is due to a significant surge in demand during an unprecedented peak in viral respiratory illnesses, including a large RSV outbreak, peak flu season, and the ongoing COVID-19 pandemic. It is the Agency's understanding that the manufacturers were allocating product. As a result, not all distributors and pharmacies were able to keep in-stock levels to their usual levels.

There are multiple manufacturers of nonprescription acetaminophen and ibuprofen oral suspension and chewable tablets as well as prescription ibuprofen oral suspension which were reported to be in short supply in late 2022. The manufacturers all reported continuing full production; however, they also reported unprecedented increased demand. In response, they reported increasing production to 24/7 to continue to get product out into distribution and onto pharmacy and hospital pharmacy shelves to meet demand.

FDA continues to offer our assistance on steps to further increase supply, such as expediting review of submissions for new manufacturing sites, suppliers, or other components to increase production. In early 2023, FDA also published guidance on compounding of certain ibuprofen oral suspension products by outsourcing facilities to help increase supply in hospitals, health systems, and pharmacies.

FDA is monitoring in-stock rates at the pharmacy/retail level as well as the manufacturers' reported production, inventory, and rate of filling orders for distributors that supply the retail sector and hospitals. All of these data sources are showing supplies are currently meeting patient needs and consumer demand.

In addition to publishing the guidance on compounding of certain ibuprofen oral suspension products to help increase supply, we also reached out to our international regulatory contacts on supply status in their countries, and all of them were experiencing increased demand as well. We

continued efforts with the manufacturers that were making products for the U.S. market to increase supply to meet demand.

* * *

Thank you again for your interest in these important issues. FDA will continue to prioritize our efforts to prevent and mitigate shortages to ensure the availability of necessary drug products for the American public. The President's FY 2024 budget includes several critical legislative proposals intended to promote FDA's response efforts that we believe would greatly enhance the work we do to address potential drug shortages. We would be happy to discuss these efforts or proposals with you further. The same letter has been sent to your cosigners.

Sincerely,

Kimberlee Trzeciak -S

Digitally signed by Kimberlee R. Trzeciak -S
Date: 2023.05.09 20:33:04 -04'00'

Kimberlee Trzeciak
Associate Commissioner for
Legislative Affairs