

Reputation and Authority: The FDA and the Fight over U.S. Prescription Drug Importation

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There is popular and bipartisan support for legalizing the importation of lower-cost medicines from Canada to help reduce the high prescription drug costs that Americans pay. Despite the wide interest in this policy, attempts over the last sixteen years to create a formal system for large-scale prescription drug importation in the United States have failed. The Trump Administration recently issued a final rule to enable the legal importation of prescription drugs from Canada, but the rule has important design flaws and seems destined to suffer a similar fate as previous efforts.

In this Article, we argue that prescription drug importation is a form of international regulatory engagement that can work, but not in the manner that recent congressional legislation or the Trump Administration has proposed. Importation of prescription drugs, even foreign versions of already-approved drugs, requires the importing nation to accept the marketing approval standards, processes, and product-specific decisions of the exporting nation as equivalent to domestic regulation. The FDA, however, has made far fewer determinations of foreign regulatory equivalence than its counterpart regulators. As a result, the statutory requirements for the FDA maintaining direct oversight over prescription drug imports from Canada are onerous and unlikely ever to be fulfilled.

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Examining U.S. prescription drug importation as a form of reliance on the equivalence of foreign regulation is, as far as we can determine, a novel inquiry, and it offers useful insights. Foreign equivalence determinations have been successfully used in pharmaceutical regulation in two contexts: (1) trade initiatives and (2) circumstances in which regulatory agencies were unable to fulfill their core institutional mandates without relying on the decisionmaking of their foreign counterparts. The FDA has not fit neatly into either of these contexts. In contrast to many of its foreign counterparts, the FDA has consolidated authority over pharmaceutical regulation, which it sustains through its reputation among its constituents—appropriators, consumers, pharmaceutical product sponsors, and the relevant medical and scientific communities—for overseeing the safety, efficacy, and quality of medicines. The FDA has resisted risking any harm to that gatekeeper reputation that might follow from its pursuit of other policy objectives, such as lowering drug prices or facilitating trade. Furthermore, FDA officials describe themselves as “the gold standard” for drug review—more thorough and rigorous about regulation than their counterparts—and, until recently, as able to fulfill their core institutional mandates without the cooperation of foreign counterparts.

Based on this analysis of the political economy of pharmaceutical regulation and international regulatory cooperation at the FDA, we propose that U.S. prescription drug importation could be successfully used to reduce generic drug shortages, a persistent public health problem that the FDA has struggled to solve independently. We argue that the same analysis can help identify other circumstances when the FDA might usefully engage foreign counterparts, such as foreign manufacturer inspections for the rapidly increasing volume of U.S. drug imports, the growing complexity of global pharmaceutical supply chains, and the technological advances in personalized medicines.

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INTRODUCTION

There is popular, bipartisan support for legalizing the importation of lower-cost medicines from Canada to help U.S. patients reduce their high prescription drug costs. Four out of five Americans favor the policy.¹ Vice President Biden and most of the previous Democratic presidential candidates are also on record supporting legalized prescription drug importation.² President Trump likewise favors allowing prescription drug importation from Canada, as did his immediate predecessors, Presidents Obama and George W. Bush.³ Six states—Vermont, Florida, Colorado, Maine, New Mexico, and New Hampshire—have passed bills allowing prescription drug imports from Canada, subject to approval by the U.S. Department of Health and

1. Ashley Kirzinger, Lunna Lopes, Bryan Wu & Mollyann Brodie, *KFF Health Tracking Poll – February 2019: Prescription Drugs*, HENRY J. KAISER FAM. FOUND. (Mar. 1, 2019), <https://www.kff.org/health-reform/poll-finding/kff-health-tracking-poll-february-2019-prescription-drugs/> [https://perma.cc/3MNB-BLMG].

2. *Health Care*, BIDEN FOR PRESIDENT, <https://joebiden.com/healthcare/> (last visited Aug. 31, 2020) [https://perma.cc/B7MP-M4KY]. Senator Bernie Sanders (I-VT) and his fellow senator and former presidential candidate Elizabeth Warren (D-MA) co-sponsored S. 469, the Affordable and Safe Prescription Drug Importation Act, which amends the Federal Food, Drug, and Cosmetic Act to require the Food and Drug Administration (“FDA”) to promulgate regulations within 180 days permitting wholesalers, pharmacies, and individuals to import certain prescription drugs from Canada. The FDA, within two years, may permit the importation of prescription drugs from other countries. Other recent U.S. presidential candidates such as Cory Booker, Pete Buttigieg, Julian Castro, John Delaney, Kamala Harris, Jay Inslee, Amy Klobuchar, Beto O’Rourke, Tim Ryan, Marianne Williamson, and Andrew Yang are all in favor. *How the Democratic Candidates Responded to a Health Care Policy Survey*, N.Y. TIMES (June 23, 2019), <https://www.nytimes.com/2019/06/23/us/politics/2020-democrats-health-care.html> [https://perma.cc/3BJ7-MHLQ].

3. See Press Release, U.S. Dep’t of Health & Hum. Servs., Trump Administration Takes Historic Steps to Lower U.S. Prescription Drug Prices (Dec. 18, 2019), <https://www.hhs.gov/about/news/2019/12/18/trump-administration-takes-historic-steps-to-lower-us-prescription-drug-prices.html> [https://perma.cc/K9XE-Y4T9]; Reuters Staff, *Obama Seeks Drug Imports Outside of Health Bill*, REUTERS (Dec. 20, 2009, 1:43 PM), <https://www.reuters.com/article/us-usa-healthcare-importation/obama-seeks-drug-imports-outside-of-health-bill-idUSTRE5BF0DW20091220> [https://perma.cc/U9NP-CV66]; Robert Pear, *Bush Hints at Policy Shift on Canadian Drug Imports*, N.Y. TIMES (Oct. 12, 2004), <https://www.nytimes.com/2004/10/12/politics/campaign/bush-hints-at-policy-shift-on-canadian-drug-imports.html> [https://perma.cc/68FE-WALT].

Human Services (“HHS”).⁴ On December 18, 2019, HHS and the Food and Drug Administration (“FDA”) issued a notice of proposed rulemaking (“NPRM”) and a draft guidance on a pathway to enable the legal importation of prescription drugs from Canada.⁵ In July 2020, President Trump issued an executive order encouraging completion of this rulemaking process.⁶ On September 24, 2020, the FDA issued the final rule, which is scheduled to go into effect on November 24.⁷

Despite the popularity of this policy, however, past attempts to legalize large-scale U.S. prescription drug importation have failed. In 2003, Congress passed the Medicare Prescription Drug, Improvement, and Modernization Act (“MMA”) of 2003 (better known as the law that created Medicare Part D), which provides the HHS secretary with the authority to permit the importation of prescription drugs from Canada. In the sixteen subsequent years, no HHS secretary or FDA commissioner appointed by a president of either party has made the certifications to Congress necessary for the relevant clause to take effect: that implementation will both “pose no additional risk to the public’s health and safety” and “result in a significant reduction in the cost of covered products to the American consumer.”⁸ HHS Secretary Azar made this certification when the final rule was issued, but it is conditional on state governments and non-federal programs sponsoring the importation program and meeting the same certification requirements that the federal government has been unable to satisfy for nearly two decades.⁹

In this Article, we argue that prescription drug importation is a form of international regulatory engagement that can work, but not in the manner that recent congressional efforts or the Trump Administration has proposed. Importation of prescription drugs, even foreign versions of already-approved drugs, requires the importing

4. COLO. REV. STAT. §§ 25.5-2.5-201 to 25.5-2.5-207 (2019); FLA. STAT. § 381.02035 (2019); ME. STAT. tit. 5, §§ 2041-2044 (2019); H.R. 1280, 2020 Gen. Court, Reg. Sess. (N.H. 2020) (enacted); N.M. STAT. ANN. §§ 26-4-1 to 26-4-10 (2020); VT. STAT. ANN. tit. 18, §§ 4651-4656 (2018).

5. Importation of Prescription Drugs, 84 Fed. Reg. 70,796 (proposed Dec. 23, 2019) (to be codified at 21 C.F.R. pts. 1, 251).

6. Exec. Order 13,938, 85 Fed. Reg. 45,757 (Jul. 24, 2020). The executive order also instructs the HHS secretary to exercise the enforcement discretion already provided in 21 U.S.C. § 384(j)(1) against individuals importing prescription drugs for personal use and to permit the re-importation of insulin upon a finding by the secretary that it is required for emergency medical care, an authority which also already existed under 21 U.S.C. § 381(d).

7. Importation of Prescription Drugs, Final Rule #2020-199 (Sept. 24, 2020) (to be codified at 21 C.F.R. pts. 1, 251), <https://www.hhs.gov/sites/default/files/importation-final-rule.pdf> [<https://perma.cc/9LA8-HDCB>] (at the time of writing, the final rule has not yet been published in the Federal Register).

8. 21 U.S.C. § 384(l)(1) (2012).

9. Importation of Prescription Drugs, Final Rule #2020-199, at 8, 68.

nation to accept the marketing approval standards and processes of the exporting nation as equivalent to domestic regulation and to rely on the product-specific decisions and oversight of the exporting nation. The FDA, however, has made far fewer determinations of foreign regulatory equivalence than either its counterpart regulators in other nations or U.S. regulators, such as the U.S. Department of Agriculture (“USDA”). Past U.S. prescription drug importation initiatives have failed because they arose under circumstances in which the FDA was unwilling to depart from that general practice and accept the equivalence of the marketing approval process of Health Canada and other foreign national regulatory authorities and to rely on their oversight. FDA officials have insisted instead on ensuring direct U.S. oversight of the prescription drug importation process, which has rendered importation too expensive and impractical to be implemented.¹⁰ Congress has acceded to FDA demands and, as a result, the statutory requirements for legal importation of cheaper prescription drugs from Canada are so onerous that HHS officials have described them as “extremely unlikely” to be fulfilled.¹¹

Examining U.S. prescription drug importation as a form of reliance on the equivalence of foreign regulation is, as far as we can determine, a novel inquiry,¹² and it offers two sets of useful insights. First, examining the theory and practice of international regulatory engagement—the circumstances in which equivalence determinations have been successful and the institutional characteristics of the regulatory agencies that use them—helps identify the reasons that the FDA has engaged in that form of cooperation far less often than its counterpart agencies.¹³ This is important because multiple independent assessments have found that unless the FDA better leverages the activities of its foreign counterparts, the agency cannot possibly oversee the rapidly increasing volume of U.S. drug imports, the growing

10. CONG. RESEARCH SERV., RL32191, PRESCRIPTION DRUG IMPORTATION: A LEGAL OVERVIEW 3–9 (2008) (summarizing various FDA statements indicating that it cannot guarantee the safety or effectiveness of imported drugs that are not FDA-approved, which the FDA has previously estimated would be prohibitively expensive).

11. Pam Belluck, *Vermont Will Sue U.S. for the Right to Import Drugs*, N.Y. TIMES (Aug. 11, 2004), <https://www.nytimes.com/2004/08/11/us/vermont-will-sue-us-for-the-right-to-import-drugs.html> [<https://perma.cc/B7YC-7G95>].

12. *But see* Kenneth A. Bamberger & Andrew T. Guzman, *Keeping Imports Safe: A Proposal for Discriminatory Regulation of International Trade*, 96 CALIF. L. REV. 1405, 1424–26 (2008) (citing importation as a form of equivalence, but the article is focused on the larger topic of import safety and does not draw on the theory and practice of regulation engagement to explore how to advance the topic).

13. *See, e.g.*, Daniel Hemel, Note, *Regulatory Consolidation and Cross-Border Coordination: Challenging the Conventional Wisdom*, 28 YALE J. ON REG. 213, 219–30 (2011) (examining theories of cross-border financial regulation among financial regulators).

complexity of global pharmaceutical supply chains, and the technological advances in personalized medicines.¹⁴ Second, this analysis reveals workable approaches to a program of U.S. prescription drug importation, a potential tool for addressing high U.S. prescription drug prices, which both disproportionately affect people who are uninsured or have high-deductible insurance plans and contribute to U.S. economic inequality. Based on that analysis, we suggest that a mechanism for U.S. prescription drug importation could be successfully used to reduce generic drug shortages and extreme price hikes among off-patent drugs that function like product shortages, and we put forward a proposal for doing so.

The Article proceeds in four parts. Part I outlines the current landscape of U.S. prescription drug importation. This section examines the role of prescription drug imports in the U.S. health care system generally and the high U.S. drug prices that drive popular demand for access to cheaper foreign versions. This section also summarizes the current pathways for legally permissible prescription drug importation under the U.S. Food, Drug, and Cosmetic Act (“FDCA”) of 1938 and recent congressional and Trump Administration efforts to harness those pathways.

Part II demonstrates that equivalence determinations are an established form of international regulatory engagement successfully used in the pharmaceutical sector in two particular contexts. First, regulatory equivalence and reliance determinations are often included in trade initiatives to reduce duplicative or unnecessarily divergent standards and conformity assessment procedures. Second, agencies

14. See COMM. ON MUT. RECOGNITION AGREEMENTS & RELIANCE IN THE REGULATION OF MEDS., NAT’L ACADS. OF SCIS., ENG’G, & MED., *REGULATING MEDICINES IN A GLOBALIZED WORLD: THE NEED FOR INCREASED RELIANCE AMONG REGULATORS* 51 (Alastair J. Wood & Patricia Cuff eds., 2020) (“Given the large number of manufacturing sites in China and India that are involved in producing drug[s] . . . for the United States . . . it has not been possible for [the] FDA . . . to inspect all of these sites . . . in order to assure the quality of products being exported to their people.”); COMM. ON STRENGTHENING CORE ELEMENTS OF REGULATORY SYS. IN DEVELOPING COUNTRIES, INST. OF MED. OF THE NAT’L ACADS., *ENSURING SAFE FOODS AND MEDICAL PRODUCTS THROUGH STRONGER REGULATORY SYSTEMS ABROAD*, at ix (Jim E. Riviere & Gillian J. Buckley eds., 2012) (“The diversity and scale of imports makes it impractical for [FDA] border inspections to be sufficient to ensure product purity and safety.”); U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-12-933, *FOOD SAFETY: FDA CAN BETTER OVERSEE FOOD IMPORTS BY ASSESSING AND LEVERAGING OTHER COUNTRIES’ OVERSIGHT RESOURCES* 38 (2012) (recommending that the FDA use tools like equivalence to leverage the resources of foreign countries to ensure exports meet U.S. requirements). The FDA has itself acknowledged the necessity of increased international regulatory cooperation. U.S. FOOD & DRUG ADMIN., 2012 REPORT TO CONGRESS ON THE FDA FOREIGN OFFICES (2012), <https://www.fda.gov/food/food-safety-modernization-act-fsma/2012-report-congress-fda-foreign-offices> [<https://perma.cc/2DFD-H67E>] (recognizing that “FDA must continue to exert its leadership as part of the global regulatory enterprise to assure that global regulatory standards are consistent with the best science and public health information available”).

have turned to regulatory equivalence determinations when those agencies could not fulfill their core institutional mandates without relying on the decisionmaking and activities of their foreign counterparts.

Part III explains why the FDA and its oversight of the prescription drug market have not fit easily into either of these two contexts. Drawing from literature on the political economy of pharmaceutical regulation and international regulatory cooperation, we argue that the FDA's limited use of equivalence determinations is unsurprising. In contrast to the European Commission ("EC"), where its Directorate General for Enterprise and Industry is charged with coordinating regulatory protection and trade, the FDA has the consolidated statutory authority as the gatekeeper for ensuring the safety, quality, and efficacy of medicines.¹⁵ To sustain that authority and its funding, the FDA depends on its reputation for protecting consumers from unsafe drugs.¹⁶ Accordingly, the FDA has resisted initiatives that might undermine that reputation and subordinate its gatekeeping mission to other policy objectives, such as lowering drug prices or facilitating trade.¹⁷ Unlike the nascent or under-resourced regulators of small or developing nations, FDA officials describe themselves as "the gold standard" for drug review—more thorough and rigorous about regulation than their counterparts in other countries¹⁸—and, until recently, able to fulfill their core institutional mandates without the cooperation of foreign counterparts. We argue that the implementation of the first U.S. mutual recognition agreement ("MRA") with the EU, after a twenty-year delay, finally occurred due to changes in global pharmaceutical production that forced the FDA to acknowledge its inability to fulfill its mandate on good manufacturing practices ("GMP") inspections alone.

Based on the foregoing analysis, Part IV outlines proposed guidelines for issues on which the FDA is more likely to successfully employ equivalence determinations as a means of international regulatory engagement. Drawing on those general guidelines, we

15. See, e.g., Hemel, *supra* note 13, at 217 (arguing that where a single agency has consolidated control over a policy matter at the domestic level, that agency is less willing to restrict its policymaking discretion through international agreements).

16. See Daniel Carpenter, *Reputation, Information and Confidence: The Political Economy of Pharmaceutical Regulation*, in RESEARCH HANDBOOK ON PUBLIC CHOICE AND PUBLIC LAW 399, 401 (Daniel A. Farber & Anne Joseph O'Connell eds., 2010) ("The regulatory power of the FDA stems from its reputation for scientific expertise and consumer protection.").

17. See Belluck, *supra* note 11.

18. David A. Kessler, *Remarks by the Commissioner of Food and Drugs*, 51 FOOD & DRUG L.J. 207, 214–15 (1996); Richard A. Merrill, *The Importance and Challenges of "Mutual Recognition,"* 29 SETON HALL L. REV. 736, 742–43 (1998).

explain in the final Part why the Trump Administration’s current effort on prescription drug importation is likely to fail. We conclude by suggesting a pathway for importing already-approved foreign versions of U.S. medications without patent protection or other forms of exclusivity but lacking insufficient generic competition. That pathway would help prevent and reduce the duration of off-patent drug shortages and price hikes, providing the context in which U.S. prescription drug importation may finally succeed.

I. THE CURRENT LANDSCAPE OF U.S. PRESCRIPTION DRUG IMPORTATION

There is nothing unusual about the use of imported pharmaceuticals in the United States. The United States is already the world’s largest importer of pharmaceuticals. At \$97 billion in imports in 2017, pharmaceutical imports represent roughly a quarter of the U.S. pharmaceutical market.¹⁹ Outsourcing of the manufacturing of an active pharmaceutical ingredient (“API”)²⁰ and of finished drugs to foreign contract manufacturers—particularly those in India, China, and Eastern Europe—more than doubled between 2001 and 2010.²¹ The FDA estimates that 80% of the APIs and 40% of the finished drugs used in the United States are imported.²² These estimates may be low, however; a recent study found that 60% of finished drugs in the United States and 90% or more of APIs were made at foreign facilities.²³

The debate over imported medicines exists not because those medicines are made abroad—most U.S. prescription drugs are. Rather,

19. U.S. DEPT OF COMMERCE, INT’L TRADE ADMIN., 2016 TOP MARKETS REPORT: PHARMACEUTICALS 8 (2016) https://legacy.trade.gov/topmarkets/pdf/Pharmaceuticals_Top_Markets_Reports.pdf [<https://perma.cc/942E-DKML>]; Thomas Bollyky & Aaron S. Kesselheim, *Pharmaceutical Protections in U.S. Trade Deals —What Do Americans Get in Return?*, 380 NEW ENG. J. MED. 1993, 1994–95 (2019).

20. An active pharmaceutical ingredient (“API”), or bulk drug substance, is “any substance that is intended for incorporation into a finished drug product and is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body,” but does not include intermediates used in the synthesis of the API. 21 C.F.R. § 207.1 (2019). Because an API is intended to diagnose, cure, mitigate, treat, or prevent disease, or to affect the structure or function of the body according to this regulation, it meets the definition of a drug under the FDCA. *See* 21 U.S.C. § 321(g)(1) (2012) (defining the term “drug” to include any articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease). Generally, an API undergoes further manufacturing into a drug product, or finished dosage form, that contains the API and excipients. *See, e.g.*, 21 C.F.R. § 210.3(b)(4) (2019) (defining the term drug product).

21. U.S. FOOD & DRUG ADMIN., PATHWAY TO GLOBAL PRODUCT SAFETY AND QUALITY 14 (2011); Ernst R. Berndt, Rena M. Conti & Stephen J. Murphy, *The Generic Drug User Fee Amendments: An Economic Perspective*, 5 J.L. & BIOSCIENCE 103, 112 (2018).

22. Bollyky & Kesselheim, *supra* note 19, at 1993–94.

23. Berndt et al., *supra* note 21, at 117–18.

such debate arises amid calls for the importation of prescription drugs made for foreign markets and approved by other nations' regulatory authorities, such as Health Canada and European Medicines Agency ("EMA"), not by the FDA. Public demand for this sort of prescription drug import may arise when there are U.S. drug shortages or on occasions when the FDA has not yet approved a medicine that patients or physicians perceive as offering therapeutic benefits for an unmet medical need. In recent years, however, the demand for prescription drug importation has been driven mostly by price; foreign versions of FDA-approved medicines are often cheaper and, therefore, are a potential source of spending relief for U.S. patients unable to afford their prescriptions.

A. U.S. Prescription Drug Spending

Average pharmaceutical prices for brand-name drugs are higher in the United States than in other countries.²⁴ The United States is distinct among high-income countries in that it offers strong drug patent protections and limits the ability of public and private payers to appraise new drugs and bargain effectively for lower prices. This combination leads companies to price their drugs at whatever the target segment of the U.S. market will bear, rather than as a benchmark of the drug's therapeutic and economic value, underlying research and development costs, or expected global revenues. In recent years, the U.S. market has borne a lot.

While prescription drugs represented about 10% of U.S. health care spending in the past,²⁵ they now comprise more than 16% of total national health care expenditures.²⁶ Prescription medication coverage

24. Aaron S. Kesselheim, Jerry Avorn & Ameet Sarpatwari, *The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform*, 316 JAMA 858, 859 (2016); Robert Langreth, Blacki Migliozi & Ketaki Gokhale, *The U.S. Pays a Lot More for Top Drugs than Other Countries*, BLOOMBERG (Dec. 18, 2015), <https://www.bloomberg.com/graphics/2015-drug-prices/> [<https://perma.cc/5293-G6Y3>].

25. Rabah Kamal, Cynthia Cox & Daniel McDermott, *What Are the Recent and Forecasted Trends in Prescription Drug Spending?*, PETERSON-KFF HEALTH SYS. TRACKER (Feb. 20, 2019), <https://www.healthsystemtracker.org/chart-collection/recent-forecasted-trends-prescription-drug-spending/#item-start> [<https://perma.cc/PL5U-U9NE>].

26. U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF THE ASSISTANT SEC'Y FOR PLANNING & EVALUATION, OBSERVATIONS ON TRENDS IN PRESCRIPTION DRUG SPENDING 1 (2016), <https://aspe.hhs.gov/pdf-report/observations-trends-prescription-drug-spending> [<https://perma.cc/FY2F-6R9R>]; Ernst R. Berndt, Rena M. Conti & Stephen J. Murphy, *The Landscape of US Generic Prescription Drug Markets, 2004-2016*, at 1 (Nat'l Bureau of Econ. Research, Working Paper No. 23640, 2017) (noting that estimates of U.S. prescription drug spending should also include prescription drugs used in the inpatient setting, since hospitals are commonly paid for such care using bundled payment).

constitutes 19% of employer-based insurance benefits,²⁷ and one commercial health plan with more than a million members recently reported that prescription drugs comprised one-fourth of its health care spending.²⁸ In 2018, U.S. per capita spending on pharmaceuticals was \$1,229, nearly 50% more than in Canada and twice as much as that of many European nations.²⁹ The Centers for Medicare & Medicaid Services predicts that Americans' drug spending will increase to more than \$1,700 per person by 2026, at which time it will constitute approximately one out of every five dollars Americans spend on health care.³⁰

B. The Current Pathways for Legally Permissible U.S. Prescription Drug Importation

As U.S. patients' spending on prescription drugs has risen, so has the demand for cheaper imports. The channels for legal importation, however, are limited, and U.S. health officials, especially at the FDA, have historically opposed expanding those channels.

Prescription drugs made for foreign markets are unlikely to comply with the requirements of the FDCA.³¹ The FDCA prohibits the introduction into interstate commerce, including importation, of any drug that is not the subject of an FDA-approved new drug application ("NDA") or, in the case of generic medicines, an abbreviated new drug application ("ANDA").³² FDA approvals are specific to the information in the NDA or ANDA, including the manufacturer, product, and its use; manufacturing location, formulation, source, and specifications of active ingredients; processing methods; manufacturing controls;

27. Kesselheim et al., *supra* note 24, at 859.

28. Michael Sherman, Gregory D. Curfman, Jason Parent & Anita Katharina Wagner, *Prescription Medications Account for One in Four Dollars Spent by a Commercial Health Plan*, HEALTH AFF.: CONSIDERING HEALTH SPENDING (Aug. 24, 2018), <https://www.healthaffairs.org/doi/10.1377/hblog20180821.820628/full/> [<https://perma.cc/D8KN-MNG9?type=image>].

29. *Pharmaceutical Spending*, ORG. FOR ECON. CO-OP. & DEV., <https://data.oecd.org/healthres/pharmaceutical-spending.htm> (last visited Aug. 31, 2020) [<https://perma.cc/92NY-RZHJ>] (use drop-down menus below the chart to select "US dollars/capita" to view spending per capita).

30. See *National Health Expenditure Projections 2017–26*, CTRS. FOR MEDICARE & MEDICAID SERVS., OFFICE OF THE ACTUARY 17 (Feb. 14, 2018), <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/NHEProjSlides.pdf> [<https://perma.cc/639T-SRKW>] (noting that national health spending is projected to reach \$5.7 trillion by 2026).

31. Federal Food, Drug, and Cosmetic Act §§ 1–901, 21 U.S.C. §§ 301–399i (2012); CONG. RESEARCH SERV., *supra* note 10, at 10.

32. 21 U.S.C. §§ 331(a), 331(d), 355(a).

labeling; and appearance.³³ If a product is manufactured, packaged, or labeled in any way that differs from the NDA—for example, it is made in a different facility or according to different specifications or labeled for sale in a different market—then the FDA considers that drug unapproved,³⁴ mislabeled,³⁵ or adulterated,³⁶ even if it is made by the company that makes the FDA-approved version of the same drug.³⁷

Further, the U.S. Prescription Drug Marketing Act forbids any party other than the manufacturer from importing prescription drugs.³⁸ This restriction means that even FDA-approved drugs manufactured in FDA-approved facilities may not be imported by a party that is not the original manufacturer.³⁹ This restriction covers “re-imported” medicines—prescription drugs manufactured in the United States or abroad (in FDA-approved facilities) and sold in foreign markets subject to their price controls and then imported back to the United States.⁴⁰

There are currently three avenues for legal importation of prescription drugs that are not approved by the FDA.⁴¹

First, the FDA has a formal policy of exercising discretion in its enforcement activities when it comes to importation of prescription drugs by patients themselves for personal use. Section 384(j) of the FDCA gives the FDA “discretion to permit individuals to make . . . importations [if] . . . the importation is clearly for personal use; and the prescription drug or device imported does not appear to present an

33. *Id.* § 355(b)(1) (listing the information that must be contained in an application to approve a new drug).

34. *Id.* § 355.

35. The labeling does not include the FDA-approved adequate directions for use. *Id.* §§ 352, 353(b)(2).

36. “Adulterated” means being held under insanitary conditions other than those FDA-approved. *Id.* § 351(a).

37. Letter from William K. Hubbard, Assoc. Comm’r for Policy & Planning, Food & Drug Admin., to Robert P. Lombardi, Esq., The Kullman Firm 1 (Feb. 12, 2003) (“[E]ven if the manufacturer has FDA approval for a drug, the version produced for foreign markets usually does not meet all of the requirements of the U.S. approval, and thus it is considered to be unapproved.”). See *United States v. 1500 90-Tablet Bottles*, 384 F. Supp. 2d 1205, 1218 (N.D. Ill. 2005) (ruling that the drug at issue was an unapproved new drug because it did not meet the FDA-approved NDA packaging requirement).

38. Prescription Drug Marketing Act of 1987 § 3, 21 U.S.C. § 381(d)(1) (2012).

39. See *id.*; *United States v. Genendo Pharm., N.V.*, 485 F.3d 958, 962–65 (7th Cir. 2007); *In re Can. Import Antitrust Litig.*, 470 F.3d 785, 789–90 (8th Cir. 2006).

40. The only scenario permitted is what is referred to as “American goods returned,” such as when the original manufacturer shifts inventory from abroad back to the United States to sell on the U.S. market. Erika Lietzan, *Demystifying Drug Importation After Impression v. Lexmark*, PATENTLY0 (June 6, 2017), <https://patently0.com/patent/2017/06/demystifying-importation-impresion.html> [<https://perma.cc/65M2-UHVB>].

41. For clarity, we note that these channels apply to both importation of unapproved prescription drugs and “re-importation” of FDA-approved prescription drugs, as the FDA has considered both to be unapproved. See 21 U.S.C. § 381(d); Lietzan, *supra* note 40.

unreasonable risk to the individual.”⁴² The FDA adopted that policy soon after the practice of personal importation became widespread enough to gain public attention: when the People With AIDS Health Group formed the first buyers’ club to import unapproved AIDS drugs for its members in the United States in 1987.⁴³ A modest portion of U.S. citizens currently travel to Canada, Mexico, or other foreign countries to purchase lower-priced prescription drugs.⁴⁴

The current version of that FDA policy requires that the imported product be for a serious condition with no effective treatment available domestically, citing as an example a situation in which a patient has initiated treatment abroad with a non-FDA-approved drug.⁴⁵ The quantity should not exceed a three months’ supply.⁴⁶ There must be no subsequent commercial sales or promotion of the imported drug in the United States.⁴⁷ On request, the patient should provide to FDA personnel the name and address of the U.S.-licensed physician responsible for treatment.⁴⁸ Decisions on personal use are based on the discretion of the FDA, and the FDA may change its policies on personal use at any time.⁴⁹ The personal use policy does not alter the FDCA or create an individual right to import unapproved drugs.⁵⁰ FDA guidance also makes clear that “the [personal use exemption] is not intended to

42. 21 U.S.C. § 384(j)(1)(B) (2012).

43. Paula Span, *Pharmacy for the Desperate: AIDS Drug Buyers’ Clubs, Dispensing Untested Hope*, WASH. POST, Apr. 8, 1992, at D1. *See also* U.S. FOOD & DRUG ADMIN., *supra* note 21, at 9–21 (detailing the FDA’s personal importation policy).

44. *Kaiser Health Tracking Poll: November 2016*, HENRY J. KAISER FAM. FOUND. 17 (Nov. 2016), <http://files.kff.org/attachment/Kaiser-Health-Tracking-Poll-November-2016-Topline> [<https://perma.cc/Q4BF-JHME>].

45. U.S. FOOD & DRUG ADMIN., *supra* note 21, at 9–24.

46. *Id.* at 9–23.

47. *See id.* (noting that the personal importation policy does not apply to commercial and promotional shipments).

48. *See id.* at 9–24 (stating that more permissive decisions may be considered when the individual provides such information).

49. *See id.* at 9–23 (explaining that all products in violation of statutes administered by FDA are subject to refusal, but the FDA may use discretion to allow admission of certain violative items).

50. *Personal Importation Policy (PIP) Frequently Asked Questions (FAQs)*, U.S. FOOD & DRUG ADMIN. 1, <https://www.fda.gov/media/83411/download> [<https://perma.cc/U4Z7-92RS>] (stressing that the personal importation policy should not be interpreted as a license to individuals to bring in such shipments). Courts have upheld the position of the FDA on personal use, finding that there is no individual right under either the Constitution, the FDCA, or the Regulatory Procedures Manual to import drugs, approved or otherwise. *See* *Benten v. Kessler*, 505 U.S. 1084, 1084–85 (1992) (upholding the personal use policy and supporting the confiscation of RU-486 imported for personal use in inducing a non-surgical abortion); *see also* Peter S. Reichertz & Melinda S. Friend, *Hiding Behind Agency Discretion: The Food and Drug Administration’s Personal Use Drug Importation Policy*, 9 CORNELL J.L. & PUB. POL’Y 493, 494 (2000) (describing the FDA’s personal use importation policy).

permit personal importation of cheaper versions of FDA approved *drugs* from . . . foreign countries.”⁵¹

The second channel for importing unapproved versions of prescription drugs enables the HHS secretary to respond to medical emergencies or drug shortages.⁵² The secretary is required to maintain a list of U.S. drug shortages,⁵³ which the FDA defines as a drug for which the demand or projected demand for a drug in the United States exceeds the supply.⁵⁴ The secretary is required to estimate the duration of the shortage, and the FDCA, as amended by the FDA Safety and Innovation Act (“FDASIA”) of 2012, enables the secretary to authorize that specific drug’s importation during that shortage.⁵⁵ The FDA has facilitated temporary importation of foreign versions of FDA-approved drugs during shortages of essential medicines that could not be resolved by manufacturers of the FDA-approved drugs.⁵⁶ The FDA focuses on shortages of medically necessary products that have a critical effect on public health, and authorizations of importation through this pathway have generally been temporary.⁵⁷

In 2003, Congress created a third channel, which empowers the secretary of HHS to permit wholesalers and pharmacists to import prescription drugs from Canada for the purpose of lowering U.S. drug costs.⁵⁸ Section 804 of the MMA amended the FDCA to allow

51. U.S. FOOD & DRUG ADMIN., *supra* note 50, at 1.

52. 21 U.S.C. § 381(d)(1)-(2) (2012).

53. 21 U.S.C. § 356e (2012).

54. 21 U.S.C. § 356c(h)(2); CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN., MAPP 4190.1 Rev. 3, DRUG SHORTAGE MANAGEMENT 14 (2018), <https://www.fda.gov/media/72447/download> [<https://perma.cc/9P9E-43ZA>].

55. *See* 21 U.S.C. § 381(d)(2).

56. *Frequently Asked Questions: Temporary Importation of Lipodox*, U.S. FOOD & DRUG ADMIN. 1 (2012), <https://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/UCM295225.pdf> [<https://perma.cc/8BRN-3UND>].

57. AMANDA K. SARATA & AGATA DABROWSKA, CONG. RESEARCH SERV., IFI 1056, PRESCRIPTION DRUG IMPORTATION 2 (2019), <https://crsreports.congress.gov/product/pdf/IF/IFI11056> [<https://perma.cc/DZ39-D36X>]. *See, e.g.*, Zachary Brennan, *FDA Allows Temporary Saline Imports to Deal With Shortages Caused by Hurricane Maria*, REG. AFF. PROFS. SOC’Y: REG. FOCUS (Oct. 11, 2017), <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/10/fda-allows-temporary-saline-imports-to-deal-with-shortages-caused-by-hurricane-maria> [<https://perma.cc/JTM9-QSB9>] (discussing the FDA’s temporary authorization of imports after Hurricane Maria); *FDA Approves Temporary Import of Hydromorphone Hydrochloride Injection*, AM. HOSP. ASS’N (Aug. 24, 2018), <https://www.aha.org/news/headline/2018-08-24-fda-approves-temporary-import-hydromorphone-hydrochloride-injection> [<https://perma.cc/52EB-R6YW>]. On July 24, 2020, President Trump issued an executive order instructing the HHS secretary to permit re-importation of insulin upon a finding by the secretary that insulin is required for emergency medical care. Exec. Order No. 13,938, 85 Fed. Reg. 45,757 (July 24, 2020). At the time of writing, the HHS secretary had not announced any finding that insulin qualifies as emergency medical care.

58. *See* 21 U.S.C. § 384 (2012) (directing the HHS Secretary to adopt regulations allowing pharmacists and wholesalers to import drugs from Canada as long as certain requirements are

importation, but the amendment comes with conditions and requirements.⁵⁹ The secretary must certify to Congress that implementation “will pose no additional risk to the public’s health and safety; and result in a significant reduction in the cost of covered products to the American consumer.”⁶⁰ If the secretary so certifies, other statutory requirements must be met: the drugs may be imported only from Canada and must be foreign versions of already FDA-approved drugs, labeled according to FDA requirements, and not misbranded or adulterated.⁶¹ There are also requirements for strict laboratory testing and recordkeeping, as well as prohibitions on the importation of controlled substances, biological products, infused drugs, intravenously injected drugs, and drugs inhaled during surgery.⁶² If those statutory requirements are met, HHS must promulgate regulations as necessary to implement the program.

In sixteen years, no HHS secretary has made the necessary certifications, so the MMA importation pathway has never been used. Each of the last four FDA commissioners has said there would be no way to ensure the safety of U.S. prescription drug imports from Canada.⁶³ When asked about the failure to implement this provision during his 2014 confirmation hearing, then-nominee Robert Califf stated:

Drugs from foreign sources that are not FDA-approved nor have such an inspection do not have the assurance of safety, effectiveness, and quality as drugs subject to FDA oversight. . . . FDA would not be able to make safety and quality determinations for prescription drugs offered for import into the United States that have not gone through the U.S. regulatory process.⁶⁴

In other words, U.S. health officials are unwilling to rely on the good manufacturing practices and inspections that Health Canada conducts or to declare that agency’s oversight as equivalent to the

met). This legislation came after years of proposed bills and one failed prior attempt to create a pathway for legal importation of foreign-approved pharmaceuticals. See Wesley J. Heath, *America’s First Drug Regulation Regime: The Rise and Fall of the Import Drug Act of 1848*, 59 *FOOD & DRUG L.J.* 169, 179–81 (2004) (describing the Import Drug Act of 1848, which was Congress’s first attempt to address the challenge of imported, adulterated drugs); Daniel L. Pollock, *Blame Canada (and the Rest of the World): The Twenty-Year War on Imported Prescription Drugs*, 30 *SETON HALL LEGIS. J.* 331, 356–67 (2006) (describing the early history of state and federal legislative initiatives to establish importation as a means to lower U.S. drug prices).

59. 21 U.S.C. § 384.

60. *Id.* § 384(l)(1).

61. *Id.* § 384.

62. *Id.* § 384(a), (d), (e).

63. Alex M. Azar II, U.S. Sec’y of Health & Human Servs., Remarks on Drug Pricing Blueprint (May 14, 2018), <https://www.hhs.gov/about/leadership/secretary/speeches/2018-speeches/remarks-on-drug-pricing-blueprint.html> [<https://perma.cc/4Q6K-735E>].

64. *Nomination of Robert Califf to Serve as FDA Commissioner: Hearing of the S. Comm. on Health, Educ., Labor, and Pensions*, 114th Cong. 82 (2015) (statement of nominee Robert Califf).

FDA's, even for versions of FDA-approved drugs with the other MMA recordkeeping and testing requirements. Without that equivalency determination and reliance on Health Canada, the FDA would have to establish its own inspection and screening processes for these particular prescription drug imports. In the past, U.S. officials have concluded, and the Congressional Budget Office's estimates have confirmed, that doing so would be prohibitively expensive, overwhelming any cost savings from the imported drugs' lower prices.⁶⁵

C. Recent Efforts to Expand U.S. Prescription Drug Importation

Members of Congress have introduced numerous bills, some with bipartisan support, to create additional channels for U.S. prescription drug imports or broaden existing channels.⁶⁶ Amid industry and HHS opposition, none of these bills have yet been enacted. For its part, Canada, which has a population about 11% of that of the United States, has expressed concern about the effect that U.S. wholesaler purchases would have on the Canadian drug supply and prices.⁶⁷

On December 18, 2019, HHS Secretary Alex Azar announced an NPRM to authorize two-year state, tribal, or territorial government demonstration projects that fulfill the requirements of section 804 of the MMA.⁶⁸ Non-federal government entities that intend to sponsor one

65. COLIN BAKER, CONG. BUDGET OFFICE, WOULD PRESCRIPTION DRUG IMPORTATION REDUCE U.S. DRUG SPENDING? 3, 5 (2004), <https://www.cbo.gov/sites/default/files/108th-congress-2003-2004/reports/04-29-prescriptiondrugs.pdf> [<https://perma.cc/9GTN-NUFW>]; CONG. RESEARCH SERV., *supra* note 10, at 2–3; HHS TASK FORCE ON DRUG IMP., U.S. DEP'T OF HEALTH & HUMAN SERVS., REPORT ON PRESCRIPTION DRUG IMPORTATION 65 (2004), <http://www.safemedicines.org/wp-content/uploads/2018/03/HHS-Report1220.pdf> [<https://perma.cc/ESG8-4YZT>].

66. *See, e.g.*, S. Amendment 178 to S. Con. Res. 3, 115th Cong. (2017) (proposed amendment to allow parallel importation of drugs from Canada); Prescription Drug Affordability Act of 2015, S. 2023, 114th Cong. (2015) (bill that would, among other things, allow the HHS secretary to negotiate lower prices for drugs covered by Medicare Part D); Pharmaceutical Market Access and Drug Safety Act of 2009, S. 525, 111th Cong. (2009) (bill that would allow greater personal and commercial importation of prescription drugs); *see also* Michael Fralick, Jerry Avorn & Aaron S. Kesselheim, *The Price of Crossing the Border for Medications*, 377 NEW ENG. J. MED. 311, 312 (2017) (noting that legislative attempts to authorize broader importation of Canadian drugs have never gained traction at the state or federal level).

67. Allison Martell, *Exclusive: Canada Warns U.S. Against Drug Import Plans, Citing Shortage Concerns*, REUTERS (July 18, 2019), <https://www.reuters.com/article/us-canada-pharmaceuticals-exports-exclus/exclusive-canada-warns-us-against-drug-import-plans-citing-shortage-concerns-idUSKCN1UD2LN> [<https://perma.cc/29BE-Y4GJ>].

68. Importation of Prescription Drugs, 84 Fed. Reg. 70,796, 70,797 (proposed Dec. 23, 2019) (to be codified at 21 C.F.R. pts. 1, 251); U.S. Dep't of Health & Human Servs., *supra* note 3. The NPRM includes another pathway to allow manufacturers themselves to "import versions of FDA-approved drug products that they sell in foreign countries that are the same as the U.S. versions," but using a new National Drug Code (NDC) to allow those manufacturers to use those imported products as a means of voluntarily cutting their prices without breaching existing supply contracts.

of these projects may submit a project proposal for FDA approval. Among other requirements, those proposals must explain how the intended projects would pose no additional risk to public health and safety and would result in a significant reduction in prescription drug costs to U.S. consumers.⁶⁹ On July 24, 2020, President Trump issued an executive order instructing the HHS Secretary to complete this rulemaking process.⁷⁰ On September 24, 2020, the FDA issued the final rule establishing a pathway for states (or other identified parties) to set up their own time-limited program to import prescription drugs from Canada.⁷¹ The rule is scheduled to go into effect on November 24, after the U.S. presidential election.⁷²

The legal and practical obstacles are likely to prevent the final rule from succeeding in its current form. First, the rule requires the direct participation and cooperation of the manufacturer, which, in most cases, will not favor the importation of lower-cost versions of its prescription drug products.⁷³ Proposals must specify the pharmaceuticals intended for import, and the foreign seller (which must be both licensed by Health Canada as a wholesaler and pre-

U.S. FOOD & DRUG ADMIN., *Safe Importation Action Plan*, U.S. DEP'T OF HEALTH & HUM. SERVS. 1 (July 31, 2019), <https://www.hhs.gov/sites/default/files/safe-importation-action-plan.pdf> [<https://perma.cc/CV3A-YNPJ>].

69. U.S. FOOD & DRUG ADMIN., *supra* note 68, at 1.

70. Exec. Order 13938, 85 Fed. Reg. 45,757 (Jul. 24, 2020). The executive order also includes two other provisions that appear as if they facilitate importation, but in actuality these provisions largely restate existing statutory authorities. First, the executive order instructs the HHS secretary to exercise the discretion already provided in 21 U.S.C. § 384(j)(1) in enforcement activities against individuals importing prescription drugs for personal use, provided it “poses no additional risk to public safety.” The December 2019 NPRM indicated, however, FDA was not amenable to implementing the personal importation provisions in section 804(j) because of the risk that unscrupulous online Canadian pharmacies pose to public safety. 84 Fed. Reg. at 70,797–98. Second, the executive order also instructs the HHS secretary to permit re-importation of insulin upon a finding by the secretary that insulin is required for emergency medical care, an authority which the secretary already possessed since 1997 under 21 U.S.C. § 381(d).

71. Importation of Prescription Drugs, Final Rule (Sept. 24, 2020) (to be codified at 21 C.F.R. pts. 1, 251), <https://www.hhs.gov/sites/default/files/importation-final-rule.pdf> [<https://perma.cc/9LA8-HDCB>] (at the time of writing, the final rule has not yet been published in the Federal Register).

72. *Id.*

73. The HHS contends “multiple manufacturers have stated (either publicly or in statements to the Administration) that they wanted to offer lower-cost versions [of their drugs] but could not readily do so because they were locked into contracts with other parties in the supply chain.” U.S. FOOD & DRUG ADMIN., *supra* note 68, at 3. It is not clear why those supply chain contracts would not permit a manufacturer to offer low-cost medicines if imported from abroad or why this approach would be preferable to releasing an authorized, lower-cost generic version of the product as some generic companies have done. Lydia Ramsey Pflanzner, *The \$300 Generic Epipen Is Here*, BUS. INSIDER (Dec. 16, 2016), <https://www.businessinsider.com/mylan-launches-authorized-generic-epipen-for-300-2016-12> [<https://perma.cc/G9PC-FC6Q>].

registered with the FDA as a foreign seller) must purchase eligible prescription drugs *directly* from the manufacturer.⁷⁴

Second, the HHS secretary made the certification required for importation under section 804(l)(1) in conjunction with the issuance of the final rule, but that certification is conditional on the sponsor ensuring that the project will result in a significant reduction in the cost to the American consumer.⁷⁵ As the FDA itself concedes, it is unclear how a sponsor can establish prior to importation that the anticipated savings of importing will exceed the anticipated costs and that those savings will go directly to consumers, as is required by section 804 of the MMA.⁷⁶ This challenge is intensified by the complex importation requirements proposed in the rule, which would increase importation costs, and by the exclusion from eligibility of biologics and other more expensive drugs, which would lower the potential financial rewards of importation.⁷⁷

74. Importation of Prescription Drugs, 84 Fed. Reg. at 70,797–98.

75. The final rule “requires the . . . Sponsor’s importation plan to explain, in a manner sufficiently detailed to allow for a meaningful evaluation, how the Sponsor will ensure that the [project] will result in a significant reduction in the cost to the American consumer.” See Importation of Prescription Drugs, Final Rule #2020-199, at 69 (Sept. 24, 2020) (to be codified at 21 C.F.R. pts. 1, 251), <https://www.hhs.gov/sites/default/files/importation-final-rule.pdf> [<https://perma.cc/9LA8-HDCB>] (at the time of writing, the final rule has not yet been published in the Federal Register). In response to the NPRM, several commentators argued that section 804(l) requires a factual finding that cost savings would result from the project before certification can be made. See *id.* at 68; Rachel E. Sachs & Nicholas Bagley, *Importing Prescription Drugs from Canada — Legal and Practical Problems with the Trump Administration’s Proposal*, 382 NEW ENG. J. MED. 1777, 1778 (2020).

76. The FDA’s preliminary regulatory impact analysis of NPRM indicated it is an open question “as to whether this proposed rule could yield non-zero benefits.” See U.S. FOOD & DRUG ADMIN., PRELIMINARY REGULATORY IMPACT ANALYSIS, INITIAL REGULATORY FLEXIBILITY ANALYSIS & UNFUNDED MANDATES REFORM ACT ANALYSIS, DOCKET NO. FDA-2019-N-5711, 9 (2020).

77. See Importation of Prescription Drugs, Final Rule #2020-199. To be eligible for importation under the final rule the drug must be approved by Health Canada and, other than labeling, satisfy the requirements of an FDA-approved NDA or ANDA. The importer must submit a Pre-Import Request to the FDA at least thirty days prior to the scheduled date of entry; the request must include the importer’s plan for testing the imported drugs for authenticity, degradation, and compliance with established FDA specifications and standards. *Id.* at 138 (to be codified at 21 C.F.R. § 251.5). Before an imported drug can be sold in the United States, the FDA must review and find those testing results acceptable, and the product must meet FDCA labeling requirements and comply with the Drug Supply Chain Security Act requirements. *Id.* at 162–66 (to be codified at 21 C.F.R. §§ 251.16-17). Sponsors will need to comply with post-importation requirements, including providing the FDA with an accounting of the cost savings to American consumers. *Id.* at 167 (to be codified at 21 C.F.R. § 251.18). On September 25, the Centers of Medicare and Medicaid Services issued guidance that prescription drugs imported through this pathway would not be eligible for Medicare rebates programs, including its “best price” policy, further diminishing the potential cost savings. CENTERS FOR MEDICARE & MEDICAID SERVICES, CMS GUIDANCE TO THE STATES ON THE FDA FINAL REGULATION “IMPORTATION OF PRESCRIPTION DRUGS” RELATED TO SECTION 804 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT (FFDCA) AND THE MEDICAID DRUG REBATE PROGRAM (Sept. 25, 2020), <https://www.medicare.gov/prescription-drugs/downloads/state-rel-187.pdf> [<https://perma.cc/2449-8QMQL>].

Third, Health Canada will likely undertake measures to thwart implementation of the system proposed. Importation of already-marketed prescription drugs would reduce their availability to Canadian patients and give manufacturers an incentive to raise prices of importation-eligible drugs in Canada. In response to the issuance of the NPRM, the Government of Canada submitted a comment opposing the proposal, promising that “Canada will employ all necessary measures to safeguard its drug supply and preserve access for Canadians to needed prescription drugs.”⁷⁸

II. ROLE OF REPUTATION AND CONSOLIDATED AUTHORITY IN EQUIVALENCE DETERMINATIONS

Importation of prescription drugs, even foreign, unapproved versions of already FDA-approved drugs, inherently involves the question of whether the importing nations are willing to accept and rely on the equivalence of the standards, processes, and product-specific decisions of the exporting nations. The good news for those who favor U.S. prescription drug importation is that equivalence determinations are an established form of international regulatory engagement. The theory and practice of such arrangements may be drawn on to identify circumstances in which U.S. prescription drug importation is more likely to succeed.

Equivalence determinations are decisions to recognize and accept foreign regulation as equivalent to and as an adequate substitute for domestic regulation.⁷⁹ These equivalence determinations come in different forms.⁸⁰ Some determinations are formal, reciprocal, and memorialized in a binding agreement, such as an MRA.⁸¹ Others are

78. Gov’t of Can., Comment Letter on Proposed Rule on Importation of Prescription Drugs (Docket No. FDA-2019-N-5711) (Mar. 8, 2020), <https://beta.regulations.gov/comment/FDA-2019-N-5711-1208> [<https://perma.cc/FYP9-NKTR>].

79. Merill, *supra* note 18, at 754.

80. Some use the term “equivalence determination” only to refer to unilateral equivalent determinations, but we adopt the view, as others have, that MRAs are functionally formal, bilateral equivalence determinations. *See, e.g., id.* at 751–54 (laying out the various models that these agreements can follow); John C. Reitz, *Recognition of Foreign Administrative Acts*, 62 AM. J. COMP. L. 589, 595–96 (2014) (noting that an equivalency determination is essentially an informal form of an MRA); Richard B. Stewart, *U.S. Administrative Law: A Model for Global Administrative Law?*, 68 LAW & CONTEMP. PROBS. 63, 66 (2005) (“[P]ractice might often blur the distinction between adoption of [a] common standard[] by . . . government regulators and mutual recognition arrangements and equivalence practices by such regulators.”).

81. *See, e.g.,* Agreement on Mutual Recognition Between the European Community and the United States of America, 1999 O.J. (L 31) (an example of a formal mutual recognition agreement). The Association of Southeast Asian Nations (“ASEAN”) countries, which include Brunei Darussalam, Singapore, and Vietnam, established a Consultative Committee on Standards and Quality (ACCSQ) and adopted the 1998 ASEAN Framework Agreement on Mutual Recognition

informal and unilateral, and may take the form of one regulator exercising enforcement discretion to monitor less closely the imported goods and services overseen by another nation's regulatory bodies, which the importing nation's regulator has judged to be reliable.⁸² In some cases, the determination of equivalence involves a combination of these elements, with a regulator unilaterally making a formal determination to accept the certification of a foreign regulator as the functional equivalent to the inspection and certification of the domestic regulator.⁸³ Arrangements have also evolved from less formal unilateral equivalence determinations to reciprocal and more formal bilateral or plurilateral arrangements, such as an MRA.⁸⁴ An equivalence determination can encompass the substantive standards of a foreign regulator or be limited to accepting the determination of the foreign regulator or a third-party certifier that the imported good or service conforms to the importing nation's standards.⁸⁵

Accepting and relying on the standards and decisionmaking of a foreign counterpart is not an easy decision for a regulatory agency. As Daniel Carpenter argues, regulators like the FDA depend on the confidence of their constituents—their reputation—for their funding and authority.⁸⁶ In the United States and most other nations, pharmaceutical regulators operate as gatekeepers, exercising administrative discretion in granting premarket approval to new pharmaceutical products and seeking to prevent harm to consumers. Before approval, regulators must have confidence that the benefits of a candidate prescription drug exceed its risks and that quality of production is sufficient and reliable. Similarly, the constituents of that regulator—appropriators, consumers, product sponsors, and the

Arrangements in order to promote an ambitious agenda of regional cooperation on standards, technical regulations, and conformity assessment. In 1998, Australia and New Zealand entered into the Trans-Tasman Mutual Recognition Arrangement, which operates to facilitate trade in goods irrespective of differences in standards or other sale-related regulatory requirements. See Debra P. Steger, *Institutions for Regulatory Cooperation in 'New Generation' Economic and Trade Agreements*, 39 LEGAL ISSUES ECON. INTEGRATION 109, 115–16 (2012) (discussing the Trans-Tasman MRA).

82. Merrill, *supra* note 18, at 751–52.

83. Anabela Correia de Brito, Céline Kauffmann & Jacques Pelkmans, *The Contribution of Mutual Recognition to International Regulatory Co-operation* 16, 24 (Org. Econ. Co-operation & Dev. Regulatory Policy, Working Paper No. 2, 2016), https://www.oecd.org/regreform/WP2_Contribution-of-mutual-recognition-to-IRC.pdf [<https://perma.cc/7B3U-8U8J>].

84. See Tzung-bor Wei, *The Equivalence Approach to Securities Regulation*, 27 NW. J. INT'L L. & BUS. 255, 295 (2007) (“Equivalence no longer means unilateral action; instead, like mutual recognition, it is conditioned on reciprocity.”).

85. Correia de Brito et al., *supra* note 83, at 16, 24.

86. See Carpenter, *supra* note 16, at 401 (“The regulatory power of the FDA stems from its reputation for scientific expertise and consumer protection.”).

relevant medical and scientific communities—must have confidence in its regulatory oversight.

This dynamic is apparent in successful international equivalence determinations, as the factors that all such determinations share are that they gain and maintain the confidence of (a) the participating regulators and (b) those regulators' domestic constituents.

Making an *ex ante* determination that another regulator's decisionmaking or inspections will be equivalent and reliable requires a high degree of trust supported by intensive information-sharing concerning the foreign regulator's standards and procedures.⁸⁷ Especially on matters of public health and safety, reaching that level of confidence may not be possible with regard to nations with less stringent regulatory authorities and histories of corruption. Even among like-minded nations of similar economic development, regulatory differences are inevitable. Regulation starts out as the answer to a domestic problem, developed within a pre-existing, national regulatory framework. While the social preferences and attitudes toward risk may be similar in two countries, their governments may still devise different rules and enforce them differently because of each country's particular institutional structures and rulemaking procedures.⁸⁸ Monitoring another nation's adoption of equivalent laws and regulations is feasible, but ensuring the consistency of interpretation and enforcement is harder.⁸⁹

The second set of challenges involves gaining and maintaining the confidence of domestic constituents in international regulatory arrangements. Policy independence and regulatory sovereignty were among the reasons (along with anti-immigration sentiments) cited by those voting in favor of the United Kingdom's June 2016 referendum to exit the European Union ("EU").⁹⁰ Even outside such polarized political

87. Pierre-Hugues Verdier, *Mutual Recognition in International Finance*, 52 HARV. INT'L L.J. 55, 96 (2011).

88. DANIEL W. DREZNER, *ALL POLITICS IS GLOBAL: EXPLAINING INTERNATIONAL REGULATORY REGIMES* 48–50 (2007); *see, e.g.*, Bamberger & Guzman, *supra* note 12, at 1424–26 (noting that U.S. officials have argued against prescription drug imports using the example that Japanese law allows the export of expired medical products whereas the U.S. law does not).

89. *See* Linda R. Horton & Kathleen E. Hastings, *A Plan that Establishes a Framework for Achieving Mutual Recognition of Good Manufacturing Practices Inspections*, 53 FOOD & DRUG L.J. 527, 531 (1998) (stating that before the FDA accepts enforcement methods of foreign governments as equivalent, it needs assurance that such activities provide the same level of product quality, safety, and efficacy); Reitz, *supra* note 80, at 596–97 (noting that MRAs “require a very high level of confidence in the foreign regulators and their regulations and a significant educational effort during which the regulators from the participating countries learn about each other's methods and standards”).

90. *Dreaming of Sovereignty*, ECONOMIST (Mar. 19, 2016), <https://www.economist.com/britain/2016/03/19/dreaming-of-sovereignty> [<https://perma.cc/ATC4-NDGZJ>].

environments, constituents have had concerns regarding the transparency, accountability, and democratic legitimacy of international regulatory arrangements and networks.⁹¹ Determinations of equivalence and reliance arrangements may circumvent administrative law procedures, such as notice-and-comment rulemaking, that seek to ensure public participation in the process of promulgating administrative regulations.⁹²

These twin challenges in achieving confidence in international regulatory cooperation are particularly manifest in the pharmaceutical sector. Prescription drugs are among the most extensively regulated consumer products; in most countries, governments regulate testing, development, production, marketing, and liability, and, in some cases, even control distribution and prices.⁹³ Deviation from rigorous regulatory oversight can lead to unsafe products that cause harm or death. There is a higher expectation regarding medicines' safety than with most other consumer products; we consume them and give them to our children and elderly at times when their well-being is at risk. Regulators naturally also want to avoid the political outcry that would accompany harm caused by an unsafe drug that had been approved based on the decision or inspection of a foreign regulator.⁹⁴

Nonetheless, international equivalence determinations and reliance arrangements in the pharmaceutical sector have increasingly been used by nations in two particular contexts. First, pharmaceutical regulatory equivalence and reliance determinations are used in trade initiatives to reduce duplicative or unnecessarily divergent standards and conformity assessment procedures. Second, regulatory equivalence determinations have been deployed in the pharmaceutical sector out of necessity when regulatory agencies have been unable to fulfill their core institutional mandate without relying on the cooperative efforts of their

91. See Vivien A. Schmidt, *The Eurozone's Crisis of Democratic Legitimacy: Can the EU Rebuild Public Trust and Support for European Economic Integration?* 10 (European Comm'n Directorate-Gen. of Econ. & Fin. Affairs, European Econ. Discussion Paper No. 15, Sept. 2015), https://ec.europa.eu/info/sites/info/files/dp015_en.pdf [<https://perma.cc/6AUZ-F4PV>].

92. Democratic legitimacy and accountability of international regulatory arrangements have been the primary occupations of global administrative law, a subfield that has emerged to track the processes, procedures, and substantive outcomes of international regulatory regimes. See, e.g., Benedict Kingsbury, Nico Krisch & Richard B. Stewart, *The Emergence of Global Administrative Law*, 68 LAW & CONTEMP. PROBS. 15, 55 (2005) (noting that when transnational governance institutions take over national administrative functions, domestic law safeguards like notice-and-comment procedures may erode); Jason Marisam, *The Internationalization of Agency Actions*, 83 FORDHAM L. REV. 1909, 1912 (2015) (defining the focus of global administrative law as being the processes, procedures, and substantive outcomes of international regulatory regimes).

93. Kai P. Purnhagen, *The Challenge of Globalization in Pharmaceutical Law—Is an International Drug Approval System Modeled After the European System Worth Considering?*, 63 FOOD & DRUG L.J. 623, 624 (2008).

94. *Id.* at 628.

foreign counterparts. Equivalence determinations have been used more often in the former context than the latter, but the trade initiatives have also been more dependent on a supporting architecture to succeed and slower to win the confidence of regulators and domestic constituents.

A. *Equivalence Determinations in International Trade*

The use of equivalence determinations has increased in international trade in response to a shift in the global production of goods and services. In the 1960s, international companies began taking advantage of lower tariffs, the containerization of shipping, and better information and communication technologies to outsource parts of their manufacturing supply chains to lower-cost, specialist suppliers abroad.⁹⁵ In the 1990s and 2000s, the use of these global supply chains expanded to services and sectors ranging from food production to medical research and development to pharmaceutical manufacturing.⁹⁶ In these unbundled global supply chains, intermediate parts and services may crisscross national borders multiple times, dramatically increasing the volume of trade.⁹⁷ The unbundling of the production of goods and services into components and stages also reduces the barriers for lower-income countries with nascent regulatory systems to participate in the global production of goods and services and to compete in the world economy.

The rise of global supply chains has increased the importance of regulation in international trade. As the number of countries and transactions in supply chains has multiplied, so have the costs of excessive, duplicative, or unnecessarily divergent regulations.⁹⁸ For

95. See generally MARC LEVINSON, *THE BOX: HOW THE SHIPPING CONTAINER MADE THE WORLD SMALLER AND THE WORLD ECONOMY BIGGER* 5 (Princeton Univ. Press 2d ed. 2016) (discussing how containerization lowered shipping costs, made capital more mobile, and increased the integration of the global economy); Thomas J. Bollyky & Petros C. Mavroidis, *A Time for Action: WTO Must Change to Promote Regulatory Cooperation*, in *BEHIND-THE-BORDER POLICIES: ASSESSING AND ADDRESSING NON-TARIFF MEASURES* 320–21 (Joseph Francois & Bernard Hoekman eds., 2019); Richard Baldwin, *Trade and Industrialization after Globalization's Second Unbundling: How Building and Joining a Supply Chain Are Different and Why It Matters* 6 (Nat'l Bureau of Econ. Research, Working Paper No. 17716, 2011), <http://www.nber.org/papers/w17716> [<https://perma.cc/7CCZ-BMK9>] (“The ICT revolution made it feasible to spatially separate some stages of production without much loss in efficiency or timeliness.”).

96. See Gary Gereffi, *A Global Value Chain Perspective on Industrial Policy and Development in Emerging Markets*, 24 *DUKE J. COMP. & INT'L L.* 433, 439 (2014) (discussing how starting in the 1990s, suppliers in low- and middle-income countries upgraded their infrastructure and capabilities to be able to handle orders for more complex goods).

97. Thomas J. Bollyky, *Better Regulation for Freer Trade*, COUNCIL ON FOREIGN REL. 2 (June 19, 2012), https://cdn.cfr.org/sites/default/files/pdf/2012/06/Policy_Innovation_Memo22_Bollyky.pdf [<https://perma.cc/26QV-BCSB>].

98. *Id.*

regulators, the shift in global production has meant that their institutional mandates to advance public goods—such as stemming climate change, containing financial crises, or reducing pollution—and achieve other regulatory objectives can no longer be met without international coordination with their regulatory counterparts.⁹⁹ In many sectors, sustaining regulatory oversight in one country depends on the ability to rely on the adequacy and consistency of regulatory oversight in other countries.¹⁰⁰

The creation of the World Trade Organization (“WTO”) in 1994 established new agreements that promote the acceptance of international standards, transparency, and equivalence determinations in regulations for industrial and agricultural products¹⁰¹ as well as measures that protect human and animal health and the environment from pests and diseases.¹⁰² With the advent of the WTO, equivalence

99. See Thomas J. Bollyky & Petros C. Mavroidis, *Trade, Social Preferences and Regulatory Cooperation: The New WTO-Think*, 20 J. INT’L ECON. L. 1, 12 (2017) (noting that regulatory cooperation not only enhances trade but can also help achieve regulatory goals more efficiently); Alan O. Sykes, *The (Limited) Role of Regulatory Harmonization in International Goods and Service Markets*, 2 J. INT’L ECON. L. 49, 70 (1999) (“[W]hen matters of domestic regulation implicate important crossborder spillovers (chlorofluorocarbons and the ozone layer, for example), it is undeniable that international co-operation is desirable to address the problem.”).

100. See Thomas J. Bollyky, *Regulatory Coherence in the TPP Talks*, in THE TRANS-PACIFIC PARTNERSHIP: A QUEST FOR A TWENTY-FIRST CENTURY TRADE AGREEMENT 171 (Chin Leng Lim, Deborah Elms & Patrick Low eds., 2012) (noting that stronger cooperation and inter-governmental coordination is necessary to oversee increasingly complex production chains); Thomas J. Bollyky, *A Role for the World Trade Organization on Regulatory Coherence*, E15 INITIATIVE 3 (2015), <https://e15initiative.org/wp-content/uploads/2015/09/E15-Regulatory-Coherence-Bollyky-Final.pdf> [<https://perma.cc/W4EY-UADR>] (noting that with food, drugs, and consumer goods, success depends on the consistency, adequacy, and predictability of regulatory oversight across national boundaries).

101. The Agreement on Technical Barriers to Trade (“TBT”) establishes rules and procedures regarding the development, adoption, and application of standards and regulations for industrial and agricultural products and the procedures (such as testing or certification) used to determine whether a particular product meets those standards or regulation. The TBT is likely to cover most pharmaceutical regulation. The TBT Agreement recommends performance- over process-based measures because there may be gains from having different approaches to meet regulatory objectives. The TBT Agreement includes a mix of legally binding obligations (like obligations to notify and explain national regulations) and a best efforts requirement to pursue mutual recognition, equivalency, and harmonization initiatives with other WTO members. See Agreement on Technical Barriers to Trade art. 2.1-2.2, 2.5-2.8, Apr. 15, 1994, 1868 U.N.T.S. 120.

102. The WTO Agreement on Sanitary and Phyto-sanitary (“SPS”) covers measures protecting human and animal health and the environment from pests and diseases. It was included in the WTO, in part, to guard against the EU reintroducing its common agricultural policy through regulation. PETROS C. MAVROIDIS, THE REGULATION OF INTERNATIONAL TRADE: THE WTO AGREEMENTS ON TRADE IN GOODS 455 (2016). It goes further than the TBT Agreement in requiring that “Members shall accept the sanitary or phytosanitary measures of other Members as equivalent, even if these measures differ from their own . . . , if the exporting Member objectively demonstrates . . . that its measures achieve the importing Member’s appropriate level of . . . protection.” The SPS Agreement also requires WTO members to adopt science-based measures and be consistent in formulating their policies. Agreement on the Application of Sanitary and Phytosanitary Measures art. 2.2-2.3, 4.1, Apr. 15, 1994, 1867 U.N.T.S. 493.

determinations and reliance arrangements began to emerge in wide-ranging areas such as competition, telecommunication and electrical goods, environmental issues, finance, and pharmaceuticals.¹⁰³ Many such arrangements are connected to trade agreements or driven by economic blocs, such as the Asia-Pacific Economic Cooperation (“APEC”).¹⁰⁴ Some agreements go further to establish more robust institutional mechanisms to foster regulatory cooperation, harmonization, and mutual recognition of regulations, standards, and conformity assessment procedures.¹⁰⁵

There is strong evidence of the economic benefits of these equivalence determinations and reliance arrangements. According to a 2011 WTO assessment, for example, those preferential trade agreements that commit to “deep” integration on reducing technical barriers to trade have lasting and substantial benefits for global supply chains, increasing trade between participating countries by almost 8%.¹⁰⁶ As a result, multinational companies and their business associations have pressed for deeper international regulatory cooperation arrangements in trade agreements to increase the interoperability and efficiency of their suppliers and subsidiaries.¹⁰⁷

There is less evidence that the current trade-driven approaches to equivalence determinations in international trade initiatives have won the confidence of regulators and consumers. Most of the equivalence determinations in trade agreements focus on reducing duplicative conformity assessments and testing.¹⁰⁸ These changes, however, have not inspired much reliance from regulators in the processes and substantive decisionmaking of their counterparts.¹⁰⁹ For

103. See Silja Baller, *Trade Effects of Regional Standards Liberalization: A Heterogenous Firms Approach* 34–35 (World Bank Policy Research, Working Paper No. 4124, February 2007), <https://openknowledge.worldbank.org/bitstream/handle/10986/7156/WP04124.pdf> [<https://perma.cc/4Z8N-UTUN>] (listing various categories of products covered by Mutual Recognition Agreements between MRA partner jurisdictions).

104. Bollyky, *supra* note 100, at 177–78; WORLD TRADE ORG., WORLD TRADE REPORT 2011, at 53, 190 (2011), https://www.wto.org/english/res_e/booksp_e/anrep_e/world_trade_report11_e.pdf [<https://perma.cc/X9VM-63QT>].

105. Steger, *supra* note 81, at 109. See generally Richard Baldwin, Simon Evenett & Patrick Low, *Beyond Tariffs: Multilateralizing Non-Tariff RTA Commitments*, in MULTILATERALIZING REGIONALISM: CHALLENGES FOR THE GLOBAL TRADING SYSTEM 79 (Richard Baldwin & Patrick Low eds., 2009) (discussing TBT provisions in PTAs that might be multilateralized at the WTO level).

106. WORLD TRADE ORG., *supra* note 104, at 44, 146; see also Correia de Brito et al., *supra* note 83, at 42–45 (examining the presence of equivalence and mutual recognition provisions in regional trade agreements).

107. Paul Mertenskötter & Richard B. Stewart, *Remote Control: Treaty Requirements for Regulatory Procedures*, 104 CORNELL L. REV. 165, 169–70 (2018).

108. See Correia de Brito et al., *supra* note 83, at 26.

109. See Elizabeth Golberg, *Regulatory Cooperation – A Reality Check* 31 (Harvard Mossavar-Rahmani Ctr. for Bus. & Gov’t Assoc. Working Paper No. 115, 2019), <https://www.hks.harvard.edu/>

example, there are fourteen MRAs involving pharmaceuticals.¹¹⁰ Most of these MRAs are limited to the inspection of good manufacturing or laboratory practices, and some are arrangements in which the exporting state certifies that the inspection met the standard of the importing state, rather than a determination that the participating states' inspection standards and processes are equivalent.¹¹¹ Additionally, the deepening regulatory arrangements proposed in negotiations of the (now) eleven-nation Comprehensive Trans-Pacific Partnership and the stalled Transatlantic Trade and Investment Partnership were condemned by some civil society and consumer groups as undemocratic, unrelated to trade, and likely to spur a regulatory race to the bottom.¹¹²

It is possible that these trade-related equivalence determinations may be advancing regulatory objectives as well as producing economic returns, but few empirical assessments have sought to determine whether that has indeed been the case.¹¹³ Most existing MRAs, pharmaceutical or otherwise, have had little, if anything, to do with managing global risks.¹¹⁴ That said, there is anecdotal evidence that the intense exchange of information required to conclude an equivalence determination has helped regulators identify shortcomings and inefficiencies in their systems and improve interoperability between national systems.¹¹⁵ More evidence of the work-sharing benefits of equivalence arrangements on inspections may

sites/default/files/centers/mrcbg/img/115_final.pdf [https://perma.cc/3A8T-TVZR] (listing the fact that regulators have little trust in their counterparts as one of the major limits on formal regulatory cooperation).

110. COMM. ON MUT. RECOGNITION AGREEMENTS & RELIANCE IN THE REGULATION OF MEDS., NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 14, at 6.

111. Correia de Brito et al., *supra* note 83, at 53 (citing the EU-Israel MRA as an example of one of the few pharmaceutical MRAs).

112. KENNETH HAAR, LORA VERHEECKE & MAX BANK, DANGEROUS REGULATORY DUET: HOW TRANSATLANTIC REGULATORY COOPERATION UNDER TTIP WILL ALLOW BUREAUCRATS AND BIG BUSINESS TO ATTACK THE PUBLIC INTEREST 5–6 (2016), https://corporateeurope.org/sites/default/files/attachments/regulatoryduet_en021.pdf [https://perma.cc/Q5NE-6Q69]; Jane Kelsey, Preliminary Analysis of the Draft TPP Chapter on Domestic Coherence 1 (Oct. 23, 2011) (unpublished memorandum), http://www.citizenstrade.org/ctc/wp-content/uploads/2011/10/TransPacific_RegCoherenceMemo.pdf [https://perma.cc/JL9F-P3L8].

113. *See* Correia de Brito et al., *supra* note 83, at 49–52 (surveying multiple studies that address the economic and trade impacts of MRAs but do not discuss the impact on regulatory objectives).

114. *Id.* at 53.

115. *See id.* at 54 (citing the process of concluding the pharmaceutical component of the US-EU MRA).

emerge as regulators gain confidence in those arrangements and put their newly redundant inspection resources to other uses.¹¹⁶

One example suggests that trade-driven equivalence arrangements on pharmaceuticals can succeed, but they may require time and supportive infrastructure to win over regulators and consumers. The EC pioneered the use of equivalence determinations, such as mutual recognition, when it became clear that, at the then-current pace, the process of harmonizing national laws and regulatory standards to create a common market would take decades.¹¹⁷ Equivalence determinations preserve national institutions and processes, provided an equivalent result may be reached. Some commentators credit equivalence determinations, such as mutual recognition, as being “one of the engines [that] knit[] together Europe.”¹¹⁸

The pharmaceutical sector was an early target for these efforts. The significant differences and disparities in national drug approval processes and timelines in the then-EU member states undermined the EC effort to unite the original twelve nations into potentially the world’s largest pharmaceutical market.¹¹⁹

The EC began working on a mutual recognition process for pharmaceutical registration in 1975 when it established a multistate,

116. Examples of MRAs include the Trans-Tasman Mutual Recognition Agreement, which produced an agreement to cooperate on developing food standards before national adoption. See Trans-Tasman Mutual Recognition Act 1997, No. 190 (Austl.), <https://www.legislation.gov.au/Details/C2019C00116> [<https://perma.cc/DT8B-PWMC>]. Examples of regional trade agreements include the Comprehensive Economic and Trade Agreement (CETA), a deal between Canada and the EU with extensive provisions on product standards, mutual recognition, and regulatory cooperation. See 2017 O.J. (L 11) 3–8 (Joint Interpretative Instrument on the Comprehensive Economic and Trade Agreement (CETA) between Canada and the European Union and its Member States) <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:L:2017:011:FULL&from=en> [<https://perma.cc/VK3E-UUWH>].

117. Verdier, *supra* note 87, at 64.

118. David Zaring, *Free Trade through Regulation?*, 89 S. CALIF. L. REV. 863, 869 (2016); see also Xinyuan Dai, *Why Comply? The Domestic Constituency Mechanism*, 59 INT’L ORG. 363, 364 (2005) (contending that domestic constituents can exercise leverage to influence the government’s international compliance decisions); Andrew Moravcsik, *Taking Preferences Seriously: A Liberal Theory of International Politics*, 51 INT’L ORG. 513, 516, 519 (1997) (elaborating on the notion that societal ideas, interests, and institutions influence state behavior in international politics by shaping state preferences); Robert D. Putnam, *Diplomacy and Domestic Politics: The Logic of Two-Level Games*, 42 INT’L ORG. 427, 434 (1988) (asserting that international negotiations are a two-level game with domestic groups pursuing their interests at the national level and national governments doing the same at the international level); Joel P. Trachtman, *International Law and Domestic Political Coalitions: The Grand Theory of Compliance with International Law*, 11 CHI. J. INT’L L. 127, 128 (2010) (arguing that international legal commitments create coalitions between those who will benefit from their state’s compliance and those who will benefit from other states’ compliance).

119. David Vogel, *The Globalization of Pharmaceutical Regulation*, 11 GOVERNANCE 1, 1–2 (1998).

or “decentralized,” procedure for drug approval. Under this process, a manufacturer would first submit its product to any national pharmaceutical regulatory agency, which would assess that application and share its decision and report a summary of product characteristics, and the approved labeling and package leaflet with other concerned EU member states. Those other member states could accept that decision, but final approval still resided with each member state and its national regulatory body. For years, the decentralized procedure had little impact on national drug approval policies, and, by 1987, only half of the marketing approvals that were issued by one member state were adopted by other member states.¹²⁰ With more time and a supportive EC infrastructure, including the Maastricht Treaty and the EMA, the performance of the decentralized procedure has slowly improved. This procedure is now the pathway through which most generic drugs are approved in the EU.¹²¹

B. Regulatory Insufficiency as a Driver of International Regulatory Cooperation

Regulatory authorities have also turned to equivalence determinations and reliance arrangements to overcome their resource limitations and to tackle cross-border externalities (e.g., climate change) that cannot be addressed by a single regulator in isolation. In these situations, necessity drives regulators to engage in equivalence determinations and reliance arrangements with counterparts in order to fulfill their institutional mandate. These regulator-driven arrangements have tended to come together more quickly than those arising from trade circumstances and have involved more substantive regulatory reliance.

For example, in 2011, COFEPRIS, Mexico’s drug regulatory agency, faced a backlog of eight thousand drug applications, mostly for generic drugs. This backlog prompted broad reforms, including establishing a mechanism for reciprocal drug approval.¹²² Under this approval procedure, the manufacturer of a drug (i.e., the product sponsor) may submit to COFEPRIS three documents from the

120. *See id.* at 3–5.

121. Sean Milmo, *Europe Strives for a More Efficient Generic-Drug Approval Framework*, 39 PHARMACEUTICAL TECH. 20, 20 (2015); Shweta Handoo, Vandana Arora, Deepak Khera, Prafulla Kumar Nandi & Susanta Kumar Sahu, *A Comprehensive Study on Regulatory Requirements for Development and Filing of Generics Globally*, 2 INT’L J. PHARMACEUTICAL INVESTIGATION 99, 99–101 (2012).

122. *Mexico Healthcare: Mexico’s Wave of Generics*, ECONOMIST: INTELLIGENCE UNIT (Oct. 21, 2014), <http://www.eiu.com/industry/article/1652410149/mexicos-wave-of-generics/2014-10-21> [<https://perma.cc/47DX-RH47>].

appropriate health authority in the country of product origin: a free sale certificate, proof of drug approval, and written evidence that the drug is being produced in compliance with good manufacturing standards.¹²³ On that basis, COFEPRIS may grant a reciprocal approval for the use of that drug in Mexico. Any new indications, dosages, or combinations of that drug may be approved through the same abbreviated approval procedure. Mexico also relaxed and simplified its import restrictions and cut its generic drug approval timelines from 360 to 60 days. In 2015, COFEPRIS estimated that, since adopting the policy, it has reduced by 90% its regulatory approval costs, increased its number of approved generic drugs, lowered pharmacy costs, and increased the share of generics in the country's market.¹²⁴ In 2012, the World Health Organization ("WHO") recognized COFEPRIS as a reference regulatory agency for other Latin American countries.¹²⁵

Another example of a regulator-driven arrangement is the EU centralized procedure, which provides a single application, single evaluation, and single marketing approval process for prescription drugs, allowing direct access to all EU national markets.¹²⁶ The principal motivation for establishing the centralized procedure was not regulatory harmonization, but rather the pooling of regional regulatory expertise on a difficult regulatory problem. In 1987, the national regulatory authorities in EU member states lacked expertise in the novel techniques needed to assess biotechnology medicines on the path to market.¹²⁷ The centralized procedure enabled these regulators to work together on biotechnology product registration applications to achieve a common decision.¹²⁸ The centralized procedure did not require

123. Hector E. Chagoya, Juan Carolos Amaro & Nuria Becerril, *Mexico – The Drug Approval Process*, in INTERNATIONAL PHARMACEUTICAL LAW AND PRACTICE § 13.04 (2012).

124. Thomas J. Bollyky & Aaron S. Kesselheim, *Can Drug Importation Address High Generic Drug Prices?* 14 (Hutchins Ctr. on Fiscal & Health Policy at Brookings, Working Paper No. 29, 2017), https://www.brookings.edu/wp-content/uploads/2017/05/wp29_bollykykesselheim_drugimportation.pdf [<https://perma.cc/H3KJ-6PXJ>].

125. PAN AM. HEALTH ORG., *PAHO Recognizes COFEPRIS As a National Regulatory Authority of Regional Reference*, WORLD HEALTH ORG. (July 2, 2012), <https://www.paho.org/en/news/2-7-2012-paho-recognizes-cofepris-national-regulatory-authority-regional-reference> [<https://perma.cc/W5YL-56SZ>].

126. Council Regulation (EEC) 2309/93 of July 22, 1993, Laying Down Community Procedures for the Authorization and Supervision of Medicinal Products for Human and Veterinary Use and Establishing a European Agency for the Evaluation of Medicinal Products, 1993 O.J. (L 214) 1.

127. HEALTH, EDUC., & HUMAN SERVS. DIV., U.S. GEN. ACCOUNTING OFFICE, EUROPEAN UNION DRUG APPROVAL: OVERVIEW OF NEW EUROPEAN MEDICINES EVALUATION AGENCY AND APPROVAL PROCESS 3–4 (1996), <https://www.gao.gov/assets/230/222342.pdf> [<https://perma.cc/QX98-QEMR>].

128. A forerunner to the centralized procedure was the "concertation procedure," launched by the EC in 1987, which required member nations to consult an EU-level committee "prior to any national decision relating to a high-technology medicinal product, with a view to arriving at uniform decisions throughout the Community." Council Directive (EEC) 87/22 of Dec. 22, 1986, on

the dissolution of participating national regulatory authorities, which was a sensitive issue of national sovereignty.¹²⁹ Member states agreed, however, to use common application documents.

The centralized procedure evolved relatively quickly. While the decentralized procedure took decades to establish, the EC created the centralized procedure in 1987 and formalized it six years later. It was the first EU-wide drug regulatory procedure in which no member state had issued an approval of a product before the procedure started.¹³⁰ The centralized procedure was initially mandatory for a small, defined list of biotechnology and high-technology products and optional for all non-biotechnological drugs considered potentially innovative. Over the years, this mandatory list has been expanded to include medicines for HIV/AIDS, cancer, diabetes, and neurodegenerative diseases; all designated orphan medicines; and certain veterinary medicines.

Within its first year of formal operation, two-thirds of the applications to the centralized procedure were submitted voluntarily (i.e., they did not involve biologic drugs that were required to use the pathway).¹³¹ The procedure effectively integrated the drug approval process for newer therapies that might have otherwise proved controversial across EU markets.¹³² The U.S. Government Accountability Office (“GAO”) estimates that the centralized procedure saved an estimated 40% of the cost and, more importantly, greatly reduced approval times for obtaining separate marketing authorizations in, at that time, fifteen EU member states.¹³³

III. THE FDA AND THE POLITICAL ECONOMY OF FOREIGN EQUIVALENCE DETERMINATIONS

The FDA has not fit neatly into either of the contexts—trade initiatives or a collaboration among under-resourced regulators—in

the Approximation of National Measures Relating to the Placing on the Market of High-Technology Medicinal Products, Particularly Those Derived from Biotechnology, 1986 O.J. (L 15) 38.

129. Alar Irs, Truus Janse de Hoog & Lembit Rägo, *Development of Marketing Authorization Procedures for Pharmaceuticals*, in *EVALUATING PHARMACEUTICALS FOR HEALTH POLICY AND REIMBURSEMENT* 5 (Nick Freemantle & Susan Hill eds., 2004) (noting that in its initial form, normal national regulatory reviews occurred after the committee review).

130. *Id.* at 6–7.

131. HEALTH, EDUC., & HUMAN SERVS. DIV., U.S. GEN. ACCOUNTING OFFICE, *supra* note 127, at 12.

132. *Id.* at 2–5.

133. *See id.* at 10 (“Pharmaceutical industry officials acknowledge that filing NDAs under the centralized procedure will allow a company to market its product(s) in all Member States within a relatively short period of time at approximately 60 percent of the cost of obtaining 15 individual marketing authorizations.”).

which equivalence determinations have succeeded. The institutional features of the FDA have made it difficult to establish workable arrangements that recognize and rely on the equivalence of foreign regulatory oversight. Despite congressional efforts to prod the FDA to pursue such arrangements, the FDA has made far fewer determinations of foreign regulatory equivalence than its counterpart regulators in other nations or U.S. regulators like the USDA.

In this Part, we identify the reasons why the FDA has been more reluctant than its counterparts to engage in foreign equivalence determinations, including its consolidated authority over drug safety, quality, and efficacy and its self-perception as the gold standard of pharmaceutical regulation internationally. These institutional preferences are reflected in the refusal of the FDA to subordinate its core mandate to other U.S. foreign policy objectives and in the FDA's approach to international agreements generally. The recent implementation of the United States' only pharmaceutical MRA, after a twenty-year delay, suggests a potential path forward to increasing the FDA's use of foreign equivalence determinations, including future U.S. prescription drug importation efforts.

A. The FDA Has Consolidated Authority on Matters Concerning Drug Safety, Quality, and Efficacy

The FDCA provides the FDA with the sole authority among U.S. federal agencies for evaluating the safety, quality, and efficacy of medicines.¹³⁴ FDA officials have historically developed U.S. procedures and standards in relative isolation from their foreign counterparts.¹³⁵

134. Until relatively recently, the Department of Homeland Security, via the U.S. Customs and Border Protection agency, was responsible for examining imported prescription drugs at the nation's international mail centers and borders and for detaining and destroying any FDA-regulated prescription drugs that did not meet statutory or regulatory requirements. The FDA has since assumed the primary responsibility for determining whether drug imports may legally enter the country. The FDA has secured authority to adjudicate the legality over drugs imports and exports and determinations of compliance under the Radiation Control for Health and Safety Act through interagency arrangements. Bijal Shah, *Interagency Transfers of Adjudication Authority*, 34 YALE J. REG. 279, 295 (2017). CONG. RESEARCH SERV., supra note 10, at 3–4:

[T]he Drug Enforcement Agency (DEA) administers the Controlled Substances Act, which is a federal statute that establishes criminal and civil sanctions for the unlawful possession, manufacturing, or distribution of certain addictive or dangerous substances, including certain prescription drugs that share these properties, such as narcotics and opiates. . . . Although many states also have their own laws that regulate drug safety, the FDA maintains primary responsibility for the premarket approval of prescription drug.

135. Gregory Shaffer, *Reconciling Trade and Regulatory Goals: The Prospects and Limits of New Approaches to Transatlantic Governance Through Mutual Recognition and Safe Harbor Agreements*, 9 COLUM. J. EUR. L. 29, 55 (2002).

The FDA participates in international pharmaceutical initiatives but is not part of a regional, political, and economic union like the EU, nor is it in a pairing of like-minded countries accustomed to cooperating on regulatory and trade initiatives, such as Australia and New Zealand.¹³⁶

Given its consolidated authority, the FDA's limited use of equivalence determinations is unsurprising. A regulator in a consolidated system enjoys wide policymaking discretion and authority at the domestic level and is less likely to engage in cross-border coordination and cooperation.¹³⁷ As Daniel Carpenter notes, autonomy is a "proximate goal" for regulators because whether they are motivated by the public benefit, personal gain, or legitimacy and reputation, autonomy is "necessary to achieve it."¹³⁸ By contrast, a regulator with constrained discretion will be more willing to bind itself to an international accord.¹³⁹

B. The FDA Considers Itself the Gold Standard of Pharmaceutical Regulation

FDA officials generally consider their pharmaceutical regulatory practices as setting the bar internationally because that has been the reality for most of the organization's history.¹⁴⁰ Long before most of its foreign peers, the FDA was an established agency with consolidated authority over pharmaceutical regulation, a standardized NDA process, an efficacy standard, and a premarket notification process. When the thalidomide scandal broke in Europe in the late 1950s, there were thousands of terrible episodes of birth defects, impairment, and deaths in newborns. The FDA, which had not approved thalidomide, was widely perceived domestically and internationally as having gotten it right.¹⁴¹ Many of the regulatory agencies that exist today in Europe and

136. *Id.* at 77.

137. *See, e.g.*, Hemel, *supra* note 13, at 228 ("Cross-border coordination will be less attractive to a regulator in a consolidated system who enjoys wide policymaking discretion at the domestic level.").

138. DANIEL P. CARPENTER, *THE FORGING OF BUREAUCRATIC AUTONOMY: REPUTATIONS, NETWORKS, AND POLICY INNOVATION IN EXECUTIVE AGENCIES, 1862-1928*, at 374-75 n.16 (2001); *see also* DANIEL P. CARPENTER, *REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 75* (2010) [hereinafter CARPENTER, *REPUTATION AND POWER*] (arguing in favor of reputation as a better explanation for what motivates regulators over the public interest and regulatory capture theories); Enrico Colombatto & Jonathan R. Macey, *A Public Choice Model of International Economic Cooperation and the Decline of the Nation State*, 18 *CARDOZO L. REV.* 925, 929 (1996) (observing that self-interested regulators prize autonomy as a means to "maximize the rough value of their bureaucracies").

139. Hemel, *supra* note 13, at 228.

140. CARPENTER, *REPUTATION AND POWER*, *supra* note 138, at 43.

141. The outcome was largely thanks to the vigilance of a single reviewer at the FDA, Frances Kelsey, who resisted approving the drug despite pressure from the manufacturer and her superiors

other high-income nations were created after the thalidomide crisis. In the first decades that followed that crisis, many of these newer agencies and the WHO drew from the FDA in formulating their pharmaceutical regulatory standards, processes, and procedures.¹⁴²

FDA officials have conceded that this mindset—the self-perception that the FDA is the “gold standard” for drug review¹⁴³ and able to fulfill its core institution mandates without the cooperation of foreign counterparts—“may not ultimately impede FDA’s willingness to enter into agreements of the mutual assistance variety, but . . . surely will be an impediment to efforts to achieve agreement on substantive standards.”¹⁴⁴ Another acknowledged component of FDA culture is the widespread sense among the staff of being overextended and under-resourced. Yet, there has been little indication, until recently, that the FDA views international collaboration as the means of reducing its workload, instead seeing it as one more burden.¹⁴⁵

It makes little difference for the present inquiry whether the FDA still deserves to be considered the gold standard for pharmaceutical regulation. At a time when only 17% of Americans report trusting the U.S. federal government all or most of the time, confidence in the FDA among the U.S. population remains relatively high, although it too has declined in recent years.¹⁴⁶ By virtue of the stable legitimacy that the FDA enjoys among the public and medical community, the agency has been able to resist the international regulatory engagements that Congress and some organized industry interests would have it pursue.

at the agency. Jeffrey Avorn, *Learning about the Safety of Drugs — A Half-Century of Evolution*, 365 NEW ENG. J. MED. 2151, 2152–53 (2011).

142. CARPENTER, REPUTATION AND POWER, *supra* note 138, at 43.

143. Kessler, *supra* note 18, at 214; Merrill, *supra* note 18, at 742–43.

144. Merrill, *supra* note 18, at 743.

145. *Id.* at 744. FDA statements have suggested that the institutional lack of interest in international cooperation also extends to food. Criticized by the GAO for its lack of reliance on foreign agency inspections, the FDA maintains that few countries seek comparability with the United States because, in part, most countries will not meet the FDA requirement that a foreign government’s domestic and export food safety systems be comparable to the U.S. system for food products under the FDA’s jurisdiction. U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-12-933, *supra* note 14, at 1–2.

146. CARPENTER, REPUTATION AND POWER, *supra* note 138, at 35 & n.16; Sarah D. Kowitz, Allison M. Schmidt, Anika Hannan & Adam O. Goldstein, *Awareness and Trust of the FDA and CDC: Results from a National Sample of US Adults and Adolescents*, 12 PLOS ONE, May 16, 2017, at 15; PEW RESEARCH CTR., BEYOND DISTRUST: HOW AMERICANS VIEW THEIR GOVERNMENT 60 (2015), <https://www.pewresearch.org/politics/2015/11/23/beyond-distrust-how-americans-view-their-government/> [<https://perma.cc/B3UD-DS4P>] (open “Complete Report PDF” at top right, and view page 60); *Public Trust in Government: 1958-2019*, PEW RES. CTR. (Apr. 11, 2019), <https://www.people-press.org/2019/04/11/public-trust-in-government-1958-2019/> [<https://perma.cc/LEB5-BRXH>].

C. The FDA Has Resisted Subordinating Its Core Institutional Mandate to Other U.S. Policy Objectives

The FDA and EC's regulatory contexts differ in many respects, including on trade. The EC Directorate General for Enterprise and Industry has the dual mission of advancing free trade in the internal market and with other nations, while ensuring public safety through high pharmaceutical product and process standards. That twofold mission has made it easier for the EMA and national pharmaceutical regulators in the EU to pursue their public health and institutional interests within trade negotiations.¹⁴⁷

In contrast to the European model, the FDA's primary mission is to protect U.S. public health, and it is not part of the U.S. government agencies that promote international trade and commerce.¹⁴⁸ The FDA Modernization Act of 1997 established an Office of International Relations and directs the FDA to "encourage" MRAs and to "support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in efforts to move toward the acceptance of mutual recognition agreements relating to the regulation of drugs, biological products, [and] devices."¹⁴⁹ Despite that legislation, the FDA has resisted subsequent initiatives that might subordinate its gatekeeper mission on pharmaceuticals to other U.S. policy objectives, such as facilitating trade, building foreign alliances, and lowering pharmaceutical pricing.¹⁵⁰

In 1998, the FDA released a compliance guide on international memoranda of understanding ("MOU"), which summarizes the agency's institutional preferences on international matters.¹⁵¹ The FDA treats these MOUs as "similar to mutual recognition agreements . . . , referred

147. Shaffer, *supra* note 135, at 39–40.

148. 21 U.S.C. § 393 (2012).

149. *Id.* § 383(b), (c). Likewise, 19 U.S.C. § 2541 provides:

The Trade Representative has responsibility for coordinating United States discussions and negotiations with foreign countries for the purpose of establishing mutual agreements with respect to standards-related activities. In carrying out this responsibility, the Trade Representative shall inform and consult with any Federal agency having expertise in the matters under discussion and negotiation.

Trade Agreements Act of 1979, 19 U.S.C. § 2541 (2012), *amended by* Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (1994).

150. The United States is also the only one of these nations that does not provide universal health care or, in most parts of the U.S. health system, negotiate or restrain pharmaceutical prices. CARPENTER, REPUTATION AND POWER, *supra* note 138, at 714.

151. U.S. FOOD & DRUG ADMIN., COMPLIANCE POLICY GUIDE SEC. 100.900 INTERNATIONAL MEMORANDA OF UNDERSTANDING (1995), <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-100900-international-memoranda-understanding> [<https://perma.cc/47GD-NXPQ>].

to in recent trade agreements,” and would include “equivalence agreements . . . [and] mutual assessment of the comparability of a foreign regulatory system.”¹⁵² In that guide, the FDA indicates that it will enter into agreements designed to meet the following goals:

1. to enhance the FDA’s ability to ensure that regulated products are safe, effective, of good quality, and properly labeled;
2. to allow the FDA to use its resources more effectively or efficiently, without compromising its ability to carry out its responsibilities; and
3. to improve communications between the FDA and foreign officials concerning FDA-regulated products.¹⁵³

While the guidance notes that the FDA will endeavor to remain aware of broader U.S. foreign policy objectives and international policies, it also emphasizes that the international activities of the FDA will place a higher priority on “improving the quality, safety, or efficacy of products offered to consumers in the United States.”¹⁵⁴ The FDA will “give a low priority to investing resources in developing a memorandum of understanding with a foreign country that covers a product where there is little likelihood of significant exports to the United States or significant risk to the public.”¹⁵⁵ The FDA has entered into product-specific MOUs, such as on the import of cantaloupe from Mexico,¹⁵⁶ as well as broader MOUs, such as on the accreditation of U.S. food exporters to China.¹⁵⁷

D. FDA Institutional Preferences Are Reflected in Its International Arrangements

The FDA also has nearly 120 confidentiality agreements with approximately thirty foreign governments and nongovernmental organizations.¹⁵⁸ These nonbinding executive agreements are distinct

152. *Id.*

153. *Id.*

154. *Id.*

155. *Id.*

156. U.S. FOOD & DRUG ADMIN., FDA - SENASICA MEXICO, MEMORANDUM OF UNDERSTANDING CONCERNING THE ENTRY OF MEXICAN CANTALOUPE INTO THE U.S. (2018), <https://www.fda.gov/international-programs/cooperative-arrangements/fda-senasica-mexico-mou-concerning-entry-mexican-cantaloupe-us> [<https://perma.cc/9BQF-D3A6>].

157. U.S. FOOD & DRUG ADMIN., MEMORANDUM OF UNDERSTANDING BETWEEN FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES OF THE UNITED STATES OF AMERICA, AND CERTIFICATION AND ACCREDITATION ADMINISTRATION OF THE PEOPLE’S REPUBLIC OF CHINA REGARDING REGISTRATION OF U.S. FOOD MANUFACTURERS EXPORTING TO CHINA, <https://www.fda.gov/media/106010/download> (last visited Aug. 31, 2020) [<https://perma.cc/N3FF-W6FN>].

from MOUs and, generally speaking, permit the FDA and its counterparts to share and protect confidential information and to explore future regulatory cooperation. In addition, the FDA also has about seventy cooperative arrangements with a similar number of governments; many are statements of intent or agreements to share information and cooperate with foreign regulatory agencies or intergovernmental organizations to ensure the safety and quality of regulated drugs, foods, and medical devices generally and U.S. imports in particular. Most are not binding, but there are a few exceptions.¹⁵⁹

The FDA has also long worked with its foreign counterparts on international standards for safe drugs, medical devices, and foods. Since 1990, the FDA has participated in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (“ICH”) with EU, Swiss, Canadian, and Japanese drug regulatory authorities and the international pharmaceutical industry.¹⁶⁰ The FDA has joined the Pharmaceutical Inspection Cooperation Scheme (“PIC/S”), an informal organization of the drug manufacturing inspectorates from thirty-nine countries that share pharmaceutical facility inspection information. The FDA also participates in regulatory forums, such as the Canada-U.S. Regulatory

158. U.S. FOOD & DRUG ADMIN., CONFIDENTIALITY COMMITMENTS (2020), <https://www.fda.gov/international-programs/international-arrangements/confidentiality-commitments> [<https://perma.cc/R23X-YHE9>]; see also Sam Halabi, *FDA's International Agreements: Typologies and Purposes*, YALE J. REG.: NOTICE & COMMENT (Jan. 19, 2016), <http://yalejreg.com/nc/fda-s-international-agreements-typologies-and-purposes-by-sam-halabi/> [<https://perma.cc/84LK-NPH6>] (“FDA has over 120 international agreements in place with about 30 countries and multilateral partners.”).

159. In 2007, the FDA entered two memoranda of agreement (“MOA”) with the People’s Republic of China aimed at improving the safety of Chinese food and drug products exported to the United States. These MOAs allow U.S. officials to inspect food and drug production facilities that export to the United States, require companies manufacturing drug components to register with state drug regulators, and permit foreign third-party certification. U.S. FOOD & DRUG ADMIN., FDA - AQSIQ CHINA, AGREEMENT ON THE SAFETY OF FOOD AND FEED (2007), <https://www.fda.gov/international-programs/cooperative-arrangements/fda-aqsiq-china-agreement-safety-food-and-feed> [<https://perma.cc/G7RU-94C5>]; U.S. FOOD & DRUG ADMIN., FDA - SFDA CHINA, AGREEMENT ON THE SAFETY OF DRUGS AND MEDICAL DEVICES (2007), <https://www.fda.gov/international-programs/cooperative-arrangements/fda-sfda-china-agreement-safety-drugs-and-medical-devices> [<https://perma.cc/BZ3M-FDCM>]. See generally THOMAS J. BOLLYKY, CTR. FOR STRATEGIC & INT’L STUDIES, GLOBAL HEALTH INTERVENTIONS FOR U.S. FOOD AND DRUG SAFETY 9 (2009), https://csis-website-prod.s3.amazonaws.com/s3fs-public/legacy_files/publication/091112_Bollyky_GlobalHealthInterventions_Web.pdf [<https://perma.cc/E3Y6-D5T7>] (discussing the two MOAs between the People’s Republic of China and the FDA).

160. There are equivalent efforts on veterinary medicines and medical devices, and the FDA participates, along with the USDA and the Office of the U.S. Trade Representative, with Codex Alimentarius, co-convened by WHO and the UN Food and Agriculture Organization, to generate standards, guidelines, and codes of practice.

Cooperation Council and APEC, which were established pursuant to trade initiatives to increase regulatory transparency and coordination.

Despite participating in these international regulatory networks, the FDA has entered into fewer equivalence determinations than the counterpart regulatory agencies of other high-income countries or related U.S. regulatory agencies. In 2012, the GAO reported that the EU had determined the equivalence of one hundred countries for fishery products and that the USDA Food Safety and Inspection Service (“FSIS”) had determined the equivalence of thirty-four countries to export meat, poultry, and processed egg products. Fifteen nations have been determined as equivalent by both the EU and FSIS.¹⁶¹ Most other ICH member nations have entered into multiple MRAs with pharmaceutical provisions: the EU (seven);¹⁶² Australia (five);¹⁶³ Canada (four);¹⁶⁴ and Switzerland (three).¹⁶⁵

Only a small handful of FDA international agreements involve equivalence determinations or reliance on a foreign regulatory agency.¹⁶⁶ The aforementioned 2012 GAO report indicates that,

161. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-12-933, *supra* note 14, at 35.

162. European Union-Switzerland; European Union-Israel; European Union-Japan; European Union-New Zealand; European Union-Canada; European Union-Australia; European Union-United States. See *Mutual Recognition Agreements (MRA)*, EUROPEAN MEDICINES AGENCY, <https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-manufacturing-practice/mutual-recognition-agreements-mra> (last visited Aug. 31, 2020) [<https://perma.cc/LEN8-XL7C>].

163. Australia-Canada; Australia-New Zealand Trans-Tasman Mutual Recognition Agreement (1997); Australia-European Union; Australia-European Free Trade Area (Republic of Iceland, the Principality of Liechtenstein, and the Kingdom of Norway); Australia-Singapore. See *International Agreements and Arrangements for GMP Clearance*, DEPARTMENT OF HEALTH, GOV'T OF AUSTL. (Sept. 19, 2017), <https://www.tga.gov.au/international-agreements-and-arrangements-gmp-clearance> [<https://perma.cc/CFJ3-N4NV>].

164. Canada-Australia; Canada-European Union; Canada-European Free Trade Area (Republic of Iceland, the Principality of Liechtenstein, and the Kingdom of Norway); Canada-Switzerland. See Health Can., *Updates – Mutual Recognition Agreements*, GOV'T OF CAN. <https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/international/mutual-recognition-agreements/updates.html> (last updated Apr. 4, 2012) [<https://perma.cc/T65B-EZQJ>].

165. Switzerland-European Union; Switzerland-Canada; Switzerland-European Free Trade Area (Republic of Iceland, the Principality of Liechtenstein, and the Kingdom of Norway). See *International Agreements (Mutual Recognition Agreements - MRA)*, STATE SECRETARIAT FOR ECON. AFFAIRS SECO, https://www.seco.admin.ch/seco/en/home/Aussenwirtschaftspolitik_Wirtschaftliche_Zusammenarbeit/Wirtschaftsbeziehungen/Technische_Handelshemmnisse/Mutual_Recognition_Agreement_MRA0.html (last updated Feb. 27, 2018) [<https://perma.cc/K2KP-6FQV>].

166. See Richard Stewart, *Global Regulatory Challenge to U.S. Administrative Law*, 37 N.Y.U. J. INT'L L. & POL. 695, 724 (2005) (noting “[t]hese regulators’ work at home is authoritative, but when they go abroad, their agreements lack the indicia of formality”). Generally speaking,

FDA clears its proposed agreements with foreign counterparts with the Department of State, under procedures governing clearance of agency agreements known as the Circular 175 process. The legal basis for this process is the State Department’s need to comply with a statute, the Case-Zablocki Act, which requires the State to inform

between 2006 and 2010, the FDA determined that five countries (Chile, China, India, Indonesia, and Vietnam) had an equivalent ability to satisfy U.S. seafood safety standards and recognized no nations as having food safety system equivalence.¹⁶⁷ Following the GAO report, the FDA has entered into three MOUs that recognize the equivalence of food safety regulatory systems in New Zealand, Australia, and Canada.¹⁶⁸

The FDA has entered into just one MRA on pharmaceutical-related matters with the EU, and it took an act of Congress to conclude the agreement and twenty years to implement. That example may be instructive to future U.S. prescription drug importation efforts, so it is summarized below.

E. The Long Road to the U.S.-EU MRA

Over the last fifteen years, the role of imported regulated products in the FDA's portfolio has changed. The volume of imported products under the FDA's purview increased from 0.5 million shipments in 1970 to 3.7 million shipments in 1996 to 6 million in 2002

Congress of executive branch agreements with other countries that were not submitted to the Senate as treaties for ratification under the U.S. Constitution.

Linda Horton, *Mutual Recognition Agreements and Harmonization*, 29 SETON HALL L. REV. 692, 712–13 (1998). Some have argued persuasively that there is little sign that the vast majority of these agreements from the FDA and other U.S. executive branch agencies receive adequate congressional scrutiny. See, e.g., Jean Galbraith, *From Treaties to International Commitments: The Changing Landscape of Foreign Relations Law*, 84 U. CHI. L. REV. 1675, 1724 (2017) (“[I]nternational law and administrative law provide accountability mechanisms for international commitments that executive branch actors make without getting specific legislative approval. For major international commitments, international negotiations and subsequent compliance procedures often provide for considerable transparency and opportunities for broader participation.”); Oona A. Hathaway, *Treaties’ End: The Past, Present, and Future of International Lawmaking in the United States*, 117 YALE L.J. 1236, 1261 (2008) (“[T]here are several areas of law in which all significant international agreements were concluded through the Article II process, and any congressional-executive agreements appear to be entered pursuant to obligations under a treaty obligation or under the sole authority of the President . . .”).

167. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-12-933, *supra* note 14, 28–29.

168. *Food Safety Systems Recognition Arrangement Between the Australian Department of Agriculture and Water Resources and the FDA of the United States of America*, U.S. FOOD & DRUG ADMIN. (Jan. 31, 2018), <https://www.fda.gov/international-programs/cooperative-arrangements/food-safety-systems-recognition-arrangement-between-australian-department-agriculture-and-water> [<https://perma.cc/NFA5-JTCK>]; *FDA - CFIA and Health Canada, Food Safety Systems Recognition Arrangement*, U.S. FOOD & DRUG ADMIN. (last updated Jan. 31, 2018), <https://www.fda.gov/international-programs/cooperative-arrangements/fda-cfia-and-health-canada-food-safety-systems-recognition-arrangement> [<https://perma.cc/L2S7-BSUJ>]; *Food Safety Systems Recognition Arrangement Between the Ministry for Primary Industries of New Zealand and the Food and Drug Administration of the United States*, U.S. FOOD & DRUG ADMIN. (Dec. 10, 2012), <https://www.fda.gov/international-programs/cooperative-arrangements/fda-new-zealand-mpi-food-safety-systems-recognition-arrangement> [<https://perma.cc/GH4T-NBNK>].

to 24 million in 2012.¹⁶⁹ Between 2005 and 2012, imports of pharmaceutical products increased by nearly 13% annually.¹⁷⁰

In 2007 and 2008, there was a series of scandals involving the safety of imported, FDA-regulated goods from China. Batches of counterfeit heparin, a blood thinner used for patients undergoing kidney dialysis or heart surgery, caused nineteen deaths and hundreds of allergic reactions in the United States and nearly 250 deaths worldwide. Under congressional questioning, FDA officials admitted they mistakenly failed to conduct an inspection of the Changzhou Scientific Protein Laboratories plant, which was ultimately identified as the source of the adulteration.¹⁷¹ Director of the Center for Drug Evaluation and Research Janet Woodcock testified that the FDA would need another \$225 million annually to inspect all foreign drug plants at the frequency many said was needed: every other year.¹⁷² She noted, however, that the agency was budgeted to only spend \$11 million on foreign drug inspections in fiscal year 2008.¹⁷³

President George W. Bush established an Interagency Working Group on Import Safety in 2007, and in 2008, the FDA opened eight foreign offices in China, Europe, India, South Africa, Latin America, and the Middle East. By 2016, however, only twenty-nine FDA staff members were assigned to work in these foreign offices, and many positions were going unfilled.¹⁷⁴ The FDA has closed its posts in Johannesburg, South Africa; Amman, Jordan; Parma, Italy; Mumbai, India; and Guangzhou and Shanghai, China.¹⁷⁵

While the FDA budget for foreign inspections is growing, it cannot keep pace with the proliferation of foreign manufacturing sites. “According to FDA officials, the agency obligated approximately \$53 million to foreign inspections in fiscal year 2010. This amount has increased each year since, rising to \$92 million in fiscal year 2015.”¹⁷⁶ The average cost of a foreign drug inspection has lessened over the years, but remains high. The average cost for an FDA foreign inspection

169. U.S. FOOD & DRUG ADMIN., *supra* note 21, at 5; Sharon Smith Holston, *An Overview of International Cooperation*, 52 FOOD & DRUG L.J. 197, 198 (1997).

170. U.S. FOOD & DRUG ADMIN., *supra* note 21, at 15.

171. Berndt et al., *supra* note 21, at 113; BOLLYKY, *supra* note 159, at 8.

172. Gardiner Harris, *Heparin Contamination May Have Been Deliberate*, F.D.A. SAYS, N.Y. TIMES (Apr. 30, 2008), <http://www.nytimes.com/2008/04/30/health/policy/30heparin.html> [https://perma.cc/2PJJN-88BW].

173. *Id.*

174. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-17-143, FDA HAS IMPROVED ITS FOREIGN DRUG INSPECTION PROGRAM, BUT NEEDS TO ASSESS THE EFFECTIVENESS AND STAFFING OF ITS FOREIGN OFFICES 12–13 (2016).

175. *Id.* at 11 n.25.

176. *Id.* at 16–17.

exceeded \$60,000 in fiscal year 2009 and declined to \$57,600 for fiscal year 2015.¹⁷⁷ The FDA performed drug inspections in sixty-eight countries between the fiscal years 2010 and 2016, but three-quarters of these inspections were conducted in ten countries.¹⁷⁸ FDA inspected establishments in India most often, with establishments in China and Germany also being among the most frequently inspected.¹⁷⁹

In fiscal year 2015, the FDA, for the first time, conducted more foreign than domestic inspections.¹⁸⁰ The FDA has also improved the accuracy and completeness of information on its catalog of drug establishments subject to inspection.¹⁸¹ Further, the GAO reported that, as of 2016, the FDA has never inspected one thousand of the approximately three thousand foreign establishments under its oversight; while high, the current rate of foreign establishments with no FDA inspection—33%—is down from 64% in 2010.¹⁸²

Faced with a growing demand for foreign inspections that the FDA could not meet alone, the agency reengaged with the EU on a long-dormant 1998 MRA to implement its provisions on determining the equivalence of post-approval pharmaceutical GMP inspections.¹⁸³ Between September 2014 and November 2017, the FDA observed the EU's internal audits of its inspectorates to ensure that each was functioning properly and did not deviate in any relevant way from EU law and the PIC/S compliance assessment program.¹⁸⁴ After observing an audit of the drug inspectorate in each of the twenty-eight EU countries, the EMA and the FDA agreed to enter into an MRA in 2017, which amended the sectoral annex to the 1998 U.S.-EU MRA.¹⁸⁵

Before implementing the amended MRA, however, the FDA insisted on additional measures to limit the potential risk of the

177. *Id.* at 17.

178. *Id.*

179. *Id.*

180. *Id.* at 14.

181. *Id.* at 13.

182. *Id.* at 20–21.

183. U.S. FOOD & DRUG ADMIN., FREQUENTLY ASKED QUESTIONS / THE MUTUAL RECOGNITION AGREEMENT 1 (July 2017), <https://www.fda.gov/media/103391/download> [<https://perma.cc/XX46-377J>]. In 2013, the FDA also established a trade office to take a more “comprehensive and proactive” role in the regulatory cooperation discussions occurring as part of trade negotiations. *FDA Takes More Active Role In TTIP, TPP Talks; Establishes Trade Team*, 31 INSIDE U.S. TRADE, no. 35, Sept. 6, 2013. More recently, the FDA has pushed for regulatory cooperation initiatives with the EU, started as part of the TIIP talks, to occur in parallel, but separate from those negotiations. *Id.*

184. U.S. FOOD & DRUG ADMIN., *supra* note 183, at 2.

185. Press Release, U.S. Food & Drug Admin., Mutual Recognition Promises New Framework for Pharmaceutical Inspections for United States and European Union (Mar. 2, 2017), <https://www.fda.gov/news-events/press-announcements/mutual-recognition-promises-new-framework-pharmaceutical-inspections-united-states-and-european> [<https://perma.cc/D96X-ALN2>].

arrangement. The amended MRA allows “FDA and EU inspectorates to use inspection reports and other related information obtained during drug manufacturing facility inspections, whether conducted by an EU or FDA inspectorate, to help determine whether a facility is manufacturing high quality drugs.”¹⁸⁶ Both the FDA and the EU reserved the right to inspect at any time and in any country. Although the original MRA covers preapproval inspections, the current implementation plan does not include them. Current GMP inspections of facilities manufacturing vaccines and plasma-derived products have also yet to be included in the implementation plan, although they may be added after 2022.¹⁸⁷ The FDA insisted on conducting capability assessments of each EU country’s inspectorates before recognizing their drug manufacturing facility inspections. The amended 2017 agreement was conditional on those assessments being completed by July 15, 2019.¹⁸⁸ When the agreement was signed in 2017, then-FDA Commissioner Scott Gottlieb commented:

At a time in which medical product manufacturing is truly a global enterprise, there is much to be gained by partnering with regulatory counterparts to reduce duplicative efforts and maximize global resources while realizing the greatest bang for our collective inspectional buck By partnering with these countries we can create greater efficiencies and better fulfill our public health goals, relying on the expertise of our colleagues¹⁸⁹

Between November 2017 and July 2019, the FDA conducted assessments of all twenty-eight member states.¹⁹⁰ Those assessments included national reviews of specific member states, which assessed a country’s conflict-of-interest policies, its laws on good manufacturing practices, samples of inspection reports, inspector training records, inventory of drug manufacturing facilities, surveillance program, and relevant standard operating procedures. On July 11, 2019, four days before the deadline, the FDA concluded its final assessment of an EU member state (Slovakia).¹⁹¹

186. U.S. FOOD & DRUG ADMIN., *supra* note 183, at 1.

187. *Id.* at 2.

188. *Id.* at 2–3.

189. Press Release, U.S. Food & Drug Admin., FDA Takes Unprecedented Step Toward More Efficient Global Pharmaceutical Manufacturing Inspections (Oct. 31, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583057.htm> [<https://perma.cc/76UF-GSRJ>].

190. See *Mutual Recognition Agreement (MRA)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/international-programs/international-arrangements/mutual-recognition-agreement-mra> (last updated May 8, 2020) [<https://perma.cc/Z6TL-22PC>].

191. *Id.*

F. The Future of Equivalence Determinations at the FDA

The FDCA provides the FDA its authority and mandate on pharmaceutical regulation, but, as Carpenter observes, the FDA's power to achieve that mandate depends on its reputation for preventing harm with professional and scientific networks, product sponsors, consumers, and media organizations.¹⁹² Accordingly, the FDA will act to defend its reputational interests, and, since it has consolidated authority over pharmaceutical regulation, it will generally act alone.¹⁹³ Other national regulatory authorities with a different mandate (e.g., the EC with its mixed mandate for trade and regulation) or less consolidated authority (e.g., a historically under-resourced authority such as COFEPRIS) may be more amenable to accepting equivalence determination and to achieving a broader range of goals. With its institutional character, history, and reputational interests, the FDA is a different animal.

The eventual accession to the U.S.-EU MRA coincided with the slow recognition that the FDA is unable to fulfill its public health mandate to inspect foreign pharmaceutical manufacturing on its own. The challenge facing the FDA goes well beyond post-approval GMP inspections. Most prescription drugs are commodities produced and sold by multinational manufacturers in global supply chains that operate all over the world, including in countries with weaker regulations than those of the United States. Today, drug manufacturers rely on expansive networks of subcontractors to do the clinical testing and production of medicines, sometimes working with as many as two hundred contracted manufacturing organizations for the production of APIs and the bulk assembly, production, and packaging of finished products.¹⁹⁴ Drugs and vaccines are reaching unprecedented numbers of people worldwide, including in low- and middle-income countries, but there are significant differences in national regulations that prevent the sharing of post-market safety surveillance data on the detection, assessment, understanding, and prevention of drug- and vaccine-related adverse effects.¹⁹⁵ Even a well-resourced regulatory agency such as the FDA will, if acting alone, struggle to maintain sufficient expertise

192. CARPENTER, REPUTATION AND POWER, *supra* note 138, at 10–11, 43–44.

193. Past efforts to alter the FDA's authority (MMA on importation) and its relationships with other U.S. agencies (FDAMA on trade) have conditioned those changes on the continued fulfillment of the FDA's mandate on public health, reinforcing the FDA's authority to oppose those changes.

194. COMM. ON MUT. RECOGNITION AGREEMENTS & RELIANCE IN THE REGULATION OF MEDS., NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 14, at 70.

195. *Id.* at 89–90; BILL & MELINDA GATES FOUND., REPORT OF THE SAFETY AND SURVEILLANCE WORKING GROUP 14–15 (2013), https://docs.gatesfoundation.org/documents/SSWG%20Final%20Report%201%2019%2013_designed.pdf [<https://perma.cc/UEY3-EQMX>].

to stay abreast of the rapidly evolving science of medicines for gene therapy and other advanced therapeutics in order to ensure the quality, safety, and efficacy of these cutting-edge medicines.¹⁹⁶ In the next Part, we explore the circumstances in which the FDA is most likely to rely on the equivalence of the processes and oversight of its foreign regulatory counterparts to fulfill its institutional mandate.

IV. GENERIC DRUG SHORTAGES ARE A PUBLIC HEALTH PROBLEM THAT IMPORTATION CAN RESOLVE

Drawing on the expressed institutional and reputational preferences of the FDA as well as reviews of common factors for successful international regulatory cooperation, eight factors should drive such cooperation involving the FDA, including the equivalence determinations that would enable prescription drug importation.¹⁹⁷ Those factors are:

1. the problem to be addressed is a public health matter within the FDA's mandate;
2. it is a problem over which the FDA does not have consolidated authority (i.e., cannot foreseeably solve it alone);
3. there is evidence to suggest the proposed equivalence determination and reliance arrangement might address the public health problem without unduly undermining the core mandate of the FDA to oversee quality and safety and to prevent consumer harm;
4. there is support among FDA constituents (appropriators, consumers, industry officials, and others) for the proposed equivalence determination and reliance arrangement;
5. there is a feasible path to implementing the equivalence determination within existing FDA authorities;
6. the counterpart governments are like-minded and at a similar level of economic development, and the FDA has or

196. COMM. ON MUT. RECOGNITION AGREEMENTS & RELIANCE IN THE REGULATION OF MEDS., NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 14, at 7.

197. See ORG. FOR ECON. CO-OP. & DEV., INTERNATIONAL REGULATORY CO-OPERATION: ADDRESSING GLOBAL CHALLENGES 94–97 (2013) (factors included the selection of: (a) issue-areas where government regulators can benefit from the cooperation by, for example, advancing their mandates on health and safety aspects; (b) areas with regulatory problems similar to those counterpart governments; (c) partners that share similar objectives of regulation and/or standards and where social, economic, political, and technological conditions are similar; (d) activities in which participating regulatory authorities have confidence in the technical and regulatory skills of counterparts, and/or where regulators trust each other; and (e) regulatory subject matter on which international standards exist).

realistically can gain confidence in their technical and regulatory skills;¹⁹⁸

7. the other participating regulatory authorities share an interest in the equivalence determination; and
8. it is a regulatory subject matter on which international standards exist.

The Trump Administration's program on prescription drug importation fails to meet most of these criteria. The FDA has made its general preferences consistently clear on prescription drug importation: it does not wish to enter into binding equivalence arrangements that permit new, unapproved medications into the United States without direct FDA oversight. The goal of lowering domestic drug prices is not sufficient to overcome that reluctance. Presidential interest and high-level congressional engagement might produce a new system of prescription drug importation, but thirty years of FDA practice and opposition on international matters suggest that such a new drug importation system will not be quickly implemented.

The fundamental flaw of the Trump Administration's program is that it largely recycles past proposals in the apparent hope that presidential interest will yield a different result. It is also difficult to imagine that the FDA will be more willing to implement the statutory requirements of section 804 of the MMA, including the certification requirement that there will be no additional risk to public health, now that importation would occur in time-limited state demonstration projects instead of directly under FDA-HHS control.¹⁹⁹ A further complicating matter is how such a scheme would work without the support of the Canadian government, which has said it opposes the Trump program.²⁰⁰

By contrast, however, the persistent problem of U.S. generic drug shortages may be an issue for which U.S. prescription drug importation might work. For years, concerns over the inaccessibility

198. Sykes, *supra* note 99, at 68:

Plainly, mutual recognition is more likely to be attractive where the preexisting differences in policy across jurisdictions are modest, and do not implicate highly sensitive issues. Thus, it is more likely to be attractive between two countries at a comparable level of development and per capita income than, for example, between a developed nation and an undeveloped nation. It is also more likely to be attractive where serious issues of human health and safety are not in play.

199. Separately, it is hard to imagine states being willing to spend the time and resources to set up an importation apparatus if that project is only a time-limited "demonstration" project without more definitive prospects for permanence. Of course, the proposal is only a notice of a potential future proposed rule, so even if it was designed to be realistically achieved, its prospects for being implemented are years away.

200. Martell, *supra* note 67.

and high prices of U.S. prescription drugs focused on patent-protected, brand-name medicines. Low-cost generic drugs—FDA-approved, interchangeable, off-patent versions of the same products made by different manufacturers—were considered part of the solution to that problem. More recently, however, price hikes and shortages of off-patent drugs or products using decades-old active ingredients have been in the news headlines and have drawn the attention of policymakers. From the rising costs of the epinephrine autoinjector (EpiPen) to the unscrupulous pricing practices of Valeant and Martin Shkreli's Turing Pharmaceuticals, widely publicized controversies involving decades-old drugs have generated congressional investigations and sparked public concern.²⁰¹ But the problem is worse than most Americans recognize; there have also been dozens of similar, less well-known episodes involving shortages of essential chemotherapy medicines and fast-escalating prices for lifesaving drugs to treat heart failure.²⁰²

Given these stories, both in the news and not, it is unsurprising that generic prescription drug prices are rising. One out of eight U.S. generic drugs in 2014 exhibited annual price growth in excess of 20%, and the average increase in generic prices that year was 38%.²⁰³ One review found that among over twenty-one thousand generic products from the years 2008 to 2015, four hundred (2%) increased more than 1,000%.²⁰⁴ Given that so many Americans rely on inexpensive generic prescription drugs (over four billion generic prescriptions were filled in 2016), these prices affect a large share of the U.S. population.²⁰⁵

A. *The Role of Generic Drugs in the U.S. Health System*

The U.S. Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Act, catalyzed the modern

201. Melody Petersen, *How 4 Drug Companies Rapidly Raised Prices on Life-Saving Drugs*, L.A. TIMES (Dec. 21, 2016, 3:35 PM), <https://www.latimes.com/business/la-fi-senate-drug-price-study-20161221-story.html> [<https://perma.cc/YA9J-YZEF>].

202. Gretchen Morgenson, *Defiant, Generic Drug Maker Continues to Raise Prices*, N.Y. TIMES (Apr. 14, 2017), <https://www.nytimes.com/2017/04/14/business/lannett-drug-price-hike-bedrosian.html> [<https://perma.cc/9XMY-8GZJ>].

203. Rena M. Conti, Kevin H. Nguyen & Meredith B. Rosenthal, *Generic Prescription Drug Price Increases: Which Products Will Be Affected by Proposed Anti-gouging Legislation?*, J. PHARMACEUTICAL POL'Y & PRAC., Nov. 21, 2018, at 6. At the time of writing, multiple federal and state investigations into price fixing by generic pharmaceutical manufacturers are ongoing. Riley Ray Griffin, David McLaughlin & Ben Elgin, *A Massive U.S. Drug Price-Fixing Probe Has Hit Major Roadblocks*, BLOOMBERG (July 30, 2019), <https://www.bloomberg.com/graphics/2019-generic-drug-price-fixing/> [<https://perma.cc/25P5-VXY5>].

204. Kesselheim et al., *supra* note 24, at 860.

205. Steven M. Lieberman & Paul B. Ginsburg, *Would Price Transparency for Generic Drugs Lower Costs for Payers and Patients?*, BROOKINGS INST. 1, 3 (2017), https://www.brookings.edu/wp-content/uploads/2017/06/es_20170613_genericdrugpricing.pdf [<https://perma.cc/TE66-37MT>].

U.S. generic drug industry by formalizing an abbreviated pathway for generic manufacturers to obtain FDA approval. No longer did manufacturers need to conduct expensive clinical trials to prove generic versions of non-patent-protected drugs were safe and efficacious. Instead, the Hatch-Waxman Act set a pathway by which a manufacturer could file an ANDA to show its drug is interchangeable with a brand-name counterpart in several ways. To be approved under the Hatch-Waxman abbreviated pathway, the generic drug must have the same active ingredient, route of administration, dosage form (e.g., pill or suppository), strength, and intended use as the approved brand-name alternative.²⁰⁶ Generic manufacturers must also meet FDA quality manufacturing standards and conduct small-scale studies to show that their products are bioequivalent to their brand-name counterparts.²⁰⁷ Bioequivalence may be demonstrated through *in vitro* studies as well as pharmacokinetic and pharmacodynamic testing, usually involving two dozen patients.²⁰⁸

Generic medicines play a critical role in the U.S. system because of their widespread use and relatively low cost. Despite the recent increases in their price, generics cost 75% less, on average, than the retail price of U.S. brand-name drugs.²⁰⁹ In 2016, generic medications constituted 89% of the dispensed medications in the United States but only 27% of overall drug spending.²¹⁰ The heavy use of generics in the U.S. health system saved an estimated \$1.67 trillion in health care costs from 2007 to 2017.²¹¹ Use of generic drugs has increased U.S. patients' access to life-saving medications, has improved medication adherence, and is associated with improved patient health outcomes.²¹² The

206. 21 U.S.C. § 355(j)(2)(A)(ii)-(iii).

207. Requirements for Submission of Bioavailability and Bioequivalence Data, 21 C.F.R. § 320.21 (2020).

208. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES FOR ORALLY-ADMINISTERED DRUG PRODUCTS – GENERAL CONSIDERATIONS 10 (2003), <https://www.fda.gov/files/drugs/published/Guidance-for-Industry-Bioavailability-and-Bioequivalence-Studies-for-Orally-Administered-Drug-Products---General-Considerations.PDF> [<https://perma.cc/BCS8-N4KT>].

209. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-12-371R, DRUG PRICING: RESEARCH ON SAVINGS FROM GENERIC DRUG USE 1 (2012).

210. Generic Pharm. Ass'n, *Generic Drugs Continue to Deliver Billions in Savings to the U.S. Healthcare System, New Report Finds*, PR NEWSWIRE (Oct. 19, 2016, 12:40 ET), <http://www.prnewswire.com/news-releases/generic-drugs-continue-to-deliver-billions-in-savings-to-the-us-healthcare-system-new-report-finds-300347698.html> [<https://perma.cc/9AA5-AP5N>].

211. ASS'N FOR ACCESSIBLE MEDS., *GENERIC DRUG ACCESS & SAVINGS IN THE U.S.* 5, 20 (2017), <https://accessiblemeds.org/sites/default/files/2017-07/2017-AAM-Access-Savings-Report-2017-web2.pdf> [<https://perma.cc/G4PS-KHUS>] (reporting data and analysis from IQVIA, then known as Quintiles IMS).

212. Joshua J. Gagne, Niteesh K. Choudhry, Aaron S. Kesselheim, Jennifer M. Polinski, David Hutchins, Olga S. Matlin, Troyen A. Brennan, Jerry Avorn & William H. Shrank, *Comparative*

Affordable Care Act depends on increased usage of generic medications to offset the costs of expanded coverage.²¹³ President Trump has suggested that any health care reform pursued by his Administration will include lowering the “artificially high price” of U.S. prescription drugs, which is likely to involve relying on competition from generic drugs as well.²¹⁴

The relatively low cost and widespread use of generics in the United States stem from the way that drugs are dispensed. Starting in the late 1970s, U.S. states began repealing the anti-substitution dispensing laws that had prevented pharmacists from substituting other versions of a drug for the specific brand-name version indicated on a prescription.²¹⁵ Surveys have consistently shown that many physicians do not know the generic name or price of the drugs they prescribe and will often continue to rely on medications’ brand names when writing their prescriptions, even after generics enter the market. Accordingly, a new series of state laws is replacing anti-substitutions laws to permit, or even require, pharmacists to substitute FDA-certified generics for branded drugs if available; in some states, the switch is required even without seeking patient consent.²¹⁶ In the late 1980s, pharmaceutical benefit managers, health maintenance organizations, and Medicaid programs followed suit, instituting strong financial incentives for patients to accept generic substitution. These insurance plans also reimbursed pharmacy drug purchases at a set maximum allowable cost, which created incentives for pharmacies to seek the cheapest version of a drug to earn the largest profit.²¹⁷ That business model has helped spur the consolidation of the pharmacy industry into large chains, such as Walmart, that could obtain the lowest drug prices by negotiating large purchases. It has also helped dramatically expand

Effectiveness of Generic and Brand-Name Statins on Patient Outcomes, 161 ANNALS INTERNAL MED. 400, 406 (2014); William H. Shrank, Tuyen Hoang, Susan L. Ettner, Peter A. Glassman, Kavita Nair, Dee DeLapp, June Dirstine, Jerry Avorn & Steven M. Asch, *The Implications of Choice: Prescribing Generic or Preferred Pharmaceuticals Improves Medication Adherence for Chronic Conditions*, 166 ARCHIVES INTERNAL MED. 332, 335–36 (2006).

213. See Ian D. Spatz, *Health Reform Accelerates Changes in the Pharmaceutical Industry*, 29 HEALTH AFF. 1331, 1331–32 (2010) (“Generics now make up 75 percent of all prescriptions but only 21 percent of prescription drug spending.” (footnotes omitted)).

214. Donald J. Trump, President, U.S., Remarks by President Trump in Joint Address to Congress (Feb. 28, 2017), <https://www.whitehouse.gov/the-press-office/2017/02/28/remarks-president-trump-joint-address-congress> [https://perma.cc/9Z9V-S9S4].

215. Patricia M. Danzon & Eric L. Keuffel, *Regulation of the Pharmaceutical-Biotechnology Industry*, in ECONOMIC REGULATION AND ITS REFORM: WHAT HAVE WE LEARNED? 433, 447 (Nancy L. Rose ed., 2014).

216. Christopher Stomberg, *Drug Shortages, Pricing, and Regulatory Activity* 7 (Nat’l Bureau of Econ. Research, Working Paper No. 22912, 2014), <http://www.nber.org/papers/w22912> [https://perma.cc/Z3CS-9N6E].

217. Danzon & Keuffel, *supra* note 215, at 433.

the role of generics in the U.S. drug market,²¹⁸ which accounted for only about 19% of prescription purchases in the United States in 1984.²¹⁹

The low-cost, high-volume generic drug market has shaped the generic manufacturing industry in ways that go beyond its increased U.S. market share. Automatic substitution at the pharmacy has meant that most generic drug manufacturers do not advertise or invest in consumer brand recognition. Competition is based on price, and manufacturers make their drugs as cheaply as possible within the bounds of quality standards. Generic drug prices fall when multiple firms enter the market, each trying to gain market share through price discounts. A recent study found that generic drug prices are driven down to 77% of the brand-name price when two competitors are in the market, 46% when there are five generic competitors, and 25% when there are nine.²²⁰ The drugs that are likely to have the most generic entrants are large-market, higher-priced, and easier-to-manufacture drugs, typically tablets for the chronic diseases that represent most of the U.S. health burden.²²¹ The greatest profit for a generic manufacturer is typically earned early in the period right after the expiration of the patent and other exclusivity on a drug, particularly if the firm earns a six-month duopoly by virtue of being the first to successfully challenge a brand-name manufacturer's patent.²²² Among mature generic products with multiple competitors, it tends to be a race to the bottom on price.²²³ As other firms enter the market, the incentive to remain a supplier diminishes as the price of the drug approaches its marginal cost.²²⁴ A manufacturer will continue to sell an older generic drug if the marginal cost of keeping that product line is low, there are strong economies of scale in that drug's production, or there are synergies with the manufacturer's other product lines.

218. Ann M. Thayer, *30 Years of Generics: The Door that Legislation Unlocked for Generic Drugs Three Decades Ago Has Blown Wide Open*, CHEMICAL & ENGINEERING NEWS (Sept. 29, 2014), <https://cen.acs.org/articles/92/i39/30-Years-Generics.html> [<https://perma.cc/5XYN-KYGBJ>] (citing IMS Health Data).

219. Bollyky & Kesselheim, *supra* note 124, at 3.

220. Chintan M. Dave, Abraham Hartzema & Aaron S. Kesselheim, *Prices of Generic Drugs Associated with Numbers of Manufacturers*, 377 NEW ENG. J. MED. 2597, 2597–98 (2017).

221. Danzon & Keuffel, *supra* note 215, at 432–33.

222. David Reiffen & Michael R. Ward, *Generic Drug Industry Dynamics*, 87 REV. ECON. & STAT. 37, 38 (2006).

223. Stomberg, *supra* note 216, at 9.

224. Clay P. Wiske, Oluwatobi A. Ogbechie & Kevin A. Schulman, *Options to Promote Competitive Generics Markets in the United States*. 314 JAMA 2129, 2129–30 (2015).

B. The Factors Driving U.S. Generic Drug Shortages and Price Hikes

When firms stop manufacturing an older, generic medication, the market for that product may undergo major changes. Both the supply and demand of a generic medicine can be inelastic, which means that the need for that drug and its production may not respond to changes in its price. The demand for a generic medicine is inelastic when that drug is a medical necessity to patients and there is no good therapeutic substitute.²²⁵ The supply of a generic drug is inelastic, particularly in the short-run, because existing suppliers must invest in and get FDA approval for any new manufacturing facilities or production lines that would be required to meet the shortfall in the supply of the drug.²²⁶ New suppliers of the drug have those same manufacturing barriers in addition to the need to run bioequivalence studies to gain FDA approval.²²⁷ Generic drug firms take a calculated risk in financing bioequivalence studies and in entering the marketplace without knowing the number of competitors that will enter the market or how quickly the price of the product will decline. New entrants typically must offer lower prices than existing producers to gain market share.

Recent examples of market failures in the U.S. generic drug industry abound and have only increased with the tragic onset of the novel coronavirus pandemic.²²⁸ The last decade has seen an increasing number of drug shortages, which the FDA defines as a “period of time when the demand . . . for the drug within the United States exceeds the supply of the drug”²²⁹ The FDA tracks drug shortages involving medically necessary products that have an important effect on public health. A medically necessary drug is used to treat or prevent a serious disease or medical condition for which no acceptable drug alternative is available in adequate supply. Drug shortages are worrisome because they can result in delaying or denying needed care to patients and may force physicians to prescribe an alternative medicine that is riskier or less effective.

225. Stomberg, *supra* note 216, at 13.

226. *Id.*

227. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-16-706, PART D GENERIC DRUG PRICES DECLINED OVERALL, BUT SOME HAD EXTRAORDINARY PRICE INCREASES 8 (2016).

228. Knvul Sheikh, *Essential Drug Supplies for Virus Patients Are Running Low*, N.Y. TIMES (Apr. 2, 2020), <https://www.nytimes.com/2020/04/02/health/coronavirus-drug-shortages.html> [<https://perma.cc/2TA7-MZ8F>].

229. 21 U.S.C. § 356c(h)(2) (“Discontinuance or interruption in the production of life-saving drugs.”).

The problem of drug shortages reached a critical point in 2011. That year, U.S. drug shortages rose to an unprecedented level with 251 medically necessary drugs approved but unavailable. The GAO found that the number of active drug shortages tripled from 154 in 2007 to 456 in 2012.²³⁰ Most of the U.S. drug shortages involved older, off-patent products.²³¹ Many of the high-profile cases concerned parenteral (generally sterile injectable) drugs, including epinephrine (used in cases of cardiac arrest and anaphylactic shock), propofol (used with anesthesia for surgery),²³² and chemotherapy agents.²³³ These shortages have struck former blockbuster drugs such as buspirone (Buspar), doxazosin (Cardura), atorvastatin (Lipitor), gabapentin (Neurontin); antivirals such as acyclovir (Zovirax); and antibiotics like tetracycline (Sumycin) and ciprofloxacin (Cipro).²³⁴ The prevalence of drug shortages for FDA-approved drugs, vaccines, and biologics has been as high as 12% in recent years, and most have involved markets that had been served by three or fewer producers.

President Obama issued an executive order in November 2011, which Congress later codified in the FDASIA, requiring manufacturers to notify the FDA of impending production disruptions in certain prescription medications.²³⁵ These early notifications provide the FDA and drug manufacturers more time to prevent disruptions in supply from turning into long-term shortages and thereby harming patients.²³⁶

With the FDASIA came the passage of the Generic Drug User Fee Amendments (“GDUFA”) of 2012, which became effective on

230. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-14-194, DRUG SHORTAGES: PUBLIC HEALTH THREAT CONTINUES, DESPITE EFFORTS TO HELP ENSURE PRODUCT AVAILABILITY 40 (2014).

231. Paul Le, Enrique Seoane-Vazquez, Rosa Rodriguez-Monguio, Erin R. Fox, Sheryl L. Szeinbach, Allen R. Duneheew & Michael Montagne, *The Prevalence of Pharmaceutical Shortages in the United States*, 8 J. GENERIC MEDS. 210, 214 (2011).

232. Janet Woodcock & Mia Wosinska, *Economic and Technological Drivers of Generic Sterile Injectable Shortages*, 98 CLINICAL PHARMACOLOGY & THERAPEUTICS 170, 170 (2013).

233. Benjamin J. Davies, Thomas J. Hwang & Aaron S. Kesselheim, *Ensuring Access to Injectable Generic Drugs — The Case of Intravesical BCG for Bladder Cancer*, 376 NEW ENG. J. MED. 1401, 1402 (2017).

234. Stomberg, *supra* note 216, at 6.

235. Exec. Order 13588, 76 Fed. Reg. 68,295 (Oct. 31, 2011); *see also* Food and Drug Administration Safety and Innovation Act, 21 U.S.C. § 356c (2012) (indicating that the FDA must employ “all appropriate administrative tools, including its authority to interpret and administer the reporting requirements in 21 U.S.C. 356c, to require drug manufacturers to provide adequate advance notice of manufacturing discontinuances that could lead to shortages of drugs that are life supporting or life sustaining, or that prevent debilitating disease”).

236. “Drug shortages are particularly challenging for acute care because of the low tolerance for delays that can occur during the search for therapeutic alternatives. . . . The act of substitution also carries a higher risk of medication errors in [emergencies] than in nonacute settings.” Serene I. Chen, Erin R. Fox, M. Kennedy Hall, Joseph S. Ross, Emily M. Bucholz, Harlan M. Krumholz & Arjun K. Venkatesh, *Despite Federal Legislation, Shortages of Drugs Used in Acute Care Settings Remain Persistent and Prolonged*, 35 HEALTH AFF. 798, 798–99 (2016).

October 1, 2014. This legislation, based on the user fee model for NDAs, provides guarantees of timely review of ANDAs in exchange for user fees paid by the ANDA applicants, which help the FDA fulfill those commitments. Under the GDUFA, the FDA committed to take regulatory action on 90% of new ANDAs within ten months of submission and to hire and train more than one thousand new generic drug reviewers by 2017.²³⁷ The FDA also issued new policy guidance to expedite applications for generic drugs that are critical to public health or have the potential to mitigate drug shortages.²³⁸ This guidance has recently been updated to provide the highest prioritization to ANDAs for which there are fewer than three generics approved and for which the drugs are in shortage.²³⁹ In July 2016, the FDA announced that it had already met its GDUFA goals.²⁴⁰ The GDUFA has been reauthorized, and the number of ANDA approvals increased dramatically from 390 approvals in 2014 to 729 in 2018—an increase of 87%.²⁴¹

Nevertheless, U.S. generic drug shortages are rising again. The number of annual new U.S. drug shortages in 2018 reached levels

237. U.S. FOOD & DRUG ADMIN., *Generic Drug User Fee Amendments*, <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm> (last updated Aug. 4, 2020) [<https://perma.cc/ECY9-ZZS5>].

238. U.S. FOOD & DRUG ADMIN., OFFICE OF GENERIC DRUGS, MANUAL OF POLICY AND PROCEDURES (MAPP) 5240.3 REV. 1, PRIORITIZATION OF THE REVIEW OF ORIGINAL ANDAS, AMENDMENTS, AND SUPPLEMENTS 2–4 (2014), <https://www.fdanews.com/ext/resources/files/08/08-07-14-ANDAPrioritization.pdf> [<https://perma.cc/DD7U-NS26>] [hereinafter MAPP 5240.3 Rev. 1].

239. U.S. FOOD & DRUG ADMIN., OFFICE OF GENERIC DRUGS, MANUAL OF POLICY AND PROCEDURES (MAPP) 5240.3 REV. 5, PRIORITIZATION OF THE REVIEW OF ORIGINAL ANDAS, AMENDMENTS, AND SUPPLEMENTS 2–3 (2020), <http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm407849.pdf> [<https://perma.cc/QV6G-KGWK>] [hereinafter MAPP 5240.3 Rev. 5]; *see also* MAPP 5240.3 Rev. 1, *supra* note 238.

240. *Prioritizing Public Health: The FDA's Role in the Generic Market Place: Hearing before Subcomm. on Agric., Rural Dev., Food & Drug Admin., and Related Agencies of the S. Comm. on Appropriations*, 114th Cong. 4 (2016) (statement of Janet Woodcock, Director, Center for Evaluation and Research, U.S. Food and Drug Administration) [hereinafter *Prioritizing Public Health*]; U.S. FOOD & DRUG ADMIN., OFFICE OF GENERIC DRUGS, ANNUAL REPORT 2016: ENSURING SAFE, EFFECTIVE AND AFFORDABLE MEDICINES FOR THE AMERICAN PUBLIC (2016), <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandagenerics/ucm542710.htm> [<https://perma.cc/WJ2U-SY73>].

241. THE IQVIA INST., MEDICINE USE AND SPENDING IN THE U.S.: A REVIEW OF 2018 AND OUTLOOK TO 2023, at 25 (2019), <https://static1.squarespace.com/static/54d50ceee4b05797b34869cf/t/5cd765e5c49ce70001f3449a/1557620199759/medicine-use-and-spending-in-the-us---a-review-of-2018-outlook-to-2023.pdf> [<https://perma.cc/HW4L-U6Z4>]. Since the enactment of the GDUFA, FDA reliance on user fees has increased from \$121 million in fiscal year 2013 to \$373 million in fiscal year 2016, or 45% of total program obligations in fiscal year 2013 to 76% in fiscal year 2016. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-17-452, APPLICATION REVIEW TIMES DECLINED, BUT FDA SHOULD DEVELOP A PLAN FOR ADMINISTERING ITS UNOBLIGATED USER FEES (2017).

unseen since President Obama's executive order. As of August 2019, there are 282 active shortages, the highest level since March 2014, and the number of active shortages has steadily increased over the last consecutive seven quarters. Just over half (55%) are injectables, and prominent shortages exist among generic injectables and other drugs for cancer and cardiovascular conditions.²⁴²

Increased demand is one factor. Americans, as a population, are aging and consuming more generic drugs, with Medicaid and Medicare rolls swelling with retiring baby boomers. The Affordable Care Act has meant more people have access to health insurance, increasing the demand for generic medications.²⁴³ The growth in generic drug manufacturing capacity has not kept up.²⁴⁴ Several other supply side factors have contributed as well.

1. Older Medicines

The prices of older medications—many of them generic—have risen dramatically, but those increases were masked by the overall trends in the U.S. market. According to a 2016 GAO study, U.S. generic drug prices fell 59% from the first quarter 2010 to second quarter 2015, but those declines occurred mostly in higher-priced drugs that were newly eligible for generic competition.²⁴⁵ By contrast, the price of more than three hundred of the 1,441 generic drugs sold in the United States throughout that same five-year period experienced price increases of 100% or more. Almost all of those three hundred drugs were older, “established” generic medicines on the market throughout the five-year period GAO studied. In the vast majority of cases, the GAO found that the elevated price for the older, established generic medicines persisted for multiple years.

Speculators observing this trend began purchasing the rights to manufacture older, single-source, off-patent drugs and drastically hiking their prices. The highest-profile case involved Turing Pharmaceuticals, which purchased the rights to pyrimethamine (Daraprim), a sixty-two-year-old treatment for toxoplasmosis, and raised its price overnight by more than 5,000%, from \$13 to \$750 per

242. AM. SOC'Y OF HEALTH-SYS. PHARMACISTS, DRUG SHORTAGES STATISTICS (2020), <https://www.ashp.org/Drug-Shortages/Shortage-Resources/Drug-Shortages-Statistics> [<https://perma.cc/8368-9PVX>].

243. Berndt et al., *supra* note 26, at 2.

244. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-14-194, *supra* note 230.

245. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-16-706, *supra* note 227.

tablet.²⁴⁶ Valeant Pharmaceuticals bought the rights to manufacture and sell off-patent but single-source isoprenaline (Isuprel) and sodium nitroprusside (Nitropress), raising their prices 500%.²⁴⁷ Rodelis Therapeutics acquired the rights to cycloserine (Seromycin), a drug treating multidrug-resistant tuberculosis, and raised its price from \$500 to \$10,800. The list continues, including price hikes for colchicine (Colcrys) for gout, which experienced a 50-fold increase,²⁴⁸ and digoxin (Lanoxin) to treat heart failures and other cardiovascular conditions.²⁴⁹

2. Lack of Competition

The recent trends in generic drug shortages and price hikes share a proximate cause: inadequate competition from qualified sources of a drug. About 10% of branded drugs with expired patents presently have no generic competition.²⁵⁰ One recent study of 1,120 generic drugs shows that drugs with a duopoly, near-monopoly, or monopoly were associated with price increases of 29%, 59%, and 116%, respectively, over the study period (2008–2013), compared with the reference baseline level of drugs with the highest level of competition.²⁵¹

The reasons for that lack of competition, however, are multiple. Fierce competition in the U.S. generic market has led to consolidation and driven out competitors.²⁵² Incentives are often insufficient to entice new manufacturers to enter generic markets for smaller markets or

246. Andrew Pollack, *Drug Goes From \$13.50 a Tablet to \$750, Overnight*, N.Y. TIMES (Sept. 20, 2015), <https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html> [https://perma.cc/9DS6-6YUD].

247. *Id.*

248. Aaron S. Kesselheim & Daniel H. Solomon, *Incentives for Drug Development—The Curious Case of Colchicine*, 362 NEW ENG. J. MED. 2045, 2046 (2010).

249. Victoria Colliver, *Prices Soar for Some Generic Drugs*, SFGATE (Jan. 1, 2014, 12:13 PM), <https://www.sfgate.com/health/article/Prices-soar-for-some-generic-drugs-5105538.php> [https://perma.cc/Y9ZR-7JVJ].

250. U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF THE ASSISTANT SEC'Y FOR PLANNING AND EVALUATION, UNDERSTANDING RECENT TRENDS IN GENERIC DRUG PRICES 11 (2016), <https://aspe.hhs.gov/system/files/pdf/175071/GenericsDrugpaper.pdf> [https://perma.cc/3LAL-JKAG] (noting that among “1,328 approved branded drugs, there is a sizable group, about 10 percent, whose exclusivities and patents have expired, but no drug companies have come forward to submit ANDAs”).

251. Letter from Edith Ramirez, Chairwoman, U.S. Fed. Trade Comm'n, to William S. Comanor and Diana L. Moss, Am. Antitrust Inst. (Jan. 28, 2016), https://www.antitrustinstitute.org/wp-content/uploads/2018/08/AAI_Teva-Allergan-Ltr-to-FTC.pdf [https://perma.cc/TFE7-4493]. See also Jonathan D. Alpern, William M. Stauffer & Aaron S. Kesselheim, *High-Cost Generic Drugs — Implications for Patients and Policymakers*, 371 NEW ENG. J. MED. 1859, 1860 (2014) (discussing how reductions in the number of generic manufacturers supplying a market can lead to price increases among the suppliers that remain).

252. S. Kumar, *Teva Buys Allergan: 3 Reasons Why It's a Blockbuster Deal*, FORTUNE (July 27, 2015, 4:22 PM), <https://fortune.com/2015/07/27/teva-buys-allergan-mergers-and-acquisitions-consolidation-botox-copaxone-healthcare/> [https://perma.cc/EM5D-5ENE].

older drugs. A 2016 report by the Office of the Assistant Secretary for Planning and Evaluation at the HHS assessed 1,328 approved brand-name drugs and found that 10% were no longer subject to patents or other forms of market exclusivity but still had not attracted drug companies to submit ANDAs.²⁵³ There is a higher incidence of insufficient generic competition for Orphan Drug Act—designated drugs with small patient populations.²⁵⁴

With the passage of the GDUFA, the FDA has significantly reduced its backlog of ANDAs, but poor-quality ANDAs and insufficient understanding of FDA requirements still slow the process. The GAO found that only 12% of the 2,030 generic drug applications reviewed by the FDA from fiscal years 2015 through 2017 were approved in the first review cycle. According to the FDA, generic drug applications go through an average of three cycles of review before being approved.²⁵⁵ A November 2016 congressional oversight hearing noted that, as a result of resubmissions, the median time required for the FDA to approve an ANDA was forty-seven months.²⁵⁶ The GDUFA fees are an additional barrier to entry for smaller generic firms and may be decreasing the numbers of the generic drug manufacturers, with more exiting and fewer entering the market over time. A recent study found that while the average number of manufacturers per generic product is five, the median has dropped to two, and the share supplied by one or two is increasing.²⁵⁷

3. Complex Generic Drugs

Another factor that has made the generic drug market less predictable is the growth in the number of complex generic drugs.²⁵⁸ Because complex generic drugs can be more difficult to produce and more intricate in formulation and delivery than simple, small-molecule tablets (although not quite as complex as protein-based medicines),²⁵⁹

253. DEPT OF HEALTH & HUMAN SERVS., *supra* note 250, at 11.

254. Ravi Gupta, Aaron S. Kesselheim, Nicholas Downing, Jeremy Greene & Joseph S. Ross, *Generic Drug Approvals Since 1984 Hatch-Waxman Act*, 176 JAMA INTERNAL MED. 1391, 1393 (2016).

255. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-19-565, FDA SHOULD TAKE ADDITIONAL STEPS TO ADDRESS FACTORS THAT MAY AFFECT APPROVAL RATES IN THE FIRST REVIEW CYCLE (2019).

256. *Prioritizing Public Health*, *supra* note 240, at 8.

257. Berndt et al., *supra* note 21, at 135.

258. NAT'L ACADS. OF SCIS., ENG'G, & MED., MAKING MEDICINES AFFORDABLE: A NATIONAL IMPERATIVE 98–99 (Norman R. Augustine, Guru Madhavan & Sharyl J. Nass eds., 2018); U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-16-706, *supra* note 227; Woodcock & Wosinska, *supra* note 232, at 170–76; Stomberg, *supra* note 216, at 28–30.

259. Zachary Brennan, *House Panel Calls on GAO to Study FDA's Approval Pathway for Complex Generics*, REG. AFF. PROF. SOC'Y (Dec. 15, 2015), <https://www.raps.org/regulatory-focus>

national regulatory authorities may be reluctant to rely on other national regulatory agencies' assessment of bioequivalence alone when considering whether to approve them. Complex generics can include narrow therapeutic index drugs, controlled-release and modified-release formulations, skin patches, inhalers, and multi-ingredient products.²⁶⁰ Other nonbiological complex drugs may include structures that cannot be isolated and fully characterized by chemical analytical means and depend on consistent, tightly controlled manufacturing to produce. Examples include iron-carbohydrate complexes, liposomes, and nano-medicines.²⁶¹

In some cases, brand-name companies have put barriers in place to approving complex generics by filing citizen petitions that argue that the generics are not comparable or by refusing to supply products for bioequivalence testing.²⁶² As a result, the FDA has been slower to approve ANDAs for complex generics, resulting in higher barriers to entry for potential competitors for these drugs.²⁶³

4. Lapses of Manufacturing Quality and Capacity

Rising challenges in maintaining sufficient quality in the supply of older generics have also been a factor in shortages of generic drugs. This is particularly true for sterile injectable drugs. In 2009 and 2010, the FDA pushed manufacturers to retool their manufacturing and supply chains with greater emphasis on quality in sterile injectable medicines. This push is reflected in the increase in the number of both

<https://perma.cc/KF9P-7B5X>]; Alicia Mundy, *New Generic Lovenox Receives FDA Approval*, WALL ST. J. (Sept. 20, 2011), <https://www.wsj.com/articles/SB10001424053111903374004576580713942376344> [<https://perma.cc/F8SQ-H2KP>].

260. Barbara Davit, April C. Braddy, Dale P. Conner & Lawrence X. Yu, *International Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences*, 15 AAPS J. 974, 978, 983 (2013); Suzanne Dunne, Bill Shannon, Colum Dunne & Walter Cullen, *A Review of the Differences and Similarities Between Generic Drugs and Their Originator Counterparts, Including Economic Benefits Associated with Usage of Generic Medicines, Using Ireland as a Case Study*, BMC PHARMACOLOGY & TOXICOLOGY, Jan. 5, 2013, at 11.

261. Daan J.A. Crommelin, Vinod P. Shah, Imre Klebovich, Scott E. McNeil, Vera Weinstein, Beat Flühmann, Stefan Mühlebachg & Jon S.B. de Vlioger, *The Similarity Question for Biologicals and Non-Biological Complex Drugs*, 75 EUR. J. OF PHARMACEUTICAL SCI. 10, 13–14 (2015).

262. Aaron S. Kesselheim & Joshua J. Gagne, *Product-Specific Regulatory Pathways to Approve Generic Drugs: The Need for Follow-Up Studies to Ensure Safety and Effectiveness*, 38 DRUG SAFETY 849, 851 (2015).

263. *EpiPen Price Increases: How Regulatory Barriers Inhibit Pharmaceutical Competition: Hearing Before the Subcomm. on Children and Families of the S. Comm. on Health, Educ., Labor and Pensions*, 114th Cong. 1 (2016) (statement of Scott Gottlieb, Resident Fellow, American Enterprise Institute).

inspections and noncompliance letters issued over those two years.²⁶⁴ The change was necessary to address quality concerns, and there are signs that the industry has adapted to the increase in regulatory oversight. There has also been, however, a reduction in the number of suppliers of sterile injectable drugs since 2012.²⁶⁵ Higher manufacturing standards and an increased emphasis on quality may be reasons why the estimated cost of a successful ANDA has increased from between \$1 to 2 million in 2005 to as high as \$15 million in 2015.²⁶⁶

Other factors have also increased the consequences of manufacturing lapses. U.S. law does not require manufacturers to maintain excess capacity.²⁶⁷ Margins in the generic industry are thin, so there is little redundant qualified manufacturing capacity, and disruptions like natural disasters have resulted in shortages of drugs and medical supplies. In 2014, Hurricane Maria in Puerto Rico incapacitated one of just three suppliers of medical saline to the United States, and the remaining two suppliers could not increase their production to cover the shortfall.²⁶⁸ In 2017, a merger between Hospira and Pfizer appears to have led to reductions in product lines and shortages of several injectable drugs, including sodium bicarbonate, which is commonly used in hospitals during surgeries, emergency events, and some chemotherapy. A public outcry and congressional inquiry followed.²⁶⁹ In July 2018, then-FDA Commissioner Gottlieb established the Agency Drug Shortages Task Force to assess the

264. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-16-595, DRUG SHORTAGES: CERTAIN FACTORS ARE STRONGLY ASSOCIATED WITH THIS PERSISTENT PUBLIC HEALTH CHALLENGE 26 (2016).

265. *Id.* at 36–37.

266. Henry Grabowski, Iain Cockburn & Genia Long, *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1291–93 (2006); Scott Gottlieb, *How Obama's FDA Keeps Generic Drugs Off the Market*, WALL ST. J. (Aug. 20, 2016, 6:25 PM ET), <https://www.wsj.com/articles/how-obamas-fda-keeps-generic-drugs-off-the-market-1471645550> [<https://perma.cc/L89W-9S7R>].

267. Woodcock & Wosinska, *supra* note 232, at 175; see also Chana A. Sacks, Aaron S. Kesselheim & Michael Fralick, *The Shortage of Normal Saline in the Wake of Hurricane Maria*, 178 JAMA INTERNAL MED. 885, 885–86 (2018) (discussing FDA efforts to increase the supply of essential medications).

268. Maryann Mazer-Amirshahi & Erin Fox, *Saline Shortages — Many Causes, No Simple Solution*, 378 NEW ENG. J. MED. 1472, 1473 (2018); Laurie McGinley, *Hospitals Scramble to Avert Saline Shortage in Wake of Puerto Rico Disaster*, WASH. POST (Oct. 11, 2017, 5:26 PM CDT), <https://www.washingtonpost.com/news/to-your-health/wp/2017/10/09/hospitals-scramble-to-avert-saline-shortage-in-wake-of-puerto-rico-disaster/> [<https://perma.cc/3ATZ-E3Y4>].

269. Letter from Richard Blumenthal, U.S. Senator, to Maureen Ohlhausen, Acting Chairperson, Fed. Trade Comm'n (Aug. 23, 2017), <https://www.blumenthal.senate.gov/imo/media/doc/Letter%20to%20FTC%20on%20Pfizer%20Drug%20Shortage.pdf> [<https://perma.cc/5UXY-M4VG>].

sources of drug shortages and propose potential long-term solutions to Congress.²⁷⁰

*C. Why Prescription Drug Importation May Work to
Address U.S. Generic Drug Shortages*

We propose that the FDA should establish a pathway for granting reciprocal drug approval to approved generic versions of U.S. medications that do not have patent protection or other forms of exclusivity but nevertheless lack sufficient generic competition. Because current models suggest that at least four generic competitors are required before substantial price reductions occur,²⁷¹ the reciprocal approval pathway should be open to generic-eligible medicines with fewer than four approved versions that were manufactured and sold in the United States during the six months prior to reciprocal approval.

The benefit of this pathway is that it allows the market to increase the supply and decrease the cost of generics in a safe and relatively fast way by introducing the possibility of international competition for U.S. generic drugs that are at risk for shortages or dramatic price hikes.²⁷² Existing manufacturers of an already-approved drug can more easily expand their production to serve the U.S. market than a new entrant can obtain an ANDA and build new manufacturing capabilities. Limiting the use of the reciprocal drug approval pathway to generic versions of drugs that are already approved and used in the United States minimizes the potential safety risks that might arise from relying on the approval of other national regulatory authorities for novel drugs (which we do not support). Further, limiting the pathway to drugs for which there is insufficient generic competition builds on existing FDA authority to permit importation to address drug shortages.

Given the expressed institutional and reputational preferences of the FDA and past examples of successful equivalence determinations, this proposal is a model of prescription drug importation that could be successfully implemented. This model draws on previous precedents and the existing platforms for regulatory cooperation in the pharmaceutical sector.

270. *Agency Drug Shortages Task Force*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/drugs/drug-shortages/drug-shortages-task-force> (last updated Oct. 30, 2019) [<https://perma.cc/FT3L-BSB4>].

271. See Dave et al., *supra* note 220, at 2597–98.

272. Alfred B. Engelberg, Jerry Avorn & Aaron S. Kesselheim, *Addressing Generic Drug Unaffordability and Shortages by Globalizing the Market for Old Drugs*, HEALTH AFF. (Feb. 23, 2016), <http://healthaffairs.org/blog/2016/02/23/addressing-generic-drug-unaffordability-and-shortages-by-globalizing-the-market-for-old-drugs/> [<https://perma.cc/FK4T-YF64>].

1. Generic Drug Shortages Are a Public Health Matter Squarely Within the FDA's Mandate

Generic prescription drug shortages are a persistent public health crisis, inflicting serious harm on patients and undermining the effective provision of medical care. The FDA has long recognized this crisis and acted accordingly. Starting in 2010, the FDA began expediting its review of submissions related to new manufacturing sites, suppliers, and specification changes to reduce potential and ongoing shortages.²⁷³ On October 31, 2011, President Obama issued Executive Order 13588, entitled “Reducing Prescription Drug Shortages,” directing the FDA to “use all appropriate administrative tools” to redress existing and potential shortages.²⁷⁴ Congress, with the passage of FDASIA, provided the FDA with new powers, responsibilities, and requirements to address the drug shortages.²⁷⁵ The FDA may seek other manufacturers that are willing and able to increase production. The FDA may also expedite inspections and reviews and exercise temporary enforcement discretion to permit the use of foreign, unapproved sources of FDA-approved medically necessary drugs.²⁷⁶

2. Generic Drug Shortages Are a Problem that the FDA Cannot Solve on Its Own

Since 2012, the FDA has implemented a variety of measures to remedy generic drug shortages. After the enactment of GDUFA, the FDA expedited the ANDA review process and significantly reduced its backlog of applications. In 2017, the FDA published its list of more than 250 off-patent, off-exclusivity drugs without approved generics “[t]o improve transparency and encourage the development and submission of abbreviated new drug applications” in markets with no competition.²⁷⁷ That list was published as part of a broader FDA Drug Competition Action Plan, one goal of which is to maintain three or more

273. Sharona Hoffman, *The Drugs Stop Here: A Public Health Framework to Address the Drug Shortage Crisis*, 67 FOOD & DRUG L.J. 1, 13 (2012).

274. Exec. Order No. 13,588, 76 Fed. Reg. 68,295, 68,295 (Nov. 3, 2011).

275. 21 U.S.C. §§ 356c-356e, 381(d) (2012).

276. U.S. FOOD & DRUG ADMIN., OFFICE OF THE CTR. DIR., MANUAL OF POLICIES AND PROCEDURES (MAPP) 4190.1 Rev. 3, DRUG SHORTAGE MANAGEMENT (2018), <https://www.fda.gov/media/72447/download> [<https://perma.cc/H25F-HRMC>].

277. *List of Off-Patent, Off-Exclusivity Drugs Without an Approved Generic*, U.S. FOOD & DRUG ADMIN. 10 (Dec. 13, 2019), <https://www.fda.gov/media/133524/download> [<https://perma.cc/2MYT-WYC8>].

manufacturers for each generic product.²⁷⁸ The FDA now grants priority review status to applications for drugs that address specific circumstances, including a lack of generics of brand-name drugs, drug shortages, and public health emergencies.²⁷⁹ Despite all these efforts, generic drug shortages are increasing in number and duration.

In recent years, the FDA launched initiatives to engage foreign manufacturers to help increase generic drug competition and reduce shortages. In the last several years, for example, the FDA used “regulatory flexibility and discretion” to allow for the temporary importation of drugs not approved for use in the United States and manufactured in Brazil, Ireland, Mexico, and Canada.²⁸⁰ In 2018, the FDA observed that regulatory barriers prevent generic drug developers from entering multiple markets, which limits competition, increases prices, and raises the risk of shortages. Accordingly, the FDA launched an initiative to harmonize generic drug approval application standards and procedures internationally.²⁸¹ In July 2018, HHS Secretary Azar also announced a new working group to examine how to safely import prescription drugs from other countries in the event of a dramatic price increase for a drug produced by one manufacturer and not protected by patents or exclusivities.²⁸² In the years that have followed, there have

278. MAPP 5240.3 Rev. 5, *supra* note 239; Press Release, U.S. Food & Drug Admin., FDA Tackles Drug Competition to Improve Patient Access (June 27, 2017), <https://www.fda.gov/news-events/press-announcements/fda-tackles-drug-competition-improve-patient-access> [https://perma.cc/2YNS-GMNG].

279. The FDA may grant priority review status to generic drug applications under several circumstances, including for: (1) first generic drugs; (2) drugs that experienced a shortage; and (3) other designations, such as for drugs that could help address public health emergencies. Applicants with priority generic drug applications may communicate with the FDA two months before the application is submitted to facilitate the FDA’s review. An eight-month priority review may be granted for priority generic drug applications with pre-submission correspondence that includes complete and accurate facilities information at least two months before submission of the application. See 21 U.S.C. § 355(j)(11) (2012); *see also* U.S. FOOD & DRUG ADMIN., GDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROGRAM ENHANCEMENTS FISCAL YEARS 2018-2022, at 4 (2020), <https://www.fda.gov/media/101052/download> [https://perma.cc/TXH9-CV9F].

280. CONG. RESEARCH SERV., IN FOCUS: PRESCRIPTION DRUG IMPORTATION 2 (2018), <https://crsreports.congress.gov/product/pdf/IF/IF11056> [https://perma.cc/GYM9-95E3]; *see also* Brennan, *supra* note 57 (providing an example of the FDA allowing temporary importation of drugs to meet demand); AM. HOSP. ASS’N, *supra* note 57 (same); FDA Approves Temporary Importation of Amino Acids, ASPEN, http://www.nutritioncare.org/News/General_News/FDA_Approves_Temporary_Importation_of_Amino_Acids/ (last visited Aug. 31, 2020) [https://perma.cc/5399-TAGU] (same).

281. Scott Gottlieb, *Advancing Toward the Goal of Global Approval for Generic Drugs: FDA Proposes Critical First Steps to Harmonize the Global Scientific and Technical Standards for Generic Drugs*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/advancing-toward-goal-global-approval-generic-drugs-fda-proposes-critical-first-steps-harmonize> (last updated Oct. 18, 2018) [https://perma.cc/3T4M-MZPH].

282. Press Release, U.S. Dep’t of Health & Human Servs., HHS Secretary Azar Directs FDA to Establish Working Group on Drug Importation to Address Price Spikes (July 19, 2018),

been no public statement regarding the membership of the working group or the timeline for its work.

3. Generic Drug Importation Addresses Shortages Without Undermining the FDA's Mandate

Past drug importation proposals purportedly sought to import drugs, but they were, in fact, designed to take advantage of other nations' governmental pricing systems that the U.S. Congress could—but will not—establish directly for U.S. payers.²⁸³ It is, therefore, unsurprising that U.S. health officials have been disinclined to overcome the complexities of ensuring the safety of already-marketed drugs imported from foreign pharmacists and wholesalers. By contrast, drug importation shows promise as a means of sustainably reducing U.S. generic drug costs and improving patients' access to safe and essential medicines.

A 2018 study (of which we were coauthors) assessed whether U.S. generic prescription drugs at risk of sudden price increases or shortages in the United States are available from independent manufacturers approved in other well-regulated settings around the world. We found that nearly two-thirds of these drugs had at least one manufacturer approved by a non-U.S. regulator and that one out of five had four or more approved.²⁸⁴ In 2015, Medicaid alone spent nearly \$700 million on generic drugs that lacked adequate U.S. competition and that could have had a manufacturer approved by non-U.S. peer regulatory agencies.²⁸⁵ In 2018, the FDA examined the set of approximately four hundred generic prescription drugs with the lowest volumes sold in the United States and found that more than a third were available from single manufacturers in another stringently regulated market.²⁸⁶

Generic prices have historically been higher in the EU and Canada than in the United States, but this ceases to be the case when there is only one FDA-approved supplier.²⁸⁷ A 2019 study empirically

<https://www.hhs.gov/about/news/2018/07/19/hhs-secretary-azar-directs-fda-establish-working-group-drug-importation-address-price-spikes.html> [<https://perma.cc/PJ8J-BCSL>].

283. Marv Shepherd, *Drug Importation and Safety of Drugs Obtained from Canada*, 41 ANNALS OF PHARMACOTHERAPY 1288, 1288–89 (2007).

284. Ravi Gupta, Thomas J. Bollyky, Matthew Cohen, Joseph S. Ross & Aaron S. Kesselheim, *Affordability and Availability of Off-Patent Drugs in the United States—The Case for Importing from Abroad: Observational Study*, BRIT. MED. J., Mar. 19, 2018, at 5.

285. *Id.*

286. Gottlieb, *supra* note 281.

287. Danzon & Keuffel, *supra* note 215, at 433 (noting that price competition among generic versions has historically resulted in the U.S. generics generally being cheaper than in Europe and other nations, although some European nations have recently adopted reforms to lower generic

shows that the average price of such U.S. drugs is 200 to 400% higher than the average price for that medicine in four countries where the government intervenes in generic drug prices.²⁸⁸

Expanding prescription drug importation to novel drugs that the FDA has never assessed is risky for patients and likely to be politically unsustainable. It is not uncommon that adverse events, sometimes serious ones, arise in relation to newly approved drugs.²⁸⁹ It is, therefore, difficult to imagine in cases involving novel drugs that patients and congressional overseers would accept the justification that regulators in Europe and Canada had assessed the use of the product.

The public health risk of prescription drug importation is much reduced by limiting its use to foreign versions of drugs already approved by the FDA and in use by U.S. patients. Fundamentally, the strategy proposed here involves much less complicated bioequivalence determinations and nonessential benefit/risk determinations than those involved in assessing a novel drug.²⁹⁰ By limiting the importation pathway to foreign versions of already-approved FDA prescription drugs, this pathway would build on the confidence that the FDA has in its decision to approve a particular ANDA, the confidence that the

prices); Olivier J. Wouters, Panos G. Kanavos & Martin McKee, *Comparing Generic Drug Markets in Europe and the United States: Prices, Volumes, and Spending*, 95 MILBANK Q. 554, 564–65 (2017) (same); see also RYAN CONRAD & RANDALL LUTTER, U.S. FOOD & DRUG ADMIN., *GENERIC COMPETITION AND DRUG PRICES: NEW EVIDENCE LINKING GREATER GENERIC COMPETITION AND LOWER GENERIC DRUG PRICES* 2–3 (2019), <https://www.fda.gov/media/133509/download> [<https://perma.cc/2QPW-KCQR>] (reporting that the most significant price declines in generics only occur with the entry of three or more competitors).

288. The comparator countries were Australia, Canada, New Zealand, and the United Kingdom. Sharat Ganapati & Rebecca McKibbin, *Non-Tariff Barriers and Bargaining in Generic Pharmaceuticals* 2, 41 (Georgetown Univ., Dept't of Econ., Working Paper No. 18-18-23, 2019), <https://ssrn.com/abstract=3313630> [<https://perma.cc/YX3H-6HGV>].

289. Karen E. Lasser, Paul D. Allen, Steffie J. Woolhandler, David U. Himmelstein, Sidney M. Wolfe & David H. Bor, *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 JAMA 2215, 2219 (2002).

290. Concerns have been raised recently about the safety of generic drugs generally. See, e.g., KATHERINE EBAN, *BOTTLE OF LIES: THE INSIDE STORY OF THE GENERIC DRUG BOOM* (2019); Anna Edney, *America's Love Affair with Cheap Drugs Has a Hidden Cost*, BLOOMBERG (Jan. 29, 2019, 3:00 AM), <https://www.bloomberg.com/news/features/2019-01-29/america-s-love-affair-with-cheap-drugs-has-a-hidden-cost> [<https://perma.cc/P77M-FDR4>]. The FDA has argued that those concerns are not supported in current data. *But see* Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., and Director of FDA's Center for Drug Evaluation and Research Janet Woodcock, M.D., on the FDA's Continuing Efforts to Maintain Its Strong Oversight of Generic Drug Quality Issues Domestically and Abroad (Feb. 22, 2019), <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-and-director-fdas-center-drug-evaluation-and-research-0> [<https://perma.cc/JA54-9VKW>] (noting that drugs manufactured outside the United States are required to meet the same standards as drugs made domestically and that FDA sample testing did not indicate any episodes of poor quality). Canada and other stringently regulated markets apply largely the same methods to ensure drug safety, and we are aware of no data to suggest that the same response would not hold for such markets.

constituents of the FDA have in that decision, and the existing safety record of that marketed product.

The pathway for prescription drug importation must be designed to preserve the FDA's role in its oversight. For example, the FDA should reserve the right to require labeling to match that of the brand-name version in the United States, which may word warnings differently than the same brand-name drug in the reciprocal country.²⁹¹ The FDA should also still reserve its authority to refuse to import an otherwise eligible generic medicine to remedy potential drug shortages, but should issue a detailed opinion on any such refusal, explaining its rationale so as to maintain the predictability of the system. In the near term, the prescription drug importation pathway should exclude complex generics so that the mechanism may build trust before it is expanded to more difficult contexts. The pathway should include a maintenance organization to monitor performance, ensure common use of terminology, and assess the possibility of extending the pathway to complex generics and other drug categories.

4. Broad, Bipartisan Support for Generic Prescription Drug Importation

The strategies proposed are competition based and designed to attract bipartisan support. Variations of this strategy have been proposed by leading figures across the political spectrum. President Trump campaigned on reducing U.S. drug prices, at one point saying that “[a]llowing consumers access to imported, safe, and dependable drugs from overseas will bring more options to consumers.”²⁹² Joshua Sharfstein, a deputy FDA commissioner during the Obama Administration, and coauthors have also called for the FDA to allow temporary importation of generic drugs approved in other stringently regulated markets in the event that prices for the U.S. versions of those generic drugs spike.²⁹³ In 2016, a bipartisan report from the Senate Special Committee on Aging also proposed that Congress “give the F.D.A. authority to allow imports of medicines in narrowly defined

291. See Aaron S. Kesselheim, Jessica M. Franklin, Jerry Avorn & Jon D. Duke, *Speaking the Same Language? International Variations in the Safety Information Accompanying Top-Selling Prescription Drugs*, 22 BRIT. MED. J. QUALITY & SAFETY 727, 731 (2013) (discussing the substantial variations in the listing of safety information in popular drugs in the U.S., Canada, U.K., and Australia).

292. David Nather, *Trump's Health Care Plan Takes (Another) Page from the Democrats*, STAT (Mar. 2, 2016), <https://www.statnews.com/2016/03/02/trump-health-care-plan/> [<https://perma.cc/8YCK-3Q3W>].

293. See Jeremy A. Greene, Gerald Anderson & Joshua M. Sharfstein, *Role of FDA in Affordability of Off-Patent Pharmaceuticals*, 315 JAMA 461, 461 (2016).

circumstances, when consumers face sharp, sudden increases in the price of off-patent drugs that have no competition.”²⁹⁴

Other stakeholders are supportive as well. A blue ribbon committee, the Committee on U.S. Drug Pricing at the National Academies of Sciences, Engineering, and Medicine, found that “[i]n the absence of evidence of harm (as opposed to the concerns surrounding potential harm) with respect to importation of generics and biosimilars when competition is lacking, and given the potential cost savings for patients, policy experiments related to generic and biosimilar importation could be useful.”²⁹⁵ The U.S. generic drug industry has expressed support for a single development pathway that would have a similar effect as this proposal here.²⁹⁶

5. Implementing U.S. Generic Prescription Drug Importation Is Feasible

Our generic prescription drug importation proposal is designed not to require major legislative changes to the FDA’s current authorities and not to undercut the agency’s essential role in evaluating and overseeing the quality, safety, and efficacy of the medicines used in the United States.

There are three possible routes to implement our suggested strategy without significant legislative changes. First, the FDA could approve an ANDA for the imported product using evidence of the marketing approval and inspection of the stringent regulatory authority that the FDA deems equivalent. While the Hatch-Waxman Act requires the submission of evidence sufficient to show that a generic drug is bioequivalent to an existing drug, it does not specify the precise nature of the evidence required. The FDA may approve an ANDA on a much abbreviated basis to address potential shortages or for public health reasons.²⁹⁷ The agency may also be able to issue approvals based on data already collected and assessed by the regulatory authority in

294. Robert Pear, *Senate Aims to Stop Firms from ‘Buying Up Drugs and Jacking Up Prices,’* N.Y. TIMES (Dec. 21, 2016), https://www.nytimes.com/2016/12/21/us/politics/prescription-drug-prices.html?_r=0 [<https://perma.cc/EQ2W-GJX3>] (“The imports would be allowed only from countries with drug safety standards similar to those in the United States and would end ‘as soon as the monopoly was broken up.’” (quoting S. REP. NO. 114-429 (2016))).

295. NAT’L ACADS. OF SCIS., ENG’G, & MED., *supra* note 258, at 123.

296. *See A Single Development Pathway Can Improve Patient Access to Generic Drugs*, ASS’N FOR ACCESSIBLE MEDS., https://accessiblemeds.org/sites/default/files/2017-07/1-aam-fact-sheet-GDUFA_0.pdf (last visited Aug. 31, 2020) [<https://perma.cc/H45S-DHJE>].

297. MAPP 5240.3 Rev. 5, *supra* note 239, at 2; 21 C.F.R. § 314.70(b)(4) (2020). A priority review may be granted following a request from the applicant (including when the request is for a supplemental ANDA under 21 C.F.R. § 314.70(b)(4))—in accordance with 21 C.F.R. §§ 314.97, § 314.70(b)(4) applies to ANDAs—or at the FDA’s initiative. *Id.*

another advanced country, if the FDA has determined that the foreign assessment is equivalent and that the authority enforces standards for good manufacturing practices that are as high as its own.²⁹⁸

Under the second option, the FDA could act on behalf of the HHS secretary and use its authority to permit the importation of unapproved drugs that have been approved in foreign jurisdictions when necessary to alleviate a drug shortage; the FDA would only do so after ensuring that the relevant drug is of adequate quality.²⁹⁹ It is already FDA policy to prioritize applications for generic drugs that “could help mitigate or resolve a drug shortage and prevent future shortages.”³⁰⁰ The FDA should recognize that rectifying inadequate competition is also a means to prevent future shortages.³⁰¹ The governing statute does not require importation be temporary, and removing that policy restriction would help to lower the cost of applying for generic drug approval in multiple country markets and to achieve the objective of preventing and remedying generic drug shortages more sustainably.

Making importation a temporary measure would assuage understandable concerns that importation measures might undermine domestic pharmaceutical production and cut the FDA out of drug regulation. The majority of finished generic drugs and API are already manufactured abroad. Restricting this mechanism to temporary importation would discourage foreign firms from incurring the fixed costs of expanding manufacturing to serve the U.S. market. In our proposal, the FDA’s role in generic drug approval is preserved to require different labeling and to reject otherwise qualified candidates for import pursuant to a detailed opinion explaining its rationale. Prescription drug importation can also include a fee to avoid

298. The FDA may also exercise its “enforcement discretion” in permitting the unapproved versions of already FDA-approved drugs from designated stringently regulated markets, which would subject them to less rigorous scrutiny than would ordinarily apply. This treatment would be based on the FDA’s determination that the exporting nation’s standards and inspections would comply with U.S. requirements. Alternatively, the FDA may affirm that the inspection and approval standards, while not identical, provide equivalent public health protection and are permitted entry as satisfying U.S. law. Richard Merrill, the former FDA general counsel, wrote:

It is possible, I suppose, that FDA could respond: “We have always acknowledged that there was more than one approach to meeting the [FDCA]’s substantive requirements; now we are simply recognizing that, e.g., the U.K. approach, is one of them.” If such a response were a plausible historical account, FDA’s agreement would simply represent a formal recognition of what had always been the law.

Merill, *supra* note 18, at 753–54; *see also* Theodore Ruger, *FDA Reform and European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2020 (1999) (proposing the approval by EU centralized procedure quality as “substantial evidence” under section 355(d) of the FDCA).

299. *See* 21 U.S.C. § 381(d)(2) (2012) (authorizing the secretary to allow the importation of drugs required for emergency medical care).

300. Greene et al., *supra* note 293, at 461.

301. *Id.*

undermining the long-term role and viability of the FDA Office of Generic Drugs or the GDUFA.

Under the third route, Congress could statutorily define an appropriate evidentiary standard by which the FDA should assess equivalence determinations of unapproved versions of FDA-approved drugs from designated, stringently regulated foreign markets. It could set an abbreviated statutory timeframe for decisions on such drugs, so long as final power to reject a new generic drug remained with the FDA.

As is the case for the first two routes, the other needed authorities are already in place. The FDASIA gives the FDA authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if the FDA determined those authorities could conduct inspections that met U.S. requirements.³⁰² The FDAMA adds international harmonization to the FDA mandate and enhances its authority to enter into MRAs with other nations. Those harmonization activities are subject to the same administrative legal framework as are other parts of the FDA mandate.³⁰³ Neither of the pathways we propose here would eliminate the FDA or its decisionmaking in generic drug approval and so should not run afoul of the U.S. Constitution's Article I doctrine of nondelegation.³⁰⁴

If the FDA proceeds, it should do so pursuant to notice-and-comment procedures—irrespective of whether these are strictly required—to ensure adequate public and stakeholder participation in establishing this pathway for prescription drug importation.

6. Other Stringently Regulated Markets Have Similar Generic Drug Approval Standards

The FDA should limit the use of this importation pathway to generic drugs from countries with stringent national regulatory

302. Food and Drug Administration Safety and Innovation Act § 712, 21 U.S.C § 384e (2012).

303. The FDA typically uses executive agreements, not treaties, to enter into commitments with its foreign counterparts. *See Horton, supra* note 166, at 712–13. The process for concluding those agreements is not overly burdensome: the State Department reviews and notifies Congress of those agreements, as is required under the Case-Zablocki Act. *Id.*; *see also* Richard A. Merrill, *FDA and Mutual Recognition Agreements: Five Models of Harmonization*, 53 FOOD & DRUG L.J. 133 (1998) (discussing the different approaches under U.S. administrative law that the FDA may undertake to implement the international equivalence agreements that it enters into).

304. The nondelegation doctrine limits the ability of Congress to delegate to statutorily created administrative agencies the legislative powers vested in it by Article I of the Constitution: “All legislative Powers herein granted shall be vested in a Congress of the United States . . .” U.S. CONST. art. I, § 1. Case law suggests that this system of prescription drug importation would likely be considered constitutional so long as the FDA retains the final authority to approve new drugs. Theodore Ruger, *FDA Reform and the European Medicines Evaluation Agency*, 108 HARV. L. REV. 2009, 2023 (1995) (citing *Todd & Co. v. SEC*, 557 F.2d 1008 (3d Cir. 1977) and *R.H. Johnson & Co. v. SEC*, 198 F.2d 690 (2d Cir. 1952)).

authorities and strong safety records,³⁰⁵ as determined through its assessment of the equivalence of those generic drug approval processes. Prior to starting that process, the FDA should establish reasonable minimum standards for assessing the equivalence of the generic drug approval processes of those regulators. Limiting the importation generic drug approval pathway to countries that satisfy these reasonable, science-based minimum standards is consistent with requirements of WTO agreements.

Once those minimum standards for equivalence are laid out, the FDA may assess its stringent regulatory agency counterparts and enter into bilateral agreements with those regulators that meet those minimum standards. Bilateral agreements can be as simple as MOUs. Those agreements should establish common technical implementation procedures and identify any nonequivalent aspects of the generic drug approval process where the FDA may still need to be directly involved. Many of the nations likely to be chosen already have reciprocal inspection agreements with each other.³⁰⁶

Studies that have assessed generic drug regulation in the United States, the EU, Canada, Australia, and Japan have found that there are many more similarities than differences in these nations' requirements.³⁰⁷ The standards for bioequivalence and study design are largely the same across these countries. Some differences exist, however, in the requirements for narrow therapeutic index drugs and more highly variable drugs. These requirements are the subject of current international harmonization efforts, but narrow therapeutic index drugs can be excluded, if necessary, until those harmonization efforts are complete.³⁰⁸

305. Examples might be Health Canada, the European Medicines Agency, the U.K. Medicines and Healthcare Products Regulatory Agency (MHRA), Australia's Therapeutics Goods Administration, New Zealand Medicines and Medical Devices Safety Authority (Medsafe), and Japan's Pharmaceuticals and Medical Devices Agency (PMDA).

306. The EU (including the U.K.), Australia, Canada, and New Zealand already have reciprocal MRAs on good manufacturing inspections. The EU and United States have an MRA for each other's inspections. *See supra* notes 162–165 and accompanying text.

307. Davit et al., *supra* note 260, at 986.

308. Crommelin et al., *supra* note 261, at 11 (noting that despite the extensive efforts at the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use to harmonize international regulations on narrow therapeutic index drugs, "no real, total global consensus has been reached yet"). One potential hurdle is the requirement in some nations that the reference drug used to establish bioequivalence is from a domestic manufacturer. *See Davit et al., supra* note 260, at 976. As long as the product is made using the same manufacturing specifications under license from the original manufacturer, applicants would not have to obtain a sample of the reference drug from each market and repeat the same bioequivalence tests.

7. Other Regulatory Authorities Share an Interest in Preventing Generic Drug Shortages

Canada and other nations have opposed reimportation proposals, under which drugs marketed in the United States are rendered inexpensive through foreign price controls and then imported back into the United States, as threatening their drug supply and potentially driving up prices. In contrast, this proposal for prescription drug importation would permit manufacturers of versions of FDA-approved drugs entry into the U.S. market and would rely on competition to reduce generic drug shortages and prevent price hikes. By facilitating access to the U.S. market for older generic drugs, a pathway for reciprocal approval would enable manufacturers to scale and improve the viability of these product lines. Pursued in this manner, other nations would share in the potential benefits that come with greater access and the improved viability to international sources of safe generic drugs.³⁰⁹

Many developed countries, including Canada and those in the EU, are using more generics and adopting reforms to further encourage their use and lower their prices. IQVIA estimates that generic medicines will account for 31% of drug spending in the non-U.S. developed markets, up from 29% in 2016 and 28% in 2011.³¹⁰ In 2015, the WHO convened a consultation on reducing global pharmaceutical shortages. Resultant WHO reports noted that medicine shortages were increasing internationally, particularly for older, off-patent drugs and treatments that are difficult to formulate, including many of the same drugs that are prone to U.S. shortages. According to the WHO, the drivers of these shortages in other nations are similar to those in the United States, including manufacturing quality and capacity disruptions, competition issues and business decisions, and market fragmentation.³¹¹

309. Aaron S. Kesselheim, *Think Globally, Prescribe Locally: How Rational Pharmaceutical Policy in the U.S. Can Improve Global Access to Essential Medicines*, 34 AM. J.L. & MED. 125, 139 (2008).

310. MURRAY AITKEN, MICHAEL KLEINROCK & DEANNA NASS, QUINTILESIMS INST., OUTLOOK FOR GLOBAL MEDICINES THROUGH 2021, at 12 (2016), <https://morningconsult.com/wp-content/uploads/2016/12/QuintilesIMS-Institute-Global-Outlook-FINAL.pdf> [<https://perma.cc/WN5V-4HPM>].

311. *Medicines Shortages: Global Approaches to Addressing Shortages of Essential Medicines in Health Systems*, 30 WHO DRUG INFO. 180, 181–82 (2016).

8. Relevant International Standards Exist or Are Being Negotiated

This proposal would build on existing infrastructure. As part of the ICH, the United States and other signatory national regulatory agencies have developed a common technical document for drug applications, as well as common guidelines on good manufacturing practices, good clinical practices, and good regulatory practices.³¹² These forms and guidelines are the foundation of any international cooperation on drug approval. Many developed nations that might be subject to a prescription drug importation pathway (e.g., Australia, Canada, New Zealand, and the United Kingdom) already follow the ICH Good Clinical Practice guidelines in assessing bioequivalence and ICH GMP guidelines to ensure that products are properly produced and packaged, as well as safe.

The United States already participates in the International Generic Drug Regulators Pilot, along with the EU, Japan, China, Mexico, and Brazil.³¹³ Launched in 2012, this pilot aims to promote the sharing of generic drug assessment-related data, the convergence of technical and data standards, and the alignment of administrative and regulatory assessment procedures.³¹⁴ The pilot is also tasked with creating a platform and database to promote deeper regulatory cooperation on generic drug approvals in the future.³¹⁵

In the past, we have argued that the FDA should leverage these international standardization initiatives with other stringent national regulatory authorities to establish a single electronic window for applications for approval of generic medicines. This proposal is outlined in depth elsewhere.³¹⁶ It has the potential to reduce the transaction costs involved in filing separate applications with each of the participating regulatory authorities, to increase the number of generic entrants, and to expedite applications.³¹⁷

In 2018, the FDA initiated a push at the ICH for common scientific and technical standards for the global development of generic drugs. The proposal covered guidelines on standards for demonstrating

312. See *ICH Standards: CTD*, ICH, <https://www.ich.org/page/ctd> (last visited Aug. 31, 2020) [<https://perma.cc/Y2NX-2TPY>].

313. Mike Ward, *Regulatory Harmonization: The International Generic Drug Regulators Pilot Project*, 28 WHO DRUG INFO. 3, 6 (2013).

314. *Id.* at 6–7.

315. *IGDRP Roadmap to 2020*, INTERNATIONAL GENERIC DRUG REGULATORS PROGRAMME 7 (Oct. 7, 2016), <https://www.fdanews.com/ext/resources/files/2017/01/01-09-17-IGDRPRoadmap.pdf> [<https://perma.cc/R3PF-MY8Q>].

316. See Bollyky & Kesselheim, *supra* note 124, at 10.

317. Fiona M. Scott Morton, *Entry Decisions in the Generic Pharmaceutical Industry*, 30 RAND J. ECON. 421, 436–38 (1999).

bioequivalence for both non-complex dosage forms and for more complex dosage forms and drug products. The goal of this harmonization effort, according to the FDA, would be to ultimately support simultaneous regulatory filings across multiple markets.³¹⁸

* * *

Two final caveats apply to our proposal for generic prescription drug importation. First, this proposal puts greater demands on the already scarce resources at the FDA. Negotiating and maintaining international arrangements requires dedicated staff and funding. The FDA has long struggled to increase its rates of foreign inspections of manufacturing sites to rough parity with domestic inspection. This strategy requires the appropriation of adequate resources for its implementation, in addition to GDUFA fees.³¹⁹ Furthermore, it necessitates that the FDA enter into robust work-sharing arrangements with participating regulators, including mutual recognition of inspection reports. Generic prescription drug importation may lower U.S. public and private healthcare costs over the long-term, but it will require an upfront investment in the FDA to achieve.

Second, the long-term consequences of internationalizing the generic drug market are unclear. It is possible that adopting the pathways proposed here may lead to more consolidation in the international generic industry because of greater economies of scale and increased ability to operate across markets. That may lead to increased efficiencies and lower costs; over the long run, it might also lead to fewer suppliers that are willing to manufacture mature generics for small patient populations. Adoption of the strategy proposed here would need to be accompanied by careful continued oversight to recognize and respond to any unintended market effects.

CONCLUSION

Prescription drug importation can work in the United States, but only if it occurs under circumstances in which the FDA is willing to accept the equivalence of the foreign national regulatory authority and

318. Gottlieb, *supra* note 281; *see also* Bollyky & Kesselheim, *supra* note 124, at 10 (discussing a generic drug application pathway that would use a single application that would be submitted to all participating national regulatory authorities).

319. U.S. DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECTOR GEN., FDA HAS MADE PROGRESS ON OVERSIGHT AND INSPECTIONS OF MANUFACTURERS OF GENERIC DRUGS 7 (2015), <https://oig.hhs.gov/oei/reports/oei-01-13-00600.pdf> [<https://perma.cc/C7QX-GWLL>] (noting that the FDA “collected nearly \$300 million in user fees” the year the GDUFA was implemented).

to rely on their oversight. Drawing from the literature on the political economy of pharmaceutical regulation and international regulatory cooperation as well as a close review of FDA's past international practices, this analysis has identified eight criteria for successful international regulatory cooperation, including the equivalence determinations that would enable U.S. prescription drug importation. Taking these steps to leverage the activities of its foreign counterparts will allow the agency to more effectively oversee U.S. drug imports, keep pace with technological advances in personalized medicines, and continue to ensure the quality and safety of complex global pharmaceutical supply chains.³²⁰ What factors should guide successful international regulatory cooperation is an important question for administrative law and for making progress on persistent health policy concerns, including U.S. generic drug shortages and price hikes, which have gained even further relevance for public health with the onset of the coronavirus pandemic.

The critically important role that generic drugs play in the United States is in jeopardy due to changing dynamics in the domestic generic drug marketplace that have reduced competition among generic manufacturers. This competition is essential to ensure sufficient supplies and reasonable prices.

The proposed U.S. prescription drug importation strategy accords with the theory and practice of international regulatory cooperation and accommodates the institutional and reputational preferences of the FDA. It need not be pursued in isolation or preclude U.S. Medicare programs from adopting a bargaining policy to reduce prices as well. But, if implemented, generic prescription drug importation has the potential to restore the balance required to maximize competition, normalize prices, and put out of business those who improperly thrive on market failures, all to the ultimate benefit of the patients who depend on lifesaving generic drugs.

320. See COMM. ON MUT. RECOGNITION AGREEMENTS & RELIANCE IN THE REGULATION OF MEDS., NAT'L ACADS. OF SCIS., ENG'G, & MED., *supra* note 14; COMM. ON STRENGTHENING CORE ELEMENTS OF REGULATORY SYS. IN DEVELOPING COUNTRIES, *supra* note 14; U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-12-933, *supra* note 14. The FDA has itself acknowledged the necessity of increased international regulatory cooperation. U.S. FOOD & DRUG ADMIN., *supra* note 14, at 2.