

## RECOMMENDATION 3: ENHANCE SUPPLY CHAIN OVERSIGHT

### Key takeaways:

- Medical product shortages jeopardize patient care and impose significant costs on the healthcare system, including over \$600 million per year for American hospitals.
- Most drug shortages are caused by manufacturing disruptions, most frequently with older, low-profit medicines.
- FDA continues to struggle with overseeing foreign drug manufacturing with the same rigor that it applies to domestic facilities.
- FDA should leverage remote inspection authorities as supplemental tools to end the COVID-19 inspection backlog.
- FDA should designate foreign manufacturing oversight as a core leadership priority and evaluate options for third-party support.
- FDA should develop and implement a rating system to incentivize quality manufacturing maturity.
- FDA should incentivize and de-risk investment in advanced manufacturing technologies to help reduce supply disruptions and address national security risks.
- FDA should address the impact of the IRA on rare disease therapy development.

As FDA works to advance the availability of critical medical products to patients, it should prioritize efforts to address drug shortages and other supply chain disruptions.

When medical products go into shortage—meaning that the supply in the United States is not sufficient to meet demand—there can be significant impacts for patients and the broader healthcare system. Patients may face delays or disruptions in their treatment, which can lead to negative health outcomes and higher costs of care, and care providers may incur substantial costs managing the impacts, which can total over \$600 million per year for American hospitals.<sup>110,111</sup> To reduce these burdens, a more resilient supply chain is needed.

FDA has made progress on combating drug shortages, but there is still considerable work to be done. While the number of drug shortages has declined significantly from its peak of 251 new shortages in 2011, the number worsened during the COVID-19 pandemic: FDA recorded between 40 and 55 new shortages per year from 2021 to 2023.<sup>112</sup> In addition, drug shortages have been lasting longer—in some cases eight years or more—so the number of ongoing shortages is also increasing.<sup>110,112</sup> Moreover, many drugs in shortage are essential medicines,<sup>113,114</sup> including common chemotherapeutic agents whose shortages could create significant challenges for cancer patients and their providers.<sup>115,116</sup>

While some shortages are driven by spikes in demand, most are precipitated by disruptions in production due to manufacturing problems.<sup>111</sup> These disruptions occur most frequently among drugs that share a certain profile: They tend

to be older, off-patent drugs with low profit margins.<sup>110</sup> They also tend to be among the more difficult drugs to manufacture properly—most are injectable drugs, which must be produced in sterile environments.<sup>110</sup> Drugs with this profile tend to go into shortage more frequently because they face several fundamental economic challenges. Low profit margins—particularly for drugs that are more complicated to make—limit economic incentives for additional manufacturers to enter the market, or for existing ones to invest in cutting-edge manufacturing technologies (above and beyond minimum regulatory requirements) that might reduce the risk of disruption. Even after a product goes into shortage, high startup costs (including the regulatory approval process) can make it challenging for new entrants to step in to help meet demand in a timely manner.<sup>110</sup>

One way for FDA to mitigate the risk of shortages is by conducting timely facility inspections, through which it can identify emerging problems in manufacturing quality and work with the manufacturer to address them before they reach the point of disrupting production, or before unsafe or ineffective products make their way to patients. Unfortunately, two major barriers are impeding this early detection capability.

First, FDA limited in-person inspections during the COVID-19 pandemic, which created a substantial backlog that continues to persist.<sup>117</sup> As of September 2024, 42% of registered drug manufacturing facilities had not been inspected in over five years.<sup>117</sup> When problems with manufacturing quality go undetected, they endanger patient safety and increase the risk of supply disruptions that could lead to shortages.

Second, a substantial portion of the drugs produced for the U.S. market—both active ingredients and finished products—are now produced in foreign facilities where FDA historically has struggled to provide adequate oversight. As of January 2024, 58% of all pharmaceutical manufacturing sites subject to FDA inspection were located outside the United States, with nearly 40% of foreign facilities concentrated in India and China.<sup>118</sup> FDA issues a disproportionate share of warning letters to manufacturers in these two jurisdictions, including for serious violations like the presence of carcinogens in medicine, destroying or falsifying data, and not following sterile manufacturing processes when required.<sup>119</sup> Even though all drugs produced for the U.S. market are legally subject to the same manufacturing and quality requirements, the practical challenges associated with conducting inspections in certain foreign jurisdictions have made it harder for FDA to ensure the applicable rules are being followed across the board.<sup>118</sup>

The agency conducts many more foreign inspections than it used to;<sup>118,120</sup> however, significant challenges remain—even after decades of effort. For example, the agency has continued to struggle with critical issues such as hiring and retaining qualified staff to conduct inspections in foreign facilities, obtaining timely visas and other forms of clearance from foreign governments, securing reliable interpreters and conducting inspections on an unannounced basis (to minimize opportunities for manufacturers to conceal problems) similar to what FDA has historically done for domestic facilities.<sup>118,120</sup>

The upshot of these persistent logistical challenges is that, in key respects, foreign manufacturing facilities may still be able to avoid the same level of regulatory scrutiny as their domestic counterparts. From a policy perspective, this is exactly backward. Given the geopolitical risks associated with the United States relying on foreign countries like China and India for critical medicines and their active ingredients,<sup>121</sup> the United States should be encouraging more domestic manufacturing—or, at the very least, reducing unintentional disadvantages.

Recent actions by the White House and FDA will help the agency advance this goal. In May 2025, President Donald Trump issued an executive order directing FDA to enhance its inspection of foreign manufacturing facilities and promote domestic production of critical medicines,<sup>122</sup> and FDA announced that it will expand the use of unannounced inspections at foreign facilities.<sup>123</sup> As FDA continues to carry out the executive order and take additional steps consistent with that policy, it should prioritize concrete actions that will help to build a more secure and resilient supply chain.

### ***Recommendation 3.1: FDA should use all available tools to clear the COVID-19 inspection backlog***

FDA's immediate priority should be ending the COVID-19 inspection backlog. In doing so, FDA should fully deploy its remote inspection tools, as appropriate, to use its resources most effectively.

During the COVID-19 pandemic, FDA implemented various tools that allowed it to continue monitoring facilities remotely, including remote records reviews and interactive evaluations using livestream video and other technologies.<sup>124</sup> These tools enabled FDA to provide oversight when travel was limited, but they do not allow for as complete an assessment as can be done in person and cannot be used in many foreign facilities due to technical and logistical issues.<sup>118</sup>

Now that FDA is catching up on inspections, it should use its remote tools in additional ways to supplement its in-person work and accelerate the in-person work that is necessary to eliminate the backlog. FDA has indicated that remote tools can be used on a targeted basis to mitigate staffing challenges, but it is still assessing how best to deploy them.<sup>118,125,126</sup> The agency should prioritize its efforts to use these tools to improve the efficiency of its in-person work. If more of the work that is amenable to remote observation can be done without an inspector onsite, it could enable inspectors to visit more facilities in a given time period, or on a single trip.

### ***Recommendation 3.2: Designate foreign manufacturing oversight as a core leadership priority and evaluate options for third-party support***

With respect to FDA's oversight of foreign manufacturing facilities, new approaches are needed to address the practical challenges that have persisted for decades. FDA leadership should take concrete actions to ensure that the agency's oversight of foreign facilities is at least as effective as its oversight of domestic ones.

First, FDA should designate this goal as a core priority of the Commissioner's office. This designation would bring focused attention and capacity and help ensure that FDA successfully follows through on key recommendations from the Government Accountability Office, such as developing and implementing an action plan for hiring and retaining qualified inspectors for foreign facilities.<sup>118</sup> High-level focus will help the agency appropriately prioritize this in the context of the recent major reorganization in FDA's inspectorate,<sup>127,128</sup> including by focusing on important organizational questions, such as whether the agency should revisit the geographic distribution of its inspectorate and renew efforts to increase its in-country presence in key jurisdictions.

Second, FDA should be maximally transparent about how effective various strategies will be at addressing the issues that persist, and where new approaches may be needed. For example, FDA has had recent success in negotiating mutual recognition agreements with regulators in Europe, which have enabled it to rely on the results of inspections conducted by these trusted partners, effectively expanding the agency's capacity and limiting duplicative work. But, to date, this reliance has been most effective for facilities in the European regulators' home countries; success has been more limited for facilities in India and China because (1) European regulators conduct relatively fewer inspections in those countries and (2) the drugs manufactured for the U.S. market are often produced in separate areas that non-U.S. regulators do not inspect.<sup>128</sup> In addition, relevant laws—including those governing confidential and trade-secret information—may place practical limits on information sharing between regulators. As FDA continues to build on this and other programs, it should ensure their limits are well understood—and, ideally, quantified—so that policymakers can assess the need for other approaches.

Third, FDA should embrace technological solutions that improve the efficiency or effectiveness of its inspection operations. For example, FDA recently developed a data dashboard to plan surveillance inspections more efficiently.<sup>129</sup> FDA should review its operations and identify other opportunities to deploy technology to improve operations and maximize the time that inspectors are able to spend conducting inspections.

Fourth, FDA should consider novel approaches to supplement its inspection resources. These approaches could include:

- *Collaborative hybrid inspections:* FDA recently participated in a pilot program by the International Coalition of Medicines Regulatory Authorities to assess the feasibility of hybrid inspections in which multiple regulators conduct an inspection through a combination of remote and in-person inspectors.<sup>130</sup> This model could enable FDA to expand its reach without having to put as many boots on the ground, but it also would require additional coordination, and could face many of the same practical issues that have limited the effectiveness of mutual recognition. FDA should assess carefully.
- *Assessments by nongovernmental third parties:* The agency already has experience with relying on accredited third parties to conduct inspections for certain types of devices,<sup>131</sup> and it could work with Congress to design a similar program to expand the reach of its foreign overnight. Although there would be legal and practical limits on how FDA could use the results of such assessments, they could be a useful tool to enable FDA to identify potential quality problems earlier than might otherwise be possible.

### **Recommendation 3.3: Develop a rating system to incentivize quality manufacturing maturity**

In addition to improving inspectional oversight, FDA should be doing more to incentivize manufacturers to invest in mature quality management systems. While FDA's Current Good Manufacturing Practice (CGMP) requirements set a regulatory minimum that applies to all drugmakers, some have begun investing in enhanced systems that apply technology and mature management principles to go beyond the minimum legal requirements and make disruptions from quality failures easier to detect and less likely to occur.<sup>110,132</sup> Unfortunately, the market does not directly reward investment in such systems. Drug purchasers typically lack information about which products are made in facilities that use these mature practices (and are therefore less likely to experience disruptions), and many manufacturers—particularly those of low-cost, low-margin drugs—may find it infeasible to invest in mature systems without the opportunity for short-term returns on investment.<sup>110</sup>

FDA can begin to address this dynamic by developing a public system for measuring and rating the maturity of the quality management system for the facility where each drug is produced.<sup>133</sup> Internally, this rating system would help FDA better predict which products are at risk of going into shortage, and take those risks into account when prioritizing surveillance and enforcement activity. Outside the agency, purchasers (both public and private) and group purchasing organizations could use public ratings to inform their contracting and reimbursement decisions (e.g., by taking ratings into account when evaluating options for multisource drugs). This would enable manufacturers to compete on quality in addition to price and realize more immediate returns on investments—as opposed to longer-term benefits, such as reducing the cost of manufacturing disruptions over time.

FDA and the U.S. Department of Health and Human Services (HHS) have proposed versions of this idea under both Republican and Democratic administrations,<sup>110,111</sup> and FDA should prioritize its implementation. FDA has the existing authority to evaluate and rate the maturity of facilities' quality management systems to prioritize its inspections,<sup>134</sup> and it can begin evaluating the extent to which it has authority to share information about those ratings with manufacturers and/or the broader public. To the extent that additional legislative authority is needed to collect information for accurate ratings, FDA should identify the gaps and communicate them to Congress.

### **Recommendation 3.4: Incentivize and de-risk investment in advanced manufacturing technologies**

Over the longer run, one of the most impactful ways to reduce the risk of supply disruptions is to make it more feasible for medical product manufacturers to invest in advanced manufacturing technologies (AMTs) that improve the reliability, quality and efficiency of production. AMTs go beyond upgrades to system maturity (as discussed above) and include technologies such as:

- *Continuous manufacturing*: Products are produced in a continuous stream, as opposed to traditional batch manufacturing in which products are produced in a set of discrete steps with pauses in between. Continuous manufacturing methods can increase manufacturing speed, make it easier to bring new production online in response to a shortage, and make it easier for manufacturers to identify potential quality issues before they arise.<sup>135–137</sup>
- *Additive manufacturing (3D printing)*: Products produced using 3D printing technology can enable greater customization (e.g., modifications to pill sizes) as well as distributed manufacturing models in which the product is printed closer to the point of care.<sup>136</sup>
- *Artificial Intelligence (AI) and machine learning (ML)*: AI and ML technologies can be deployed to improve manufacturing processes, such as by identifying optimal parameters to improve efficiency, controlling and monitoring processes, and detecting potential problems.<sup>138</sup>

FDA has encouraged the adoption of AMTs, most notably by providing manufacturers with early engagement and technical assistance through the agency's Emerging Technology Program.<sup>136</sup> Unfortunately, the success of these efforts has been limited. As of October 2022, FDA had approved only 16 applications for drugs using AMTs—a drop in the bucket compared to the thousands of new and supplemental drug applications that FDA approves each year.<sup>136</sup> The primary barriers have less to do with technological feasibility and more to do with the uncertain business case for investing in technology that is not only more expensive but carries significant regulatory uncertainty given that the existing regulatory framework was designed for conventional manufacturing.<sup>136</sup>

Improving the feasibility of adopting AMTs would not only help reduce supply disruptions but would also, to the extent that technologies are adopted by domestic firms, help

address national security risks posed by having the production of critical medicines concentrated in certain foreign countries. FDA should take steps to reduce the barriers to AMT adoption, including:

- *Updating the regulatory framework to support AMTs*: FDA should reduce the regulatory uncertainty that makes adopting AMTs riskier than it needs to be. The agency has already started this process by issuing guidance on technical and regulatory considerations for using continuous manufacturing technologies,<sup>137</sup> but significant challenges remain in applying FDA's regulations, particularly for other types of AMTs such as using AI and ML in the manufacturing process.<sup>138</sup> FDA should prioritize a comprehensive effort to update its regulations as needed, issue guidance on how existing regulations apply to new technologies, and ensure that staff are appropriately trained when they encounter new approaches. As a first step, FDA could issue a request for information (RFI) to begin assessing ways in which current regulations are outdated or pose challenges for deploying AMTs.
- *Expand the benefits of using AMTs*: In 2022, Congress authorized a new AMT designation program, under which FDA can review and designate certain AMTs outside the context of a product application, then provide early assistance and expedited review for product developers who use designated AMTs.<sup>139</sup> This program has the potential to make it more attractive for developers to adopt AMTs, as FDA recognized in its implementing guidance.<sup>135</sup> As FDA continues to implement the program, it should look for opportunities to expand the benefits of AMT designation, such as clarifying how the use of designated AMTs can simplify or streamline compliance with post-market requirements. In addition, FDA should further incentivize AMT adoption through other programs; for example, as FDA develops a quality maturity rating program, it could implement a policy that using AMTs will increase a facility's rating.