

Ensuring Americans' Access to Pharmaceuticals: A Primer and Road Map for Policymakers

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KEY TAKEAWAYS

COVID-19 has heightened public worries about the ability to access prescription drugs, with particular concern about those made outside the United States.

To ensure Americans can access prescription drugs, policymakers should reform laws and regulations that have had unintended adverse effects on drug supply chains.

These reforms would not only increase the reliability and safety of America's drug supply but also likely increase the number of drugs made domestically.

The COVID-19 pandemic has prompted concerns in the Trump Administration and Congress about the reliability of America's pharmaceutical supply chain. The primary focus has been on the extent to which drugs are manufactured outside the United States and particularly in certain countries, namely China. Their concerns are motivated by the safety of drugs consumed by Americans, shortages of some drugs, the potential for natural events to create supply disruptions, and the national security implications of importing drugs or their ingredients from countries whose government policies are unreliable or even adverse to U.S. interests.

However, the geographical distribution of pharmaceutical manufacturing is just one aspect of how best to ensure the availability and quality of drugs consumed by Americans. Consequently, any proposed policy changes should be evaluated in that broader context. This *Background*

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provides policymakers a brief overview of pharmaceutical manufacturing and supply chains, identifies key considerations that policymakers should take into account, and offers recommendations for ensuring a more dependable drug supply.

The Drug Manufacturing Web

Most drugs are chemical entities, and the process of manufacturing them involves several steps, from acquiring the raw materials to synthesizing active pharmaceutical ingredients (APIs) to creating the finished dosing forms (FDF)—the final products intended for use in patients.¹ A drug must also be tested—which, for novel drugs, includes an extensive clinical trial regimen—and its manufacturing plant inspected before the U.S. Food and Drug Administration (FDA) will approve it for marketing and distribution to pharmacies, hospitals, or clinics where it is dispensed or administered to patients.

Within the overall process a particular company may focus on only one step or on two or more consecutive steps. Also, the facilities used in each step of the process may be located in different places, even when owned by the same parent company. Indeed, supply chain arrangements can differ even by product. For instance, suppose a company manufacturing FDFs of several different drugs at one factory also manufactures some APIs at another plant. That company may use the APIs produced at its own facility to manufacture some drugs while simultaneously sourcing from other companies the APIs needed to manufacture other drugs at the factory producing FDFs.

While conceptually drug manufacturing follows a sequence of steps, as a practical matter the components of the process are more akin to a supply “web” than a strictly linear supply “chain,” as there are many different companies specializing in different functions within the overall process.

The Role of FDA Regulation

The FDA regulates the manufacture of both the APIs and the FDFs of drugs intended for use in the United States to ensure that they are effective (do what they are intended to do) and safe (not contaminated or tampered with).² The

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1. APIs are the substances in drugs that are “intended to furnish pharmacological activity.” They are manufactured in bulk using ingredients sourced from suppliers of basic and specialty chemicals. The FDFs of drugs also include “excipients” that act as binders, fillers, diluents, preservatives, absorption enhancers, and coatings, etc. The basic distinction is that, unlike APIs, excipients do not have a *direct* pharmacological effect, though sometimes an excipient is included to modify the API’s pharmacological effect. For instance, a “quick acting” formulation will contain an excipient that accelerates the body’s absorption of the API, while an “extended release” formulation will include an excipient that gradually releases the API over time.
 2. The specific concerns are the avoidance of any impurities or contaminants, the correct potency of the active ingredients, the safety of any excipients, and the consistency of the finished products.

FDA's authority in this area encompasses the manufacturing facilities, the production equipment and processes employed, the ingredients used, and quality control testing.³ The FDA also regulates the post-production labeling, packaging, wholesaling, and distribution of drugs by the manufacturer and any other companies performing one or more of those post-production functions.⁴

However, the FDA's regulation of manufacturing does not extend to a factory's environmental impact, workplace health and safety regulations, employment law, etc. On those and similar matters, facilities are subject to the applicable national and local laws where they are located.

The FDA's authority over drug manufacturing applies to all drugs produced for the U.S. market and to all companies and facilities with any role in the supply chain for those drugs—from the production of APIs to the delivery of FDFs to end users—even if those facilities are located outside the United States. Furthermore, the FDA's regulatory standards and requirements are the same regardless of where the activity subject to regulation occurs.

Differences by Product Type

Another important factor that influences drug manufacturing and supply chains are the physical and financial characteristics associated with the different types of drugs—novel drugs, generic drugs, products that require special manufacturing, and biologic drugs.

Novel Drugs. For any novel drug, additional time, effort, cost, and regulatory oversight must be devoted to creating an appropriate manufacturing process. Furthermore, in order to obtain regulatory approval, the sponsor must be able to produce the drug in its finished form for use in the clinical trials supporting its application. Those trials vary but often incur significant time and expense.⁵ Once a novel drug is approved, it will have some period

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3. See, for instance, U.S. Food and Drug Administration, "Guidance for Industry, Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-q7a-good-manufacturing-practice-guidance-active-pharmaceutical-ingredients> (accessed October 7, 2020).
 4. The United States and other countries require that pharmaceutical products sold within their borders be accompanied by certain specified information, broadly referred to as the product's "labeling." Because the required information can be extensive, it is often in the form of package inserts. Also, governments typically set different requirements for the information intended for health professionals versus that intended for patients. The former contains extensive scientific information while the latter provides plain language instructions on how to use the product effectively and safely. In practice, a given factory may produce FDFs of a particular drug for distribution to multiple countries, each with different labeling requirements. Also, a manufacturer may outsource post-production product labeling to a firm that specializes in that function.
 5. The FDA defines the terms applicant, or drug sponsor, to mean the "person or entity who assumes responsibility for the marketing of a new drug, including responsibility for compliance with applicable provisions of the Federal Food, Drug, and Cosmetic Act and related regulations." In most cases, the sponsor is a corporation, but it could also be an individual, partnership, government agency, or nonprofit institution such as a university or charity.

of market exclusivity based on the laws governing patents and marketing approvals, during which the sponsor will be able to sell the drug at whatever price it sets.⁶

These circumstances create unique considerations for a company seeking marketing approval for a novel drug. On the one hand, the sponsor must invest in creating manufacturing capacity before the drug is approved, but it risks that investment becoming worthless if the drug fails to get final marketing approval. That risk incentivizes the sponsor to limit its up-front investment in manufacturing. On the other hand, if the drug is approved, the sponsor will have a time-limited period during which it can maximize its revenues from selling the drug. That “up-side” risk creates a powerful counter-incentive to have enough manufacturing capacity to meet expected demand as soon as the drug receives final approval.

The balances struck between these countervailing incentives will inherently vary—not only among companies but also from drug to drug—and will reflect other considerations such as competing capital needs within a company or the projected size of the market for a particular drug.

However, the overarching effect is that the sponsor of a novel drug has powerful financial incentives to tightly manage every aspect of the drug’s supply chain and manufacturing process. Consequently, companies producing novel drugs are likely to keep more of the manufacturing process “in-house,” prioritize reliability and quality when contracting with suppliers and vendors, and have backup plans for addressing possible production interruptions.

Generic Drugs. Companies manufacturing generic drugs (that is, copies of older drugs for which no manufacturer has rights to market exclusivity) face significantly different dynamics than those for novel drugs. First, producing a generic drug consists of essentially replicating the ingredients and processes used by the innovator company and thus entails somewhat lower (though still substantial) up-front investment. Second, once a generic drug is made by two or more companies, the market for the drug inherently becomes extremely price competitive, with very thin—and volatile—profit margins.

Generic drug makers therefore have strong incentives to reduce costs wherever possible. That, in turn, makes generic drug makers more likely

6. While periods of market exclusivity are commonly thought of as a function of patent laws, marketing approvals can also provide for an overlapping period of market exclusivity (or “regulatory exclusivity”) to compensate innovators for the time spent proving a product’s safety and efficacy. For instance, if a patent grants the innovator 10 years of exclusivity, but the first five years of that patent are spent on the development and testing needed to get marketing approval, then the innovator would have only five years remaining of exclusive rights to sell the product. A law granting 10 years of exclusivity starting on the date of market approval would assure the innovator of receiving a full 10 years of exclusive rights to sell the product it developed based on its initial patent.

to outsource functions, prioritize lower costs when contracting with suppliers and vendors, and be much less concerned about the possibility of production interruptions.

Products Requiring Special Manufacturing. Additional considerations come into play when manufacturing some drugs or certain types of FDFs. For instance, relative to oral dose forms, the manufacture of doses for injection or infusion typically involves different excipients, different manufacturing processes, additional contamination risks, and special post-production storage and handling. Also, some drugs have characteristics that entail special production considerations. For instance, because some people have a life-threatening allergy to penicillin and its derivatives, a factory producing penicillin must strictly prevent any contamination of other drugs made at the same facility. These special considerations are relevant regardless of whether the drug is a novel or generic one and have little effect on the basic economics of novel drug versus generic drug production. However, they can entail greater cost, complexity, and regulatory requirements relative to other drugs. That can mean fewer production sites with concomitant higher probabilities of supply chain disruptions and shortages.

Biologic Drugs. Most drugs are created primarily through chemical synthesis.⁷ In contrast, biologic drugs are produced using living cells from a plant, animal, or microorganism.⁸

As the FDA notes, “Because, in many cases, there is limited ability to identify the identity of the clinically active component(s) of a complex biological product, such products are often defined by their manufacturing processes.”⁹ Thus, while it is often possible to change the manufacturing process for a chemical drug without affecting the finished product, that is often not the case with biological products. Another key implication is that it is much more difficult to ensure the consistency of a finished biological product, even when it is produced by the same manufacturer using the same processes at the same facility.

Consequently, the production of biologics is more complex and more costly, requires different and more frequent product testing, and entails

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7. Chemical synthesis is the process of applying physical and chemical manipulations to the starting ingredients in order to combine or convert them into the desired product.
 8. Biological products include “vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.” U.S. Food and Drug Administration, “What Are ‘Biologics’ Questions and Answers,” <https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/what-are-biologics-questions-and-answers> (accessed October 7, 2020).
 9. U.S. Food and Drug Administration, “Frequently Asked Questions About Therapeutic Biological Products,” <https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/frequently-asked-questions-about-therapeutic-biological-products> (accessed October 7, 2020).

closer and more extensive regulatory oversight. As a result, biologic drug production involves sophisticated manufacturing processes, highly skilled workers, and a greater risk of production interruptions and shortages. Given these considerations, it is not surprising that the vast majority of the world's biologics are produced in the United States, Canada, and Western Europe.¹⁰

Business Considerations Relevant to Plant Siting

For any industry, company decisions on siting manufacturing facilities entail a range of considerations. In the case of drug manufacturing, these factors include (1) financial considerations, particularly corporate taxes; (2) business climate, particularly legal certainty and the availability of skilled workers; and (3) the relative costs of construction, operation, and environmental regulation.

For instance, the expansion of drug manufacturing in Ireland, Puerto Rico, and Singapore was primarily a function of favorable corporate tax policies augmented by reliable legal systems and the availability of skilled workers. Those considerations are more important when producing novel drugs that have market exclusivity and high profit margins or products (such as biologics) that involve more complicated and sophisticated manufacturing processes.

In contrast, less developed countries, such as China and India, primarily offer the advantage of lower construction and operating costs (e.g., utilities, wage rates, environmental regulations). Those cost differentials are more relevant when producing generic drugs, which are characterized by very thin profit margins and little need for intellectual property protections.

Current Global Distribution of Drug Manufacturing

The primary driver of recent concerns about the reliability of the U.S. drug supply has been the extent to which drugs are being manufactured outside the United States and particularly in certain countries, namely China.

Those concerns have been fanned by a number of assertions about American dependence on foreign-produced drugs that are either misleading or unverifiable.¹¹ In fact, for drugs consumed in the United States,

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10. A recent analysis of total global biologic production (by volume) finds that 37 percent occurs in North America and another 33 percent occurs in Western Europe. Because that analysis included veterinary biologic products as well as facilities that do not meet U.S. and EU standards, an even greater share of the human biologics consumed in the United States are produced in either North America or Western Europe. See Ronald A. Rader and Eric S. Langer, "Worldwide Biopharmaceutical Manufacturing Capacity Analysis: Growth Continues Across the Board," BioProcess International, September 15, 2018, <https://bioprocessintl.com/business/economics/worldwide-biopharmaceutical-manufacturing-capacity-analysis-growth-continues-across-the-board/> (accessed October 7, 2020).
 11. Eric Boehm, "Why You Shouldn't Trust Anyone Who Claims 80 Percent of America's Drugs Come from China," *Reason*, April 6, 2020, <https://reason.com/2020/04/06/why-you-shouldnt-trust-anyone-who-claims-80-percent-of-americas-drugs-come-from-china/> (accessed October 7, 2020).

there is currently no reliable and comprehensive information about the respective shares produced domestically versus those imported from other countries.

What is available, however, is information on all domestic and foreign facilities that manufacture APIs or FDFs for the U.S. market. Those sites, as well as facilities that perform related functions—such as testing, packaging, and labeling—must register with the FDA and are subject to FDA inspection. The agency maintains a database of all such facilities, the Drug Establishments Current Registration Site, which it continually updates.¹²

As of May 2020, of the FDA-regulated manufacturing facilities that produce APIs for drugs sold in the U.S. market, 26 percent are located in the United States, 26 percent are in EU member countries, 19 percent are in India, 13 percent are in China, and 2 percent are in Canada, with other countries accounting for the remaining 14 percent.¹³ Of the FDA-regulated facilities that manufacture FDFs for the U.S. market, 46 percent are located in the United States, 19 percent are in EU member countries, 10 percent are in India, 7 percent are in China, and 4 percent are in Canada, with other countries accounting for the remaining 14 percent.¹⁴

Key Considerations for Policymakers

Drug shortages have been a persistent problem that the FDA and the relevant congressional committees were addressing well before the novel coronavirus pandemic.¹⁵ Those efforts have produced useful insights into pharmaceutical supply chain issues and yield four key considerations for policymakers:

1. Drug shortages primarily occur with generic drugs and drugs that require more specialized manufacturing. An FDA analysis of 163

12. The Drug Establishments Current Registration Site may be searched through the U.S. Food and Drug Administration at <https://www.accessdata.fda.gov/scripts/cder/drls/default.cfm> (accessed October 7, 2020), and the current data set may be downloaded through Data.gov at <https://catalog.data.gov/dataset/drug-establishments-current-registration-site> (accessed October 7, 2020).

13. U.S. Food and Drug Administration, “Statement of Judith McMeekin, Pharm. D., Associate Commissioner for Regulatory Affairs, Mark Abdo, Associate Commissioner for Global Policy and Strategy, Douglas C. Throckmorton, M.D., Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research,” Committee on Finance, U.S. Senate, “Covid-19 and Beyond: Oversight of The FDA’s Foreign Drug Manufacturing Inspection Process,” June 2, 2020, p. 4, <https://www.finance.senate.gov/imo/media/doc/02JUN2020.FDAJNT.STMNT.pdf> (accessed October 7, 2020).

14. *Ibid.*

15. For instance, in response to a 2018 congressional request, the FDA convened a taskforce to examine the causes of drug shortages and identify potential solutions. See U.S. Food and Drug Administration, “Drug Shortages: Root Causes and Potential Solutions: A Report by the Drug Shortages Task Force,” 2019, <https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions> (accessed October 7, 2020).

drugs that went into shortage during 2013–2017 found that 67 percent were generics, 63 percent were sterile injectables, and 47 percent were both. Only 17 percent were oral-formulation, non-generic drugs.¹⁶

2. Drug shortages are caused mostly by product quality or safety issues involving ingredients or manufacturing processes. The FDA's analysis found that “of the 163 drugs in shortage, 62 percent went into shortage after supply disruptions occurred that were associated with manufacturing or product quality problems.”¹⁷
3. The generic drug industry faces unique circumstances that contribute to limited production capacity for some drugs, the shift to more foreign sourcing, and supply disruptions due to quality or safety issues.¹⁸ As previously noted, the generic drug industry is characterized by competition on price, uncertain revenues, very thin profit margins, and the need for significant up-front investment.
4. The geographic location of drug manufacturing is a secondary factor. Product safety recalls, production interruptions, and drug shortages occur with domestically manufactured drugs as well as with those made in other countries.¹⁹

In order to ensure that America has a sufficient and reliable supply of drugs, policymakers should focus primarily on generic drug manufacturing, as that is the sector where most of the issues arise. Current generic drug competition is almost entirely focused on price. A generic drug maker has pricing power only when it becomes the sole source for a drug or when industry-wide production of the drug is otherwise unable to meet demand. In contrast, novel drugs with market exclusivity provide much larger financial returns, giving their manufacturers both the incentives and the means to invest in more resilient manufacturing and more dependable sources of quality ingredients.

16. *Ibid.*, p.12.

17. *Ibid.*, p. 33.

18. *Ibid.*, pp. 21–23.

19. For instance, see Sydney Lupkin, “When Medicine Makes Patients Sicker,” *Kaiser Health News*, January 4, 2019, <https://khn.org/news/how-tainted-drugs-reach-market-make-patients-sicker/> (accessed October 7, 2020).

For policymakers, this indicates that the issues they need to address are centered less on FDA approvals of new generic drug applications and more on the policies that impact the financial decisions of the generic drug industry and the FDA's role in regulating drug manufacturing.²⁰

Ensuring a More Reliable Drug Supply

Beginning with the 1984 Hatch–Waxman Act, federal policy has consistently encouraged production of low-priced generic drugs.²¹ Those policies have been so successful that today about 90 percent of all prescriptions in the United States are filled with generic drugs.²² While these policies have resulted in enormous savings to consumers, they also effectively turned generic drug manufacturing into a commodity industry.²³ Even so, policymakers can encourage generic drug companies to invest in more robust and resilient manufacturing and more consistent production quality, thereby reducing product shortages and product defects.

Adopt a Grading Approach to Regulating Drug Manufacturing.

Today, the FDA and equivalent agencies in other countries regulate drug manufacturing based on Current Good Manufacturing Practices (CGMP).²⁴ The FDA conducts site inspections to verify compliance with CGMP and can exclude from the U.S. market products that are not manufactured in accordance with CGMP.

These regulations are designed as “minimum standards” for companies to meet. One drawback of this approach is that it does not identify and reward companies that exceed the minimum required standards. Implementing better practices can enable a manufacturer to achieve more consistent and reliable production of defect-free products. However, doing so entails additional costs, and the manufacturer will not be able to pass on those costs if drug wholesalers, pharmacy benefit managers, and other drug purchasers are focused exclusively on obtaining the lowest price.

20. As the Drug Shortages Task Force noted, “Multiple generic companies are often approved to market drugs that are in shortage but make business decisions not to market them.” Indeed, the FDA’s analysis of drug shortages found that, “just prior to the shortage, there were on average three companies per drug in shortage that were not marketing their approvals.” See FDA, “Drug Shortages: Root Causes and Potential Solutions,” p. 38.

21. Drug Price Competition and Patent Term Restoration Act, Public Law No. 98–417.

22. Association for Accessible Medicines, “The Case for Competition: 2019 Generic Drug and Biosimilars Access and Savings in the U.S. Report,” 2019, <https://accessiblemeds.org/sites/default/files/2019-09/AAM-2019-Generic-Biosimilars-Access-and-Savings-US-Report-WEB.pdf> (accessed October 7, 2020).

23. *Ibid.* See p. 10 for savings estimates.

24. For a brief overview, see U.S. Food and Drug Administration, “Facts About the Current Good Manufacturing Practices (CGMPs),” <https://www.fda.gov/drugs/pharmaceutical-quality-resources/facts-about-current-good-manufacturing-practices-cgmps> (accessed October 7, 2020).

Another drawback is that updating CGMP standards can inadvertently exacerbate drug shortages. Basically, whenever the FDA “raises the bar” of CGMP minimum standards, it risks creating production disruptions or discontinuations.

As the FDA’s Drug Shortages Task Force noted in its 2019 report, CGMP standards “do not include more advanced levels of quality management, which aim to robustly detect vulnerabilities and address them in order to prevent the occurrence of problems, nor do they establish a culture that rewards process and system improvements.”²⁵

A better approach would be to shift from the current binary (pass/fail) design to a graded system.²⁶ Essentially, the CGMP minimum standards would be supplemented by a set of superior manufacturing management practices identified by the FDA and industry. The FDA’s manufacturing inspections could then note the extent to which a manufacturing facility has implemented best practices for anticipating and minimizing the occurrence of production problems. Those best practices would encompass not only the factory’s internal operations but also supply chain vulnerabilities, plans for responding to production disruptions (e.g., natural disasters), and contracts with ingredient suppliers and service vendors.²⁷

Independent entities could then use these results to score or rate manufacturing facilities. That would enable purchasers to identify and preference contracting with more reliable manufacturers. Those manufacturers would, as a result, be able to charge a premium relative to their competitors, effectively rewarding them for making additional investments in manufacturing reliability.

The overall effect would be to incentivize competition among generic drug makers based on consistency and reliability, not just price.

This design would also make updating the CGMP minimum standards less disruptive. Whenever a better manufacturing practice or technology becomes available, companies would have incentives to voluntarily adopt it. As more companies adopted the new practice or technology, it would increasingly become the de facto industry standard. Then, where appropriate, the FDA could update its CGMP minimum standards to reflect the improvements without risking significant production disruptions. Thus, this approach would not only encourage continuous innovation in manufacturing improvements but also provide a smoother path for updating minimum drug manufacturing standards.

25. U.S. Food and Drug Administration, “Drug Shortages: Root Causes and Potential Solutions,” p. 8.

26. The FDA’s Drug Shortages Task Force identified this conceptual shift as one of its top recommendations.

27. *Ibid.* See discussion in Appendix B, pp. 65–71.

Congress should establish a formal mechanism for the FDA and industry to collaborate in designing, implementing, and periodically updating a reformed regulatory design. Two precedents for such an approach are the process by which the FDA and industry negotiate proposed amendments to user-fee statutes—which Congress must reauthorize every five years—and the long-standing International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the membership of which consists of regulatory bodies (the FDA and equivalent agencies in other countries) and drug companies.²⁸

Cross-Reference Drug Product Codes. Drug purchasers should have relevant information when making purchasing decisions—including the sources of the products they buy. As the FDA’s Drug Shortages Task Force noted:

Currently, purchasers have only limited information that can be used to assess the state of quality management of any specific facility and have little information linking the drug products they buy with the facilities where they were manufactured. The lack of information does not enable the market to reward drug manufacturers with price premiums for mature quality management, back-up manufacturing capabilities, or risk-management plans, nor does it penalize manufacturers that fail to invest in modernization of manufacturing equipment and facilities to ensure a reliable supply. Thus, manufacturers are more likely to keep costs down by minimizing investments in manufacturing quality, which eventually leads to quality problems, triggering supply disruptions and shortages.²⁹

In order to make informed decisions, drug purchasers need to know the specific facility at which the FDF was produced, as problems with drug safety and production reliability can invariably be traced to specific manufacturing sites. Alternative proposals, such as requiring labeling of FDFs or APIs by either the company that made it or the country where it was produced (or both), would be inadequate for assessing manufacturing consistency and reliability.

The FDA already assigns unique National Drug Codes (NDC) to finished drug products and unique FDA Establishment Identifier (FEI) codes to drug manufacturing facilities, and it maintains searchable public databases for

28. More information can be found at International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, <https://www.ich.org> (accessed October 7, 2020).

29. U.S. Food and Drug Administration, “Drug Shortages: Root Causes and Potential Solutions,” p. 6.

each of those registration systems.³⁰ Congress and the FDA should require that both the applicable NDC and FEI codes be included on drug packaging, and the FDA should construct a searchable database that cross-references both identifiers. That would enable purchasers to preference contracting with more reliable manufacturers (even though those manufacturers might charge marginally higher prices than their competitors) and, in cases of safety recalls, identify other drugs that might have been affected because they were made at the same facility.

Encourage Government Drug Purchasing Based on Consistency and Reliability. Once better, factory-level product source data is available, purchasers can reward manufacturers that offer greater consistency and reliability—not just lower prices. The FDA’s Drug Shortages Task Force noted:

This could be done through several different mechanisms, such as paying higher prices for drugs manufactured at top-rated facilities, requiring a certain quality maturity rating as a condition of contracting, or guaranteeing purchase of a set volume of products from sites achieving a certain quality maturity rating.³¹

While such changes will need to be implemented mainly by purchasers in the private market, the federal government can also implement better purchasing practices in federally funded health care programs.

Current law requires manufacturers to issue rebates to Medicaid for generic drugs. Manufacturers must also issue price discounts for generic drugs included on the Federal Supply Schedule (FSS) and those purchased under the 340B program for health care providers serving low-income patients.³² These federal purchasing policies all exacerbate the pricing pressures on generic drug manufactures that have resulted in more foreign manufacturing and drug shortages.

30. See U.S. Food and Drug Administration, “National Drug Code Directory,” <https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory> (accessed October 7, 2020), and U.S. Food and Drug Administration, “Drug Establishments Current Registration Site,” <https://www.fda.gov/drugs/drug-approvals-and-databases/drug-establishments-current-registration-site> (accessed October 7, 2020).

31. U.S. Food and Drug Administration, “Drug Shortages: Root Causes and Potential Solutions,” p. 9.

32. The statutory Medicaid rebate amount for generic drugs is currently set at 13 percent of the Average Manufacturer Price (AMP)—which is defined as the average price paid to manufacturers by wholesalers for drugs distributed to retail pharmacies. For a drug to be covered by Medicaid, the manufacturer must also agree to sell the drug to 340B participating providers at prices that do not exceed AMP minus the Medicaid rebate percentage and make the drug available for procurement, with applicable price concessions, through the FSS. The FSS is the mechanism through which the federal government directly purchases drugs for use by the Department of Veterans Affairs, the Department of Defense, the Public Health Service (which includes the Indian Health Service), and the Coast Guard.

Particularly counterproductive was Congress's decision in 2015 to apply to multi-source generic drugs the requirement that manufacturers also rebate any difference between an increase in the average price of a drug and the general inflation rate—which had previously applied only to single-source drugs.³³ As the FDA's Drug Shortages Task Force noted:

Drug shortages persist because they do not appear to resolve according to the “textbook” pattern of market response. In this more typical pattern, prices rise after a supply disruption and provide an incentive for existing and new suppliers to increase production until there is enough supply of a product to meet demand. In this respect, the market for prescription drugs and especially generic drugs differs from other markets.³⁴

Rather than imposing further price concessions on already low-priced generic drugs, Congress should eliminate these provisions so that purchasers of drugs for federally funded programs are also able to incentivize and reward generic drug makers for improving production consistency and reliability. While the federal government might end up paying more for some generic drugs, the cost to taxpayers would likely be less than the alternative of the federal government directly subsidizing the expansion of manufacturing capacity.³⁵

Increase FDA Inspections of Manufacturing Sites. FDA inspections of both U.S. and foreign drug manufacturing sites fall into one of three categories: surveillance, pre-approval, and for-cause.³⁶

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33. For more information, see Richard Manning and Fred Selck, “Penalizing Generic Drugs with the CPI Rebate Will Reduce Competition and Increase the Likelihood of Drug Shortages,” Bates White Economic Consulting, September 12, 2017, https://www.bateswhite.com/media/publication/142_CPI%20Rebate.Manning_Selck.pdf (accessed October 7, 2020).
34. U.S. Food and Drug Administration, “Drug Shortages: Root Causes and Potential Solutions,” p. 5.
35. For example, see U.S. Department of Health and Human Services, “HHS, Industry Partners Expand U.S.-Based Pharmaceutical Manufacturing for COVID-19 Response,” May 19, 2020, <https://www.hhs.gov/about/news/2020/05/19/hhs-industry-partners-expand-us-based-pharmaceutical-manufacturing-covid-19-response.html> (accessed October 7, 2020). See also generic drug industry support for “grants and low-cost loans for plant construction or refurbishment” in Association for Accessible Medicines, “A Diverse, Resilient Supply Chain for Prescription Medicine Will Moderate the Risk of Drug Shortages and Ensure Patient Access during the COVID-19 Pandemic and Beyond,” March 2020, <https://accessiblemeds.org/sites/default/files/2020-03/AAM-Buy-American-One-Page.pdf> (accessed October 7, 2020).
36. Surveillance inspections are periodic “check-ups” intended to monitor ongoing compliance with manufacturing and quality standards and are the largest category. In 2018, surveillance inspections accounted for 70 percent of U.S. facility inspections and 69 percent of foreign facility inspections. That reflects efforts by the FDA over the past decade to bring foreign facility inspections up to levels similar to those for domestic facility inspections. Pre-approval inspections are part of the FDA's process for reviewing each application to market a new drug, including an application to market a new version of a generic drug. For-cause inspections are 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 more detailed discussion and related data, see U.S. Food and Drug Administration, “Statement of Judith McMeekin, Pharm. D., Associate Commissioner for Regulatory Affairs, Mark Abdo, Associate Commissioner for Global Policy and Strategy, Douglas C. Throckmorton, M.D., Deputy Director for Regulatory Programs, Center for Drug Evaluation and Research,” pp. 6–7.

While the FDA has successfully addressed the previous imbalance between domestic and foreign inspections, total inspections have not increased in recent years. In large measure that reflects resource constraints and vacancies in certain positions.

Foreign facility inspections also involve additional challenges, such as obtaining visas to enter countries, suitable translators, and logistical obstacles to implementing unannounced inspections (which are the norm for domestic inspections).

Congress has given the FDA authority to exclude from the U.S. market drugs produced at a facility that delays or refuses to permit inspection (which the agency sometimes encountered at foreign facilities),³⁷ but it could do more.

Specifically, Congress should appropriate additional funding for the FDA's inspection activities—especially foreign inspections—allow inspectors to operate out of U.S. embassies, and ensure that inspectors are supported by competent and independent translators.³⁸

Using Tax Policy to Encourage U.S. Manufacturing

The Tax Cuts and Jobs Act (TCJA), enacted in December 2017, reduced the federal corporate income tax rate from 35 percent to 21 percent.³⁹ After factoring in state corporate income taxes, the average combined U.S. corporate tax rate in 2020 is now 25.77 percent, down from 38.91 percent in 2017.⁴⁰

This rate is now somewhat lower than the equivalent rates for other countries with significant production of novel drugs, such as Canada (26.47 percent), France (32.02 percent), Germany (29.9 percent), Japan (29.74 percent), and South Korea (27.5 percent), but somewhat higher than Israel (23 percent) and Switzerland (21.15 percent) and still significantly higher than Ireland (12.5 percent), Singapore (17 percent), and the United Kingdom (19 percent).⁴¹

37. Food and Drug Administration Safety and Innovation Act, Public Law No. 112-144, § 707.

38. See U.S. Government Accountability Office, "COVID-19 Complicates Already Challenged FDA Foreign Inspection Program, Statement of Mary Denigan-Macaulay, Director, Health Care, Committee on Finance, U.S. Senate, "Covid-19 and Beyond: Oversight of The FDA's Foreign Drug Manufacturing Inspection Process," June 2, 2020, pp. 19–26, <https://www.finance.senate.gov/imo/media/doc/02JUN2020.GAO.STMNT.pdf> (accessed October 7, 2020). In particular, the GAO identified the need to ensure that translators are both independent of the companies being inspected and competent in translating technical and scientific terminology.

39. Tax Cuts and Jobs Act, Public Law No. 115-97, § 13001.

40. Organization for Economic Co-operation and Development (OECD), "Table II.1. Statutory corporate income tax rate," <https://stats.oecd.org/Index.aspx?QueryId=78166> (accessed October 7, 2020). The average combined rate is the national tax rate plus the average subnational tax rate (if any) minus any allowed deductions against the national tax for subnational taxes paid.

41. *Ibid.* Singapore is not a member of the OECD. See the Inland Revenue Authority of Singapore, Corporate Tax Rates, <https://www.iras.gov.sg/irashome/Quick-Links/Tax-Rates/Corporate-Tax-Rates/> (accessed October 7, 2020).

Lower corporate tax rates encourage business expansion in general, but as Ireland's experience shows, they are particularly relevant for businesses that produce high-margin products, such as pharmaceutical companies selling novel drugs with market exclusivity rights. Consequently, further reducing U.S. corporate tax rates would encourage more domestic production of novel drugs.

The TCJA also provides for temporary 100 percent expensing of investments in production assets, meaning that a company can deduct the full cost of those assets from its corporate income taxes in the year that the asset is purchased rather than gradually deducting those costs over a number of years according to a depreciation schedule.⁴²

However, this provision lasts only through 2022 and is then phased down to 20 percent in 2026. Further, it applies only to assets with useful lives of 20 years or less—which means it applies to equipment but not to buildings.

Congress could encourage more domestic manufacturing of generic drugs by making the 100 percent expensing provision permanent and include the cost of constructing, expanding, or renovating manufacturing facilities.⁴³ Alternatively, Congress could adjust the depreciation allowances for structures so as to apply “neutral cost recovery.” That would achieve the same basic policy objective but smooth the fiscal effects (on both corporate taxpayers and government tax revenues) over time.⁴⁴

While these changes would broadly encourage more domestic manufacturing, they would be particularly helpful in encouraging more domestic manufacture of generic drugs. That is because facilities and equipment entail larger up-front capital investments and longer lead times for generic drug makers relative to manufacturers of many other products.

Recommendations

Congress and the FDA could take a number of immediate steps to ensure a more reliable drug supply:

- **Replace the current pass/fail system** for drug facility inspections with a grading system that encourages manufacturers to invest in improving production reliability.

42. Tax Cuts and Jobs Act, § 13201.

43. See Adam Michel, “Why Full Business Expensing Is Vital for Post-COVID-19 Economic Recovery,” Heritage Foundation *Commentary*, April 30, 2020, <https://www.heritage.org/taxes/commentary/why-full-business-expensing-vital-post-covid-19-economic-recovery>.

44. For further analysis, see Erica York, “Options for Improving the Tax Treatment of Structures,” Tax Foundation, May 19, 2020, <https://taxfoundation.org/neutral-cost-recovery-for-buildings/> (accessed October 7, 2020).

- **Require that both the applicable NDC and FEI codes be included on drug packaging** and construct a searchable database that cross-references both codes so that drug purchasers can identify the most reliable manufacturing facilities—thus encouraging generic drug makers to compete on qualities other than price.
- **Eliminate the requirements for rebates or discounts** on multi-source generic drugs purchased through Medicaid and other federally funded health programs.
- **Appropriate additional funding to the FDA to enable more facility inspections**, both in the United States and abroad, and to better support foreign facility inspections.
- **Keep corporate tax rates low and allow companies to fully expense their investments** in new production assets—including manufacturing facilities.

Conclusion

While foreign manufacture of pharmaceuticals for the U.S. market is not a problem *per se*, in some instances—particularly with generic drugs—it does reflect economic factors that have made America’s drug supply less reliable. Policymakers should focus on better understanding and addressing those underlying factors. That will not happen if policymakers simply promote increased domestic production as an end in itself. Policymakers should reward improved production consistency and reliability in drug manufacturing—regardless of where the factories are located. Doing so would not only ensure a more secure supply of drugs for American consumers but would also make the United States a more attractive place to manufacture more of those drugs.

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