

CAN DRUG IMPORTATION ADDRESS HIGH GENERIC DRUG PRICES?

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INTRODUCTION

For years, concerns over the inaccessibility and high prices of U.S. prescription drugs focused on on-patent brand-name medicines. Low-cost generic drugs—Food and Drug Administration (FDA)-approved, interchangeable 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 generic drugs have dominated news headlines and 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. But 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.¹ While most generic drugs remain an inexpensive and critical part of a physician's therapeutic arsenal, these cases reveal failures in the generic drug market that can lead to substantial patient harm.

In response, we propose a sustainable strategy to address price spikes among U.S. generic drugs and improve patients' access to safe medicines. We begin by outlining the important role of generic medicines in the U.S. health system and the market failures that have contributed to recent price hikes and shortages. Next, we consider the various strategies that have been proposed to address those market failures and the reasons that those strategies are likely to fall short in fixing the problem. Third, we propose a three-pronged approach for increasing competition in the U.S. generic drug market, while minimizing any attendant risks to patient safety or undermining the institutional role of the FDA. This proposal centers on the use of reciprocal drug approval and draws on previous precedents and the existing platforms for regulatory cooperation in the pharmaceutical sector. Last, we apply our proposal to show how it might affect international competition among a cohort of U.S. drugs currently eligible for generic competition, but lacking sufficient competition to achieve substantial price reductions.

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I. THE SOURCES OF MARKET FAILURE IN U.S. GENERIC DRUGS

A. Background

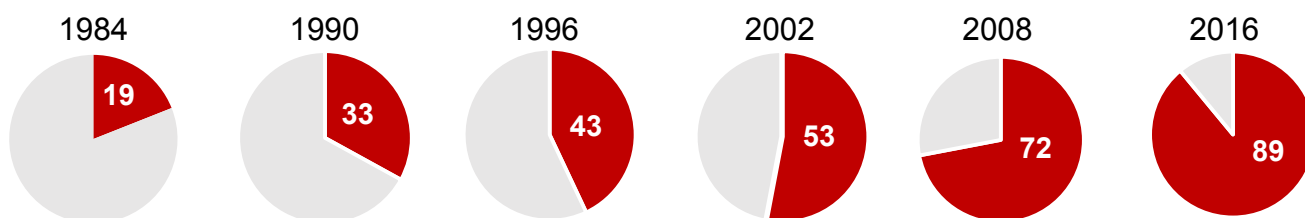
The U.S. Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Act, catalyzed the modern U.S. generic drug industry by formalizing an abbreviated pathway for generic manufacturers to obtain FDA approval. No longer did manufacturers need to conduct expensive clinical trials to prove generic versions of non-patent-protected drugs were safe and efficacious. Instead, the Hatch-Waxman Act set out a pathway by which a manufacturer could file an abbreviated new drug application (ANDA) that shows its drug is the same as 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 v. suppository), strength, and intended use. Generic manufacturers must also meet FDA quality manufacturing standards and conduct sufficient studies to show that their products are bioequivalent to their brand-name counterparts. Bioequivalence may be demonstrated through *in vitro* studies and pharmacokinetic and pharmacodynamic testing, usually involving a couple dozen patients.

Generic medicines play a critical role in the U.S. system because of their widespread use and low cost. Generics cost 75 percent less, on average, than the retail price of a U.S. brand-name drug.² In 2016, generic medications constituted 89 percent of the dispensed medications in the United States, but only 27 percent of overall drug spending.³ The heavy use of generics in the U.S. health system saved an estimated \$1.68 trillion in healthcare costs from 2005-2014.⁴ 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.⁵ The Affordable Care Act depends on increased usage of generic medications to offset the costs of expanded coverage.⁶ 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 generics as well.⁷

The low cost and widespread use of generics in the United States stems 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 any versions of a drug made other than that indicated on a prescription.⁸ Surveys consistently show that many physicians do not know the generic name of the drugs they prescribe or their prices and will often continue to rely on medications' brand names when writing their prescriptions even after generics enter the market. The new series of state laws permitted, or even required, pharmacists to substitute FDA-certified generics in lieu of branded drugs if available, in some states even without seeking patient consent.⁹ In the late 1980s, pharmaceutical benefit managers (PBMs), health maintenance organizations (HMOs), 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 incentivized pharmacies to seek the cheapest version of a drug to earn the largest profit.¹⁰ That business model has helped spur the consolidation of the pharmacy industry into large chains, such as Wal-Mart, that could obtain the lowest drug prices. It has also helped dramatically expand the role of generics in the U.S. drug market (Figure 1).¹¹ IMS Health projects that generics will comprise roughly 91 percent of U.S. prescriptions by 2020.¹²

Figure 1: The expanding role of generics in the U.S. drug market

% of prescriptions for generics



Source: IMS Health

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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. It has also led to consolidation in the generic drug industry. The generic market is now made up of a handful of very large, multinational companies with billions of dollars in profits, as well as many smaller firms. Generally, there is not much overlap between manufacturers of generic and originator pharmaceuticals, with a few exceptions of firms such as Teva and Novartis that produce both.

Generic drug prices fall when multiple firms enter the market, each trying to gain market share through price discounts. An FDA study found that generic drug prices are driven down to 55 percent of the brand-name price when two competitors are in the market, 33 percent when there are five generic competitors, and 13 percent when there are 15.¹³ The drugs that are likely to have the most generic entrants are large-market, higher-priced, and easier-to-manufacture drugs, typically solid pills for the chronic diseases that represent most of the U.S. health burden.¹⁴ 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 duopoly.¹⁵ Among mature generic products with multiple competitors, it tends to be a race to the bottom on price.¹⁶ As other firms enter the market and the price of the drug approaches its marginal cost, the incentive to remain a supplier diminishes.¹⁷ 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.

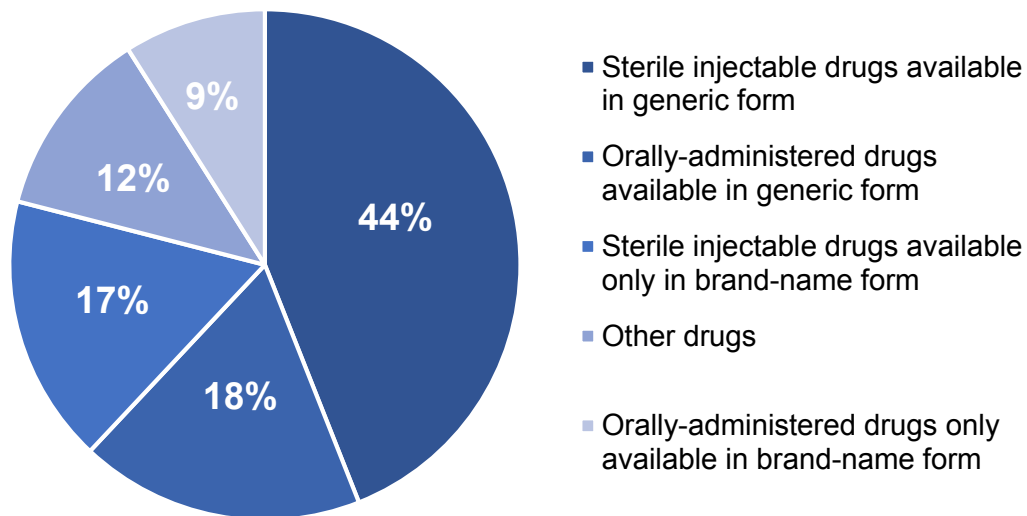
When firms stop manufacturing an older generic medication, it can lead to major changes in the market for that product. Both the supply and demand of a generic medicine can be inelastic, which means that the need for that drug and its production may not respond to changes in its price. The demand for a generic medicine is inelastic when that drug is a medical necessity to patients and there is no good therapeutic substitute.¹⁸ 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.¹⁹ New suppliers of the drug have those same manufacturing barriers plus the need to run bioequivalence studies to gain FDA approval.²⁰ 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 get market share.

B. Recent market failures in U.S. generic market

Recent examples of market failures in the U.S. generic drug industry abound. 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 U.S. exceeds the supply of the drug.”²¹ 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 more risky or less effective.

The issue 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 U.S. Government Accountability Office (GAO) found that the number of active drug shortages tripled from 154 in 2007 to 456 in 2012.²² Most of the U.S. drug shortages involved older, off-patent products.²³ Many of the high-profile cases concerned parenteral (generally sterile injectable) drugs, including epinephrine (used to address cardiac arrest and anaphylactic shock), propofol (used with anesthesia for surgery),²⁴ and chemotherapy agents.²⁵ But, as Figure 2 shows, there have been shortages in oral generic drugs as well. 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).²⁶ The prevalence of drug shortages for FDA-approved drugs, vaccines, and biologics has been as high as 12 percent in recent years and most have involved markets that had been served by three or fewer producers.

Figure 2: Distribution of critical drug shortages reported from June 2011 through June 2013, by route of administration and product type

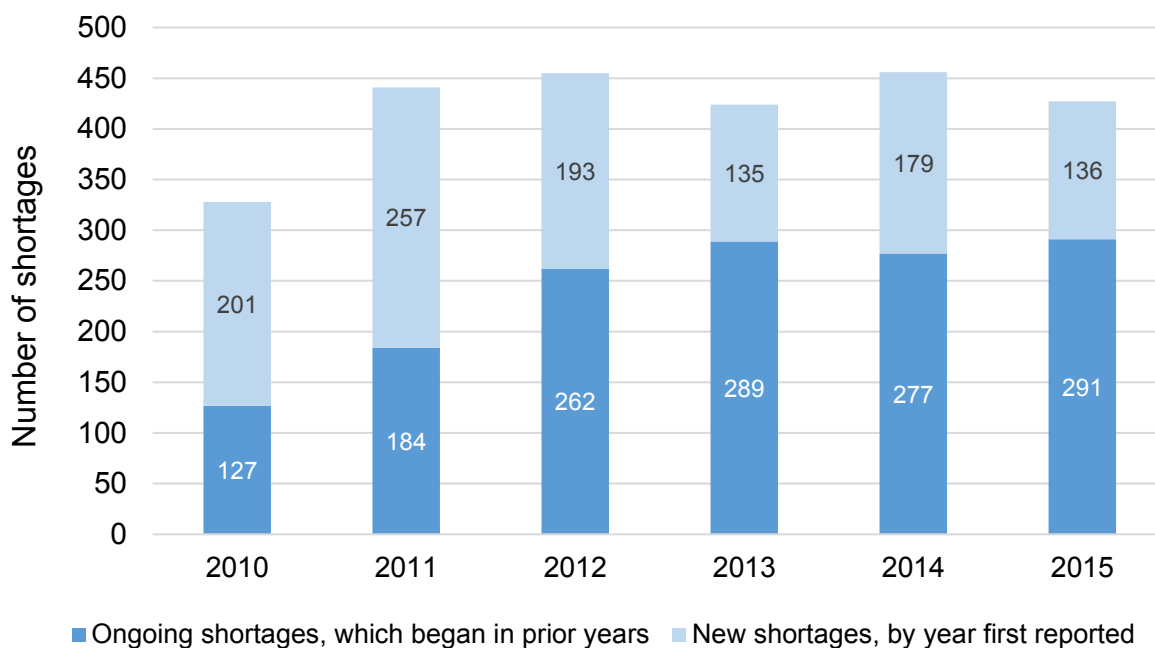


Source: U.S. Government Accountability Office, *Drug Shortages: Public Health Threat Continues, Despite Efforts to Help Ensure Product Availability*, GAO-14-194 (Washington, DC, 2016), 15, <http://www.gao.gov/assets/670/660785.pdf>

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President Obama issued an executive order in 2012, which Congress later codified in legislation, requiring manufacturers to notify the FDA of impending production disruptions in certain prescription medications.²⁷ These early notifications provide the FDA and drug manufacturers more time to take measures to prevent disruptions in supply from turning into long-term shortages and harming patients. These measures have helped the FDA reduce the number of drug shortages since 2012, but shortages have persisted as a public health concern, as Figure 3 shows.

Figure 3: Number of U.S. drug shortages from January 2010 through December 2015



Source: GAO-16-595. U.S. Government Accountability Office, *Drug Shortages: Certain Factors Are Strongly Associated with This Persistent Public Health Challenge*, GAO-16-595 (Washington, DC, 2016), 27, <http://www.gao.gov/assets/680/678281.pdf>

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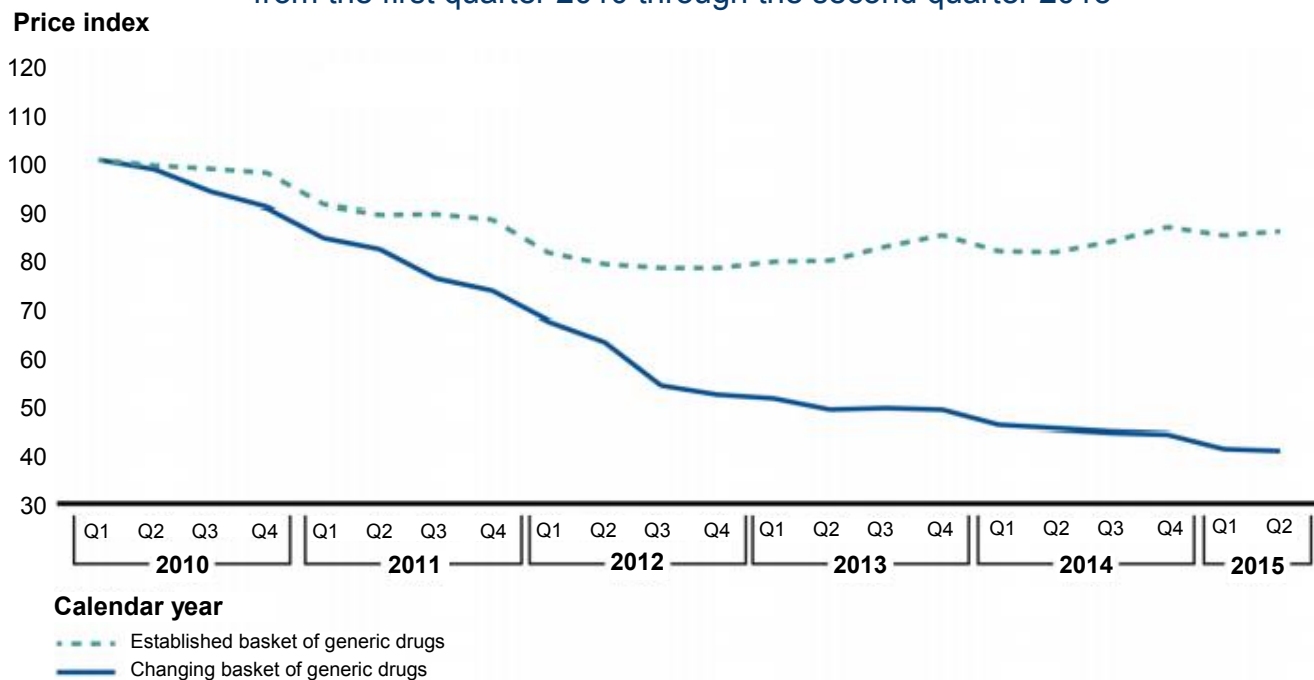
There have also been dramatic increases in the price of older generic medications that had been masked by the overall trends in the U.S. market. According to a 2016 GAO study, U.S. generic drug prices fell 59 percent from the first quarter 2010 to second quarter 2015, but those declines occurred mostly in higher-priced drugs newly eligible for generic competition.²⁸ In contrast, more than 300 of the 1,441 generic drugs sold in the United States throughout that same 5-year period experienced price increases of 100 percent or more. In almost all of those cases, that price increase involved an older, “established” generic medicine (on the market throughout the five year period GAO studied). Figure 4, taken from that GAO report, shows the polarized pricing trends between the older, established basket of generics and the newer, “changing basket” of generics. 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 generic drugs and drastically hiking their price. The most high-profile case involved Turing Pharmaceuticals, which purchased the rights to pyrimethamine (Daraprim), a 62-year old treatment for toxoplasmosis, and raised its price overnight by over 5,000 percent, from \$13 to \$750 per tablet.²⁹ Valeant Pharmaceuticals bought the

rights to manufacture and sell single-source isoprenaline (Isuprel) and sodium nitroprusside (Nitropress), raising their price 500 percent.³⁰ Rodelis Therapeutics acquired the rights to cycloserine (Seromycin), a drug treating multidrug-resistant tuberculosis, and raised price from \$500 to \$10,800. The list goes on and on, including price hikes for colchicine (Colcrys) for gout (50-fold),³¹ and digoxin (Lanoxin).³²

Figure 4: Price trends under Medicare Part D for the changing basket and established basket of generic drugs

from the first quarter 2010 through the second quarter 2015



Source: GAO-16-706. U.S. Government Accountability Office, Generic Drugs Under Medicare: Part D Generic Drug Prices Declined Overall But Some Had Extraordinary Price Increases, GAO-16-706 (Washington, DC, 2016), 11, <http://www.gao.gov/assets/680/679022.pdf>

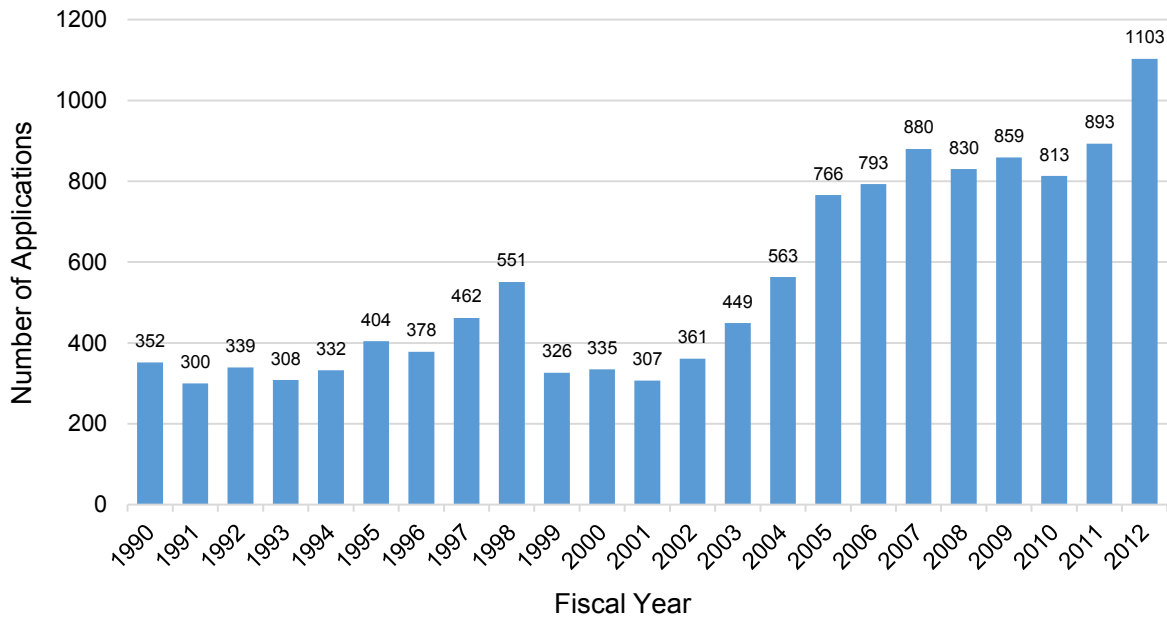
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C. The causes of market failures in the U.S. generic drug market

The proximate cause of the recent trends in generic drug shortages and price hikes are the same: inadequate competition from qualified sources of a drug. One of us has a forthcoming study of 1,120 generic drugs that shows drugs with a duopoly, near-monopoly, and monopoly were associated with price increases of 29 percent, 59 percent, and 116 percent, respectively over the study period (2008-2013), compared with the reference baseline level of drugs with the highest level of competition.³³

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.³⁴ Incentives are often insufficient to entice new manufacturers to enter generic markets for smaller market or older drugs. A 2016 report by the Office of the Assistant Secretary for Planning and Evaluation at the U.S. Department of Health and Human Services assessed 1,328 approved branded drugs and found that 10 percent were no longer subject to patents or other forms of market exclusivity, but still had not attracted drug companies to come forward and submit ANDAs.³⁵ There is a higher incidence of insufficient generic competition for orphan-designated drugs with small patient populations.³⁶

Figure 5: Number of ANDAs submitted per year

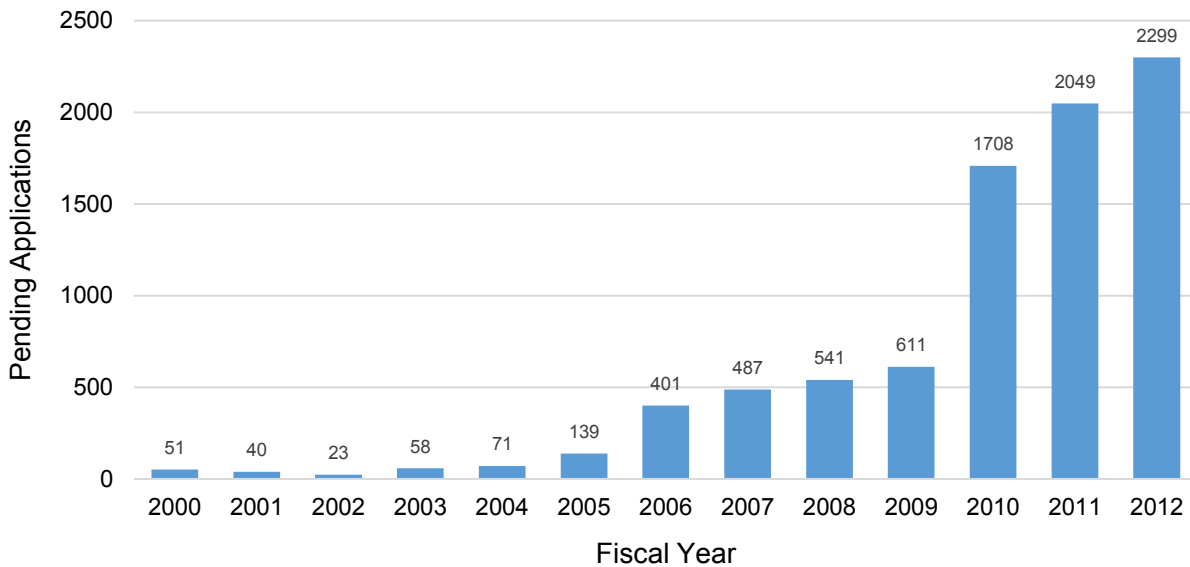


Source: Woodcock (2016). Woodcock, Janet. Statement to the House, Committee on Oversight and Government Reform. Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA), Hearing, Feb 4, 2016. Available at: <https://www.fda.gov/NewsEvents/Testimony/ucm485057.htm>

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A recent backlog at the FDA has also contributed. A sharp increase of the number of ANDAs since 2005 (Figure 5) and limited funding for Office of Generic Drugs resulted in delays in review. By 2012, that backlog reached 2,299 ANDAs and 1,873 prior approval supplements (Figure 6). Delays in getting ANDAs approved deterred new market entrants that might have otherwise responded to higher prices and increased supply.

Figure 6: ANDAs pending over 180 days



Source: Woodcock (2016). Woodcock, Janet. Statement to the House, Committee on Oversight and Government Reform. Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA), Hearing, Feb 4, 2016. Available at: <https://www.fda.gov/NewsEvents/Testimony/ucm485057.htm>

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Rising challenges in maintaining sufficient quality in the supply of older generics has also been a factor. This is particularly true for sterile injectable drugs. In 2009 and 2010, 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 inspections and uptick in the number of noncompliance letters issued over those two years. The change was necessary and there are signs that the industry has adapted to these changes, but it led to a reduction of the number of suppliers of sterile injectable drugs in 2012.³⁷ Higher manufacturing standards and an increased emphasis on quality may be one reason why the estimated cost of a successful ANDA has increased from \$1-2 million in 2005 to as high as \$15 million in 2015.³⁸

Another factor that has made the generic drug market less predictable is the growth of complex generic drugs. Complex generic drugs are more intricate in formulation or delivery than simple, small-molecule pills, but not quite as complex as protein-based medicines.³⁹ These are drugs in which national regulatory authorities may be reluctant to rely on bioequivalence alone. Complex generics can include narrow therapeutic index drugs, controlled release and modified release formulations, skin patches, inhalers and multi-ingredient products.⁴⁰ Non-biological complex drugs (NBCDs) are made up of a complex of closely related structures that cannot be isolated and fully characterized by chemical analytical means, and depend on consistent, tightly controlled manufacturing to produce. Examples of NBCDs include iron-carbohydrate complexes, liposomes, and nano-medicines.⁴¹

Complex generics can be more difficult to produce and require greater testing to demonstrate bioequivalence. In some cases, brand-name companies have put barriers to approving complex generics in place by filing Citizens Petitions that argue that the generics are not comparable or by refusing to supply product for bioequivalence testing.⁴² 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. Scott Gottlieb, President Trump's nominee to lead the FDA, has cited the epinephrine autoinjector and enoxaparin as examples of complex generics as part of his contention that new regulatory guidance or pathways may be needed to facilitate approval of such ANDAs.⁴³

II. EXISTING AND PROPOSED REFORMS FOR GENERIC DRUG MARKET FAILURES

The FDA has undertaken a series of useful measures to address the market failures in the U.S. generic drug market. These measures began with the passage of the Generic Drug User Fee Amendments (GDUFA) of 2012, which became effective as of October 1, 2014. This legislation, modeled on the user fee model for new drug applications, provides guarantees of more timely review of ANDAs in exchange for user fees paid by the ANDA applicants that will help FDA fulfill those commitments. Under GDUFA, the FDA committed to take regulatory action on 90 percent of new ANDAs within 10 months of submission and to hire and train more than 1,000 new generic drug reviewers by 2017.⁴⁴ 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.⁴⁵ This guidance on prioritization has recently been updated to include “‘first generics’ for which there is no generic approved; ‘sole-source’ drug products for which there is only one approved generic product marketed; and drugs that are in shortage, among others.”⁴⁶ In July 2016, the FDA announced it had already met its goals under GDUFA and approved 630 generics in FY 2016, a new record for ANDA approvals that included 73 first generic drugs.⁴⁷

This is substantial progress. Still, in September 2016, a Congressional oversight hearing noted that more than 4000 generic drug applications were awaiting approval and the median time required for the FDA to approve ANDAs was 47 months.⁴⁸ The FDA pointed out that only 2,200 of these ANDA applications are with FDA reviewers, while the remainder are technically pending but need to be resubmitted by the manufacturer to respond to FDA concerns.⁴⁹ ANDA backlogs are also not the only reasons for lack of competition in U.S. generics, which also include lack of sufficient financial interests to invest in entering or expanding production for smaller-market, older generic drugs.

There have been many other reforms proposed to address recent shortages and price hikes for U.S. generic medicines. Most have substantial shortcomings or are likely to address only a portion of the problem. Senator Tom Cotton (R-AR), for example, has proposed the use of Priority Review Vouchers (PRVs) to encourage more generic drugs.⁵⁰ PRVs were first established in 2007 to apply to neglected tropical diseases (NTDs) and offer faster regulatory review to manufacturers that successfully register a qualifying medicine. That voucher may be sold and the returns from that sale are meant to incentivize and fund drug development. Under Cotton's legislation, the first and second generic versions of all drugs would receive expedited review plus a PRV. However, PRVs have already raised efficiency and safety concerns as currently applied to review of new drug applications.⁵¹ Better ideas include proposals: to waive ANDA fees for first generics;⁵² for government purchasers to enter into long-term generic drug purchasing contracts, such as is done for childhood vaccines;⁵³ to accelerate review of generic drug manufacturers with impeccable manufacturing quality records;⁵⁴ and to encourage pharmacists to substitute clinically similar drugs within the same therapeutic class in carefully selected circumstances in which evidence exists that substitution is possible.⁵⁵

Former Deputy FDA Commissioner Joshua Sharfstein and his coauthors have also called for the FDA to allow temporary importation of generic drugs approved in other stringently regulated markets in the case of a spike in the prices of the U.S. versions of those generic drugs.⁵⁶ The idea of expanding international competition to address price spikes in generic drugs is an excellent one. The authors proposed making importation a temporary measure, reflecting their concern that importation measures might cut the FDA out of generic drug regulation. That worry is understandable, but restricting this mechanism to temporary importation is likely to discourage foreign firms from incurring the fixed costs of expanding manufacturing to serve the U.S. market. Tying the mechanism to price hikes may also be gamed by incumbents who fluctuate their prices in order to avoid triggering the mechanism.

III. A THREE-PART STRATEGY FOR PROGRESS

The proposal outlined here has multiple aims. First and foremost, it is intended to provide a mechanism for sustainably reducing U.S. generic drug costs and improving patients' access to safe and essential medicines. 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. Our strategies should not require major legislative changes to the FDA's current authorities and are designed not to undercut the Agency's essential role in ensuring the quality, safety, and efficacy of the medicines used in the United States.

Our proposal has three parts: (1) reauthorizing GDUFA (GDUFA II); (2) establishing a single window pathway for approving generic medicines for use in multiple countries; and (3) creating a pathway for reciprocal approval of generic drugs. We explain the rationale for each component of our strategy as well as the precedents and existing infrastructure to support it. In subsequent sections of this paper, we conduct an analysis of the potential utility of our three-part strategy for U.S. drugs currently eligible for generic competition and lacking sufficient competition to achieve low prices. We use that analysis as basis for a discussion of the broader benefits and risks of our proposals.

Prong I: GDUFA II reauthorization

Passing the Generic Drug User Fee Act Reauthorization (GDUFA II), pending before Congress, is essential to increasing U.S. patients' access to low-cost, safe, and affordable drugs. The fees would generate the resources that the FDA needs to accelerate its progress in reducing the ANDA backlog. It would enable the FDA to partially address the challenge of complex generics. The FDA has credibly argued that GDUFA II resources would allow them to meet more often with makers of these complex generics to provide guidance on technical and regulatory questions.⁵⁷ The current GDUFA II bill includes increased resources for supporting the review and quality of ANDAs for complex generics.⁵⁸ The FDA should also commit to broadening its policy on granting expedited regulatory review to ANDAs for drugs for which three or fewer manufacturers are actively serving the U.S. market. The highest priority should still be given to applications to market a drug for which there is currently only one manufacturer. GDUFA reauthorization could also be used to establish fees for the use of the streamlined international regulatory pathways outlined below.

Prong II: Single window multi-country generic drug application pathway

The FDA should work with other stringent national regulatory authorities to establish a single electronic window for applications for approval of generic medicine. This pathway would have a single application that could be simultaneously submitted to all participating national regulatory authorities. The benefit of this pathway is that it would make it easier, faster, and cheaper for generic drug manufacturers to file ANDAs to serve U.S. patients. The single window application would reduce the transaction costs involved with filing separate applications with each of the participating regulatory authorities. The ability to reach a potentially larger market in multiple countries with lower costs should increase the number of generic entrants and expedite applications.⁵⁹

More generic entrants and more competition should reduce the risk of price hikes and shortages. This single window pathway would not, however, eliminate the FDA's separate assessment of these ANDAs. The application would be the same and made simultaneously to all participating national regulatory authorities, but each of those authorities would retain the ability to review and grant approval for their marketplaces.

The single window can also be designed to include a fee-sharing arrangement and be voluntary, preserving the ability of manufacturers to apply directly to a particular national regulatory authority. The pathway could be initially limited to the United States, Canada (HealthCanada), and the European Union (the European Medicines Agency [EMA]), but over time be expanded to the United Kingdom (Medicines and Healthcare products Regulatory Agency [MHRA]), Australia (Therapeutic Goods Administration [TGA]), New Zealand

(New Zealand Medicines and Medical Devices Safety Authority [Medsafe]), Japan (Pharmaceuticals and Medical Devices Agency [PMDA]), and other well-respected regulatory authorities.

This single window would build on existing infrastructure. As part of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (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.⁶⁰ These forms and guidelines are the foundation for any international cooperation on drug approval.

Studies that have assessed generic drug regulation in the United States, the European Union, Canada, Australia, and Japan have found that there are many more similarities than differences in their requirements.⁶¹ The standards for bioequivalence and study design are largely the same across these countries. There are, however, some differences that exist in the requirements for more narrow therapeutic index and highly variable drugs. These requirements are the subject of current international harmonization efforts, but can be excluded if necessary from the single window pathway until those harmonization efforts are complete.⁶² One potential hurdle is the requirement in some nations that the reference drug used to establish bioequivalence is from a domestic manufacturer.⁶³ A single window application pathway would not depend on eliminating that requirement. 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.

One example of international cooperation is the recently concluded U.S.-Canada Common Electronic Submissions Gateway Project (CESG).⁶⁴ This project established a single window by which manufacturers may simultaneously submit an electronic common technical document application (an e-CTD) for approval of a new drug to Canada and the United States. Establishing this pathway did not require new legislative authority for the FDA, but it did necessitate the United States and Canada to enter into agreements to support joint development of the web-based gateway and its ongoing funding (done through a Cooperative Research and Development Agreement). Bilateral working groups were established to develop the co-management and ownership of the gateway. A bilateral maintenance organization was established to monitor the gateway, ensure the consistent use of terminology, and resolve questions as they arise. The gateway goes into effect in the United States on May 5, 2017, but is already in use in Canada.⁶⁵ HealthCanada reports that 86 percent of its e-CTDs are already using that single pathway.

It is not hard to imagine expanding this single window to the EMA. The EU already has a centralized procedure for its member states, which has several attractive elements that should be considered in the future development of single window for multi-country generic drug approval. It is designed to enable national regulators in the EU to work together on applications, with the intention of pooling scarce resources and achieving a common decision. It did not usurp the ability of participating regulatory authorities around Europe to make the final decision to approve a medicine for use. The centralized procedure also evolved fairly quickly, from a pilot in 1987 to full use by 1993. It has also been scalable, expanding over time well beyond its initial remit (limited to biotechnology products). Finally, the centralized procedure has been popular, with most applicants now voluntarily using the pathway instead of seeking approval in individual member states.⁶⁶

Prong III: Reciprocal drug approval pathway

There is nothing new about the use of imported pharmaceuticals in the United States. The United States is already the world's largest importer of pharmaceuticals. With \$86 billion in imports in 2015, imports represented roughly a quarter of the U.S. pharmaceutical market.⁶⁷ The FDA estimates that 80 percent of the active pharmaceutical ingredients and 40 percent of the finished drugs used in the United States are imported from other countries.⁶⁸ Imported generic medicines, however, are subject to the same FDA regulatory approval processes irrespective of whether those drugs have been approved for use by other stringent national regulatory authorities.

The FDA should also establish a pathway for granting reciprocal drug approval to approved generic versions of U.S. medications without patent protection or other forms of exclusivity, but lacking insufficient generic competition. Reciprocity is a mechanism by which one national regulatory authority approves the use of a medicine based on the approval of that medicine by another national regulatory authority. Although the mechanism is generally called reciprocal drug approval, the term "reciprocal" can be a misnomer as it is sometimes used to refer to a situation where one national regulatory authority relies upon the approvals of another authority, but that second regulatory does not return the favor by relying on approvals made by the first authority. We propose that drugs lacking sufficient generic competition be defined as generic-eligible medicines if they have fewer than four approved versions being manufactured and sold within the prior six months in the United States. Current models suggest that at least four generic competitors are required before substantial price reductions occur.⁶⁹

The benefit of this pathway is that it introduces the possibility of international competition for U.S. generic drugs that are at risk for shortages or dramatic price hikes. It is easier for the existing manufacturers of an already-approved drug to expand their production to serve the U.S. market than it would be for a new entrant to 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 avoids 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. It also makes it harder for manufacturers to use the reciprocal drug approval pathway to circumvent the FDA since it will be impractical to wait for episodes of insufficient generic competition to occur before marketing a drug.

The FDA should limit the use of reciprocal approval for generic drugs to countries with stringent national regulatory authorities and strong safety records (i.e., HealthCanada, EMA, MHRA, TGA, PMDA), as determined through an 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 reciprocal generic drug approval pathway to countries that satisfy these reasonable, science-based minimum standards is consistent with requirements of the World Trade Organization agreements. Once those minimum standards for equivalence are laid out, the FDA may assess and enter into bilateral agreements with regulators meeting those minimum standards, which can be done as simple memoranda of understanding. Those agreements should establish common technical implementation procedures and identify any non-equivalent aspects of the generic drug approval process that the FDA may still need to do.

This reciprocal drug approval pathway may also be designed in a manner that preserves the FDA's role in generic drug approval. For instance, the FDA may wish to reserve the right to require different labeling to match labeling of the brand-name version in the United States, which may have different wording of warnings than the label of the same brand-name drug in the reciprocal country.⁷⁰ Once finalized, the FDA must still be able to refuse to grant reciprocity on an ANDA, but should be required to issue a detailed opinion explaining its rationale. That decision should be appealable to the FDA Commissioner. In the near-term, the reciprocal approval pathway should exclude complex generics so trust in the mechanism can be built before expanding 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 aspects of the drug approval process.

The approach outlined here for establishing a reciprocal generic drug approval pathway is based on the successful model of the International Civil Aviation Organization. That entity established a broad framework for assessing regulatory equivalence under the Chicago Convention on International Civil Aviation in 1944.⁷¹ The establishment of deeper arrangements for mutual acceptance of civil aviation regulatory certifications has occurred in bilateral arrangements that are concluded through processes similar to those proposed here.⁷² The benefit of this approach is that it has been proven to work in other areas, greatly facilitating international air travel and safety. It is also designed to ensure and preserve the role of the national regulatory authority to fulfill their domestic mandate to their constituents.

With the same goal in mind, we also suggest that the fee structure should be designed so that applicants are incentivized to use the single window pathway for their ANDAs whenever possible. Otherwise, there is a risk that those applicants may wait for eligibility under the reciprocal approval pathway rather than proceeding through the single window. At the same time, the option of a reciprocal drug approval should be maintained to address circumstances when manufacturers discontinue making an older generic medication and new international sources for that drug are needed.

This proposed reciprocal drug approval pathway builds on existing infrastructure and legislative authority. The 2012 FDA Safety and Innovation Act gave the FDA authority to enter into agreements to recognize drug inspections conducted by foreign regulatory authorities if the FDA determined those authorities are capable of conducting inspections that met U.S. requirements.⁷³ Pursuant to that authority, the FDA and EMA concluded an agreement on mutual recognition of inspection reports, which was added as an amendment to the existing 1998 US-EU Mutual Recognition Agreement.⁷⁴

The United States already participates in the International Generic Drug Regulators Pilot, along with the EU, Japan, China, Mexico and Brazil.⁷⁵ Launched in 2015, 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.⁷⁶ The pilot is also tasked with creating a platform and database to promote deeper regulatory cooperation on generic drug approvals in the future.⁷⁷ There are successful examples of reciprocal drug approval. The EU, for example, also offers a decentralized market procedure. In this decentralized procedure, the product sponsor submits its application to a reference member state, which assess that application and shares its report, summary of product characteristics, approved labeling and package leaflet, which other concerned EU member states

may approve. The decentralized procedure is the pathway through which most generics are approved in EU.⁷⁸

In 2011, COFEPRIS, Mexico's drug regulatory agency, faced a backlog of 8,000 drug applications, mostly for generics. This backlog prompted COFEPRIS to adopt broad reforms, including establishing a mechanism for reciprocal drug approval.⁷⁹ In Mexico's version, the product sponsor for a drug approved and actively manufactured in another country must only produce a free sale certificate, proof of drug authorization, and written evidence of compliance with good manufacturing standards from the appropriate health authority in country of product origin.⁸⁰ On that basis, Mexico may approve the use of that drug. Any new indications, dosages, or combinations of that drug may be approved through the same abbreviated procedure. Mexico also relaxed and simplified its import restrictions and cut its generic drug approval times from 360 to 60 days. COFEPRIS estimates that it has achieved a 90 percent reduction in its regulatory approval costs, increased its number of approved generics, lowered pharmacy costs, and increased the share of generics in the country's market.⁸¹ In 2012, the World Health Organization (WHO) recognized COFEPRIS as a regional reference regulatory agency, competent and efficient enough in the performance of the WHO-recommended health regulation functions to guarantee the safety, efficacy, and quality of medicines.⁸²

IV. AN EMPIRICAL APPLICATION OF THE SINGLE WINDOW AND RECIPROCAL GENERIC APPROVAL PATHWAYS

To determine the potential application of the proposed single window and reciprocal generic approval pathways, we examined U.S. drugs that lack adequate generic competition and assessed their availability in other countries with stringent national regulatory authorities. We did so in two steps.

First, we leveraged and updated the recent analysis of U.S. generic drug competition in Gupta et al. (2016).⁸³ Gupta et al. used the Drugs@FDA database to determine the number of novel therapeutics approved in tablet or capsule formulation since the Hatch-Waxman Act, a period that extended from September 30, 1984 to January 11, 2016. That assessment excluded combinations with non-novel therapeutics and drugs ineligible for generic competition. We updated the results in Gupta et al. to reflect subsequent generic entrants for those drugs through March 10, 2017. Those updated results show that 69 out of the 210 (33 percent) of the drugs approved over that study period met the eligibility requirements and had fewer than four approved generics in the United States. Thirty-five of these eligible drugs (17 percent of the total approved) have no generic versions. The remaining 34 eligible drugs (16 percent of the total) each have between one and three generic versions.

Second, we looked for the 69 drugs with insufficient generic competition in US in the comparable databases for the EMA, HealthCanada, PMDA, TGA, Medsafe, Cofepris, Swissmedic (Switzerland), Medicines Control Council (South Africa), and the Israel Health Ministry. These regulatory authorities were chosen using two criteria: (a) they were included on a list of nations identified as high-quality regulatory authorities in a recent U.S. bill that proposed to create a system of international drug reciprocity,⁸⁴ and (b) the regulators had publicly accessible English-language drug approval databases.

Third, we examined Medicare Part D spending for the drugs with insufficient U.S. generic competition made by at least one different manufacturer approved by other stringent regulatory authorities. This analysis was conducted using the Centers for Medicare and Medicaid Services (CMS) drug spending database for Medicare Part D.⁸⁵

Table 1: Potential sources of international generic competition for non-patent protected prescription drugs in the United States

Category	Number of drugs	0 generic competitors	1 generic competitor	2 generic competitors	3 generic competitors
U.S. drugs with insufficient generic competition	69*	35	13	7	14
U.S. generic drugs with insufficient competition made by at least one different manufacturer approved outside the U.S.**	44	18	10	5	11
<i>EMA or Health Canada</i>	22	7	5	4	6
<i>Other regulators</i>	37	17	7	3	10
Could reach sufficient competition (defined as 4 or more different manufacturers) with foreign regulator-approved sources of that drug**	23	6	2	4	11
<i>EMA or HealthCanada</i>	11	3	0	2	6
<i>Other regulators</i>	15	3	0	2	10

* Note: 8 of the 77 drugs identified in Gupta et al. as having insufficient generic competition have 4 or more generic competitors as of 3/10/17

** The columns or rows might not add up due to overlap in the generic manufacturers in these market

Source: Centers for Medicare and Medicaid Services. "2015 Medicare Drug Spending Data." <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/2015MedicareData.html>.

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As seen in Table 1, our results show that 44 of the 69 drugs (64%) without adequate U.S. generic competition had versions of that drug with the same dosage and route of administration made by at least one different manufacturer in one or more of these other markets. We break those results down further by the number of U.S. generic competitors. For example, Table 1 indicates that 10 of the drugs that have only one U.S. generic competitor each have at least one different manufacturer for the same version of that drug approved outside of the United States. The results in Table 1 also show the number of drugs made by a different manufacturer approved in EU and Canada versus the other countries assessed. In addition, Table 1 shows how many of these 69 U.S. drugs had a sufficient number of manufacturers in other markets to potentially reach our threshold of adequate generic competition (four or more generics). Those results are listed separately for EMA/HealthCanada and other regulators assessed.

Table 2 shows the median amount that Medicare Part D program spent in 2015 for the 44 drugs with insufficient U.S. generic drug competition. The column marked "all studied drugs," indicates both the median amount spent per drug, and in parentheses, the total amount spent for all the drugs in that category. For example, Medicare Part D spent a median of \$8.6 million for the 44 drugs with insufficient

U.S. generic competition in 2015 and approximately \$2.4 billion total on these drugs that same year. Those results are broken down to show the distribution of these costs for the different categories of drugs with insufficient U.S. generic competition. For example, Medicare Part D spent a median of \$5.7 million per drug without a U.S. generic competitor and approximately \$1.6 billion total. The results in Table 2 also show the amount that Medicare Part D spent on drugs that have versions made by a different manufacturer approved in the EU and Canada and in the other countries assessed. Finally, Table 2 shows the amount that Medicare Part D spent in 2015 for the drugs that had a sufficient number of manufacturers approved in other markets to potentially reach our threshold of adequate generic competition (four or more generics). Those results are listed separately for EMA/HealthCanada and other regulators assessed.

Table 2: Aggregate spending in Medicare Part D program on drugs with insufficient U.S. generic competition in 2015 (in thousands)

Median amount per drug	All studied	0 generic competitors	1 generic competitor	2 generic competitors	3 generic competitors
U.S. generic drugs with insufficient competition made by at least one different manufacturer approved outside the USA*	\$8,593 (\$2,386,756)	\$5,711 (\$1,625,872)	\$11,562 (\$107,346)	\$9,164 (\$312,322)	\$7,302 (\$441,215)
<i>EMA or Health Canada</i>	\$7,948 (\$914,887)	\$4,268 (\$177,725)	\$8,593 (\$43,542)	\$9,237 (\$309,533)	\$17,663 (\$384,086)
<i>Other regulators</i>	\$4,426 (\$1,975,700)	\$4,989 (\$1,460,406)	\$4,493 (\$68,664)	\$2,789 (\$12,717)	\$13,725 (\$433,912)
U.S. generic drugs with insufficient competition made by at least one different manufacturer approved outside the U.S.**	\$7,302 (\$1,876,708)	\$87,803 (\$1,408,606)	\$2,430 (\$4,860)	\$5,976 (\$22,028)	\$7,302 (\$441,215)
<i>EMA or Health Canada</i>	\$9,237 (\$568,087)	\$82,763 (\$165,526)	0	\$9,237 (\$18,474)	\$17,663 (\$384,086)
<i>Other regulators</i>	\$7,249 (\$1,680,545)	\$621,540 (\$1,243,079)	0	\$1,777 (\$3,554)	\$13,725 (\$433,912)

* The columns or rows might not add up due to overlap in the generic manufacturers in these markets
 ** Note: 4 drugs of the original 44 do not have spending information available from Medicaid Part D database

Source: Centers for Medicare and Medicaid Services. "2015 Medicare Drug Spending Data." <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/2015MedicareData.html>

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Our analysis has several limitations. Our analysis of the number of drugs that would potentially benefit from the proposed pathways is conservative, since we limited our assessment to the subset of therapeutics that were novel and approved in tablet or capsule formulation since the Hatch-Waxman Act. However, our assessment of the amount that Medicare Part D spent in 2015 on these drugs with insufficient generic competition may be overstated. The CMS drug spending dashboard does not disaggregate its spending on different versions of a medication. It is, thus, possible that some of the Medicare Part D spending was devoted to dosage or routes of administration for a drug that have generic competition. This proportion of that spending is likely small as most of the 44 drugs with insufficient U.S. generic competition had other dosages or routes of administration approved by the FDA. The Medicare Part D figures included do not include the amounts spent on these 44 drugs by other U.S. federal and state health programs such as Medicare Part B or Medicaid; insurers; or out of pocket by patients.

This analysis shows that international sources of approved generic drugs could improve the supply and increase the competition for a meaningful number of generic drugs. First, this is particularly true for drugs that have no generic version or only one generic version approved in the United States. Second, the potential contribution of international sources of generic drugs rises with the number of regulators eligible to participate in the reciprocal drug approval mechanism. Restricting the use of that mechanism to EMA and HealthCanada meaningfully reduces, but does not eliminate, the potential benefits of having reciprocal drug approval. Third, international reciprocal drug approval may not be sufficient, when used on its own, to address the shortages and price hikes that might arise with many generic drugs. This suggests the need for a multifaceted approach that addresses the domestic causes of generic drug market failures, while also introducing new sources of international competition. This multifaceted approach cannot succeed without increasing the resources and capacity of the FDA.

V. A BENEFIT-RISK ASSESSMENT

A. The potential benefits of the strategy proposed

U.S. patients would meaningfully benefit from the three-pronged strategy proposed in this paper. The single window pathway should encourage more ANDAs sooner for generic-eligible medicines. The reciprocal drug approval pathway would substantially reduce the incremental cost and time required to gain approval to market a generic drug in the US if that drug is already being sold in another advanced health care system. The combination of these approaches should increase the supply and level of competition for generic medicines in the United States. For patients who rely on generic medicines, this would be a welcome result. The potential benefits that come with greater access to international sources of safe generic drugs is also likely to increase in the future. Many developed countries, including those in the EU and Canada, are using more generics and adopting reforms to further encourage their use and lower their prices. IMS Health estimates that generic medicines will account for 31 percent of drug spending in the non-US developed market, up from 29 percent in 2016 and 28 percent in 2011.⁸⁶

The multi-pronged pathway proposed here also reduces the safety risks that might otherwise arise with reciprocal drug approval by limiting its use to generics and maintaining the role of the FDA. Expanding the use of international reciprocal drug approval to drugs that the FDA has never assessed is risky for patients and likely to be politically unsustainable. It is not uncommon that adverse events, sometime serious ones, arise that could be temporally connected to the use of a drug. In that circumstance, it is difficult to imagine that the press and Congressional overseers would accept the justification that regulators in Europe and Canada had assessed the use of the product. The risks of the strategy proposed here are much reduced by limiting its application to generic versions of drugs already approved by the FDA and used by U.S. patients. Fundamentally, the strategy proposed here involves much less complicated bioequivalence determinations and not essential benefit/risk determinations involved in assessing a novel drug. This strategy further reduces those risks by preserving the FDA's ability to refuse reciprocity on a case-by-case basis and to require changes in labeling.

The dual pathway approach proposed here also introduces potential international generic competition in U.S. market without spurring a regulatory race to the bottom or undermining the long-term role and viability of the FDA Office of Generic Drugs. The differentiated fee structure means there is lower cost to using the

single window pathway, rather than the reciprocal pathway, for drugs that become eligible for generic competition after that single window pathway has been established.

The strategy suggested here should not require significant legislative changes to implement. 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 be able to approve an ANDA based on data already collected and assessed by the regulatory authority in another advanced country, if the FDA has determined that that assessment is equivalent and that enforces standards for good manufacturing practices as high as its own.⁸⁷ The FDA also already permits the temporary importation of unapproved drugs that have been approved in foreign jurisdictions when necessary to alleviate a drug shortage, after ensuring that the drug is of adequate quality.⁸⁸ Further, it is already FDA policy to prioritize applications for single-source generic drugs that “could help mitigate or resolve a drug shortage and prevent future shortages.” The FDA should recognize that addressing inadequate competition is also a means to “prevent future shortages.”⁸⁹ Removing the temporary restriction on importation and lowering the cost of applying for generic drug approval in multiple country markets would help achieve the objective more sustainably.

The U.S. Food Modernization Act of 1997 added international harmonization to the FDA mandate and enhanced its authority to enter into mutual recognition agreements with other nations. Those harmonization activities are subject to same administrative legal framework as other parts of the FDA mandate. The FDA typically uses executive agreements, not treaties, to enter into commitments with its foreign counterparts. 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. The FDA has entered into binding memoranda of understanding with counterpart regulatory agencies including a 1998 mutual recognition agreement with EU, recently amended to add inspections.⁹⁰ Neither of the pathways we propose here would eliminate the FDA or its decision-making in generic drug approval and so should not run afoul of the U.S. Constitution’s Article I doctrine of nondelegation.⁹¹

The strategy proposed here might also assist the FDA in complying with the requirements of President Trump’s recent Presidential Executive Order on Reducing Regulation and Controlling Regulatory Costs without having to eliminate necessary regulations.⁹² This executive order requires the FDA and other U.S. regulatory agencies to eliminate two existing regulations for each new regulation adopted. The executive order also requires that the costs of each new regulation must be offset by the elimination of costs associated with at least two existing regulations. The order, however, also charges the Director of the U.S. Office of Management and Budget with providing guidance to agencies on how to implement the executive order. Reportedly, OMB may allow regulatory agencies to count savings achieved through regulatory cooperation to the requirements under the executive order. If so, there are substantial potential “regulatory savings” to be gained from the strategy proposed here. The GAO estimated that the EU centralized procedure saved 40 percent of costs versus separate marketing approval applications.⁹³ COFEPRIS estimated a 90 percent reduction in generic drug regulatory approval costs from adopting its reciprocal pathway.⁹⁴

Another potential benefit of the strategy advocated here is that it may be able to attract broad-based political support. The U.S. generic drug industry has expressed support for a single development pathway

that resembles the single window proposed here.⁹⁵ The current president campaigned on reducing U.S. drug prices, at one point saying “[a]llowing consumers access to imported, safe and dependable drugs from overseas will bring more options to consumers.”⁹⁶ Though it remains unclear what his envisioned mechanism would be for implementing this proposal, the concept of re-importation has been proposed before and rejected in Democratic and Republican administrations alike. Scott Gottlieb wrote last year that a reasonable version of Trump’s re-importation proposal would involve “foreign-approved versions of medicines already sold in the [United States].”⁹⁷ He also wrote that any strategy for reducing drug prices should begin with “reforming the market for generic drugs” so that “[s]peculators shouldn’t be able to take advantage of consumers by securing monopolies on old drugs where legitimate patents have long lapsed, and then inappropriately jacking up the prices.”⁹⁸

C. The potential risks of the strategy proposed

There remain risks and shortcomings to the strategy proposed in this paper. First, the prices of generic drugs tend to be higher in other developed country markets than in United States. Generic markets in other high-income countries are not as pharmacy-driven as in the United States, but rather physician-driven and subject to quirks of national price controls.⁹⁹ This difference has historically meant less competition on price and greater purchasing of higher-priced, branded generics and a lower market share for generics overall (conversely, brand-name drugs are substantially less expensive outside the United States).¹⁰⁰ There are signs that these practices are changing, especially in the EU and Canada,¹⁰¹ but generic drug prices still vary widely across EU countries.¹⁰² This fact suggests that international reciprocal drug approval is likely to be most useful for U.S. drugs with few competitors and high prices.

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 as a result of greater economies of scale and more ability to operate across markets. That may lead to increased efficiencies and lower costs; it might also lead to fewer suppliers over the long run that are willing to manufacture mature generics for small patient populations. Adoption of the strategies proposed here would need to come with careful continued oversight to recognize and respond to any unintended market effects.

Third, this proposal puts greater demands on the already scarce resources at the FDA. Negotiating and maintaining international arrangements requires dedicated staff and funding. Increasing the number of applications may only add to the ANDA backlog that already exists at the FDA. The agency 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. In turn, it also necessitates that the FDA enter into robust work-sharing arrangements with participating regulators, including mutual recognition of inspection reports.¹⁰³

CONCLUSION

The critically important role that generics 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 assure sufficient supplies and reasonable prices. The three-pronged strategy outlined here can restore the balance required to maximize competition, normalize prices, and put those who improperly thrive on market failures out of business to the ultimate benefit of the patients who depend on life-saving generic drugs.

ENDNOTES

- 1 Morgenson, Gretchen. 16 Apr 2017. "Same Pills, Higher Cost." *New York Times*, BU1.
- 2 Government Accountability Office. 2012. "Drug pricing: research on savings from generic drug use." <http://www.gao.gov/assets/590/588064.pdf>. (Jan 2012).
- 3 Generic Pharmaceutical Association. 2016. "Generic Drugs Continue to Deliver Billions in Savings to the U.S. Healthcare System, New Report Finds"; *PR Newswire*. <http://www.prnewswire.com/news-releases/generic-drugs-continue-to-deliver-billions-in-savings-to-the-us-healthcare-system-new-report-finds-300347698.html>.
- 4 Uhl, Kathleen. 2016. "A Record-setting Year for Generic Drugs." *FDA Blog*. <https://blogs.fda.gov/fdavoices/index.php/2017/02/2016-a-record-setting-year-for-generic-drugs/>; QuintilesIMS Institute. Outlook for Global Medicines through 2021 (IMS Health, 2016).
- 5 Shrank, WH et al. 2006. "The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions." *Archives of Internal Medicine*. 166(3): 332-7; JJ Gagne, et al. 2014. "Comparative effectiveness of generic and brand-name statins on patient outcomes." *Annals of Internal Medicine* 161: 400-407.
- 6 Spatz, ID. 2010. "Health reform accelerates changes in the pharmaceutical industry." *Health Affairs* 29(7): 1331-6.
- 7 The White House, Office of the Press Secretary. "Remarks by President Trump in Joint Address to Congress, U.S. Capitol, Washington DC." February 28, 2017. <https://www.whitehouse.gov/the-press-office/2017/02/28/remarks-president-trump-joint-address-congress>.
- 8 Danzon, PM and EL Keuffel. 2014. "Regulation of Pharmaceutical-Biotechnology" in *Economic Regulation and Its Reform: What Have We Learned?* ed. Nancy L. Rose. (Washington, D.C.: National Bureau of Economic Research Conference Report, 2014), 407-484.
- 9 Christopher Stomberg. 2014. "Drug Shortages, Pricing, and Regulatory Activity." NBER Working Paper No. 22912. <http://www.nber.org/papers/w22912>.
- 10 Danzon and Keuffel (2014). See n. 8.
- 11 Thayer, Ann M. 2014. "30 Years Of Generics: The door that legislation unlocked for generic drugs three decades ago has blown wide open." *Chemical & Engineering News* 92 (39): 8-16. (citing IMS Health Data).
- 12 QuintilesIMS Institute (2016). See n. 4.
- 13 U.S. Food and Drug Administration. 2005. "FDA analysis of retail sales data from IMS Health, IMS National Sales Perspective, 1999-2004." <https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm129385.htm>.

- 14 Danzon and Keuffel (2014). See n. 8.
- 15 Refen, D and MR Ward. 2005. "Generic Drug Industry Dynamics." *Review of Economics and Statistics* 87(1): 37-49.
- 16 Stomberg. 2014. See n. 9.
- 17 Wiske, CP, OA Ogbechie, and KA Schulman. 2015. "Options to Promote Competitive Generics Markets in the United States." *JAMA* 314(20):2129-30.
- 18 Stomberg (2014). See n. 9.
- 19 Stomberg (2014). See n. 9.
- 20 Government Accountability Office. 2016. "Part D Generic Drug Prices Declined Overall But Some Had Extraordinary Price Increases." GAO-16-706.
- 21 "Discontinuance or interruption in the production of life-saving drugs." 21 U.S. Code § 356c.
- 22 Government Accountability Office. 2014. "Drug shortages: public health threat continues, despite efforts to help ensure product availability." GAO-14-194.
- 23 Le, P. 2011. "The prevalence of pharmaceutical shortages in the United States." *Journal of Generic Medicines* 8(4): 210-8.
- 24 Woodcock, J. and M. Wosinska. 2013. "Economic and Technological Drivers of Generic Sterile Injectable Shortages." *Nature* 98(2): 170-176.
- 25 Davies, BJ, TJ Hwang, and AS Kesselheim. 2017. "Ensuring Access to Injectable Generic Drugs — The Case of Intravesical BCG for Bladder Cancer." *N Engl J Med* 376: 1301-03
- 26 Stomberg (2014). See n. 9.
- 27 "Executive Order 13588 - Reducing Prescription Drug Shortages." October 31, 2011.
<https://obamawhitehouse.archives.gov/the-press-office/2011/10/31/executive-order-13588-reducing-prescription-drug-shortages>; "Food and Drug Administration Safety and Innovation Act," 21 U.S.C. 356(c).
- 28 Government Accountability Office (2016). See n. 20.
- 29 Pollack, Andrew. 2015. "Drug Goes From \$13.50 a Tablet to \$750, Overnight." *New York Times*. Sept. 20, 2015.
https://www.nytimes.com/2015/09/21/business/a-huge-overnight-increase-in-a-drugs-price-raises-protests.html?_r=1.
- 30 Pollack, Andrew. 2015. "Once a Neglected Treatment, Now an Expensive specialty Drug." *New York Times*. Sept. 21, 2015. B1.
- 31 Kesselheim, AS and DH Solomon. 2010. "Incentives for Drug Development — The Curious Case of Colchicine." *N Engl J Med* 362: 2045-2047.

- 32 Colliver, V. 2014. "Prices soar for some generic drugs." *SF Chronicle*. Jan 1 2014.
- 33 Comanor, W.S. and D.L. Moss. 2016. "Re: Review of the Teva-Allergan Merger." American Antitrust Institute. http://www.antitrustinstitute.org/sites/default/files/AAI_Teva-Allergan%20Ltr%20to%20FTC.pdf
- 34 Kumar, S. 2015. "Teva buys Allergan: 3 reasons why it's a blockbuster deal." *Forbes Magazine*. July 27, 2015.
- 35 Department of Health and Human Services. 2016. "Understanding Recent Trends in Generic Drug Prices." ASPE Issue Brief. January 27, 2016. <https://aspe.hhs.gov/system/files/pdf/175071/GenericsDrugpaperr.pdf>.
- 36 Gupta, Ravi et al. 2016. "Generic Drug Approvals Since 1984 Hatch-Waxman Act." *JAMA Internal Medicine* 176 (9): 1391-93.
- 37 Government Accountability Office (2016), see n. 19; JD Alpern, WM Stauffer, and AS Kesselheim. 2014. "High-Cost Generic Drugs — Implications for Patients and Policymakers." *N Engl J Med* 371: 1859-1862.
- 38 Grabowski, Henry, Iain Cockburn, and Genia Long. 2006. "The Market for Follow-on Biologics: How Will It Evolve?" *Health Affairs* 25: 1291-93; Scott Gottlieb. 2016. "How Obama's FDA keeps generic drugs off the market." *The Wall Street Journal*. August 20, 2016.
- 39 Brennan, Zachary. 2015. "House Panel Calls on GAO to Study FDA's Approval Pathway for Complex Generics." Regulatory Affairs Professionals Society. December 15, 2015; Alicia Mundy. 2010. "FDA Approves Generic Lovenox." *Wall Street Journal*. July 24 2010.
- 40 Dunne, Suzanne et al. 2013. "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 Pharmacol. Toxicol* 14: 1–19; Barbara Davit et al. 2013. "International Guidelines for Bioequivalence of Systemically Available Orally Administered Generic Drug Products: A Survey of Similarities and Differences," *The AAPS Journal* 15 (4): 974-90.
- 41 Crommelin, Daan J.A. et al. 2015. "The similarity question for biologicals and non-biological complex drug," *European Journal of Pharmaceutical Sciences* 75: 10-17.
- 42 Kesselheim, A.S. and J.J. Gagne. 2015. "Product-Specific Regulatory Pathways to Approve Generic Drugs: The Need for Follow-up Studies to Ensure Safety and Effectiveness." *Drug Saf.* 38(10): 849-53.
- 43 Gottlieb, Scott. "EpiPen Price Increases." Statement before Senate Committee on Health, Education, Labor and Pensions; Subcommittee on Children and Families. October 7, 2016.
- 44 Food and Drug Administration. 2012. "Generic Drug User Fee Amendments of 2012 (GDUFA)." <http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm>
- 45 Food and Drug Administration. 2014. "Manual of policy and procedures: MAPP 5240.3 Rev. 1: prioritization of the Review of Original ANDAs, Amendments, and Supplements." Revised 8/1/2104.

<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm407849.pdf>.

- 46 Food and Drug Administration. 2014. "Prioritization of the Review of Original ANDAs, Amendments, and Supplements." <http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/UCM407849.pdf>.
- 47 Woodcock, Janet. "Prioritizing Public Health: The FDA's Role in the Generic Market Place." Statement before the Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies, United States Senate. September 21, 2016; Office of Generic Drugs, Food and Drug Administration. 2016. "Annual Report 2016: Ensuring Safe, Effective and Affordable Medicines for the American Public." <https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/abbreviatednewdrugapplicationandgenerics/ucm542710.htm>.
- 48 Sen. Jerry Moran. "Prioritizing Public Health: The FDA, Role in the Generic Drug Marketplace Opening Statement." Committee on Appropriations Subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies. September 21, 2016.
- 49 Zachary Brennan. 2016. "Generic Drug Backlog: A Dive into the Confusing Numbers." *Regulatory Affairs Professionals* (Nov. 1, 2016).
- 50 Office of Tom Cotton. "Cotton Introduces the Safely Advancing Valuable and Inexpensive New Generic Solutions Act." September 22, 2016. https://www.cotton.senate.gov/?p=press_release&id=511; Kurt R. Karst. 2017. "The Lower Drug Costs Through Competition Act: Prioritized Review for Some ANDAs . . . and a Priority Review Voucher." *FDA Law Blog*. February 01, 2017.
- 51 Kesselheim, A.S. 2009. "Priority review vouchers: an inefficient and dangerous way to promote neglected-disease drug development." *Clin Pharmacol Ther*. 85(6): 573–575.
- 52 Food and Drug Administration. 2017. "Abbreviated New Drug Application (ANDA) and Prior Approval Supplement (PAS) Fees." <https://www.fda.gov/ForIndustry/UserFees/ucm319568.htm>
- 53 Kesselheim, A.S. "Why are some generic drugs skyrocketing in price?" Testimony before the Senate Committee on Health, Education, Labor & Pensions. November 20, 2014. <http://www.help.senate.gov/imo/media/doc/Kesselheim.pdf>.
- 54 Davies et al. (2017), see n. 25.
- 55 Kesselheim, A.S., H. Avorn, and A. Sarpatwari. 2016. "The High Cost of Prescription of Drugs in the United States: Origin and Prospects for Reform." *JAMA* 316(8): 858-871.
- 56 Greene, J.A., G. Anderson, and J.M. Sharfstein. 2016. "Role of FDA in Affordability of Off-Patent

- Pharmaceuticals.” *JAMA* 315(5): 461-62.
- 57 Woodcock (2016), see n. 49.
- 58 Woodcock, Janet. “Generic Drug User Fee Act Reauthorization (GDUFA II) & Biosimilar User Fee Act Reauthorization (BsUFA II).” Testimony before the United States House of Representatives Committee on Energy and Commerce Subcommittee on Health. March 2, 2017.
- 59 Scott Morton, F.M. 1999. “Entry Decisions in the Generic Pharmaceutical Industry.” *The RAND Journal of Economics* 30 (3): 421-40.
- 60 See “International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.” <http://www.ich.org/home.html>.
- 61 Davit et al. (2013), see n. 41.
- 62 Daan, J.A., Crommelin et al., The similarity question for biologicals and non-biological complex drug, *European Journal of Pharmaceutical Sciences* Vol. 75, Aug. 30, 2015, 10-17.
- 63 Davit et al. (2013), see n. 41.
- 64 Srivastava, Vikesh. “The Common Electronic Submissions Gateway Project: Fostering international Collaboration and Innovation.” Health Canada. March 13, 2017. (presentation on file with author)
- 65 Brousseau, Zachary. “May Deadline for FDA’s eCTD Transition Approaches.” Regulatory Professional Affairs Professionals. Feb. 13, 2017. <http://www.raps.org/Regulatory-Focus/News/2017/02/13/6479/May-Deadline-for-FDAs-eCTD-Transition-Approaches/>.
- 66 See discussion in: Thomas J. Bollyky. 2012. “Safer, Faster, Cheaper: Improving Clinical Trials and Regulatory to Fight Neglected Diseases.” Center for Global Development Working Group Report; J. John Lee. 2005. “What is Past is Prologue: The International Conference on Harmonization and Lessons Learned from European Drug Regulations Harmonization.” *U Pa J Int’l Econ L* 26: 151.
- 67 International Trade Administration, U.S. Department of Commerce. “2016 Top Markets Report Pharmaceuticals: A Market Assessment Tool for U.S. Exporters.” May 2016.
- 68 U.S. Food and Drug Administration. “FDA Globalization.” Updated June 24, 2016. <https://www.fda.gov/InternationalPrograms/FDABeyondOurBordersForeignOffices/>.
- 69 U.S. Food and Drug Administration (2005), see n. 13.
- 70 Kesselheim, A.S., J.M. Franklin, J. Avorn, and J.D. Duke. 2013. “Speaking the same language? International variations in the safety information accompanying top-selling prescription drugs.” *BMJ Qual Saf.* 22(9): 727-34.
- 71 European Aviation Safety Agency. 2013. “Agreement between the USA and the EU on cooperation in the regulation of civil aviation safety.” <https://www.easa.europa.eu/document-library/bilateral-agreements/eu-usa>.

- 72 Ibid. See discussion of this ICAO model in M Jennison. 2013. "The Future of Aviation Safety Regulation: New US-EU Agreement Harmonizes and Consolidates the Transatlantic Regime, but What is the Potential for Genuine Regulatory Reform?" *Air and Space Law* 38(4): 333–50; Parker, R.W. and N. Eisner. 2016. "Learning from Experience: Three Case Studies in International Regulatory Cooperation, A Report Prepared for the European Commission." SSRN. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2780605; Hoekman, Bernard and Charles Sabel. "Trade Agreements, Regulatory Sovereignty and Democratic Legitimacy." (draft manuscript on file with authors).
- 73 "Federal Food, Drug and Cosmetic Act." § 809
- 74 U.S. Food and Drug Administration. "Mutual Recognition promises new framework for pharmaceutical inspections for United States and European Union". March 2, 2017. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm544357.htm>.
- 75 See "International Generic Drug Regulators Programme (IGDRP)." www.igdrp.com/about-us.
- 76 World Health Organization. 2014. "The International Generic Drug Regulators Pilot." *WHO Drug Information* 28(1): 3.
- 77 International Generic Drug Regulators Programme (IGDRP). "Roadmap to 2020." October 7, 2016. <http://www.igdrp.com/sites/default/files/IGDRP%20Roadmap%20to%202020.pdf>.
- 78 Milmo, Seab. 2015. "Europe Strives for a More Efficient Generic-Drug Approval Framework." *Pharmaceutical Technology* 39 (3); Handoo, S., V. Arora, D. Khera, P.K. Nandi, and S.K. Sahu. 2012. "A comprehensive study on regulatory requirements for development and filing of generics globally." *Int J Pharm Investing* 2(3): 99-105.
- 79 *The Economist: Intelligence Unit*. "Mexico's wave of generics." October 21, 2014. <http://www.eiu.com/industry/article/1652410149/mexicos-wave-of-generics/2014-10-21>.
- 80 Chagoya, Hector E., Juan Carolos Amara, and Nuria Becerril. 2012. "Mexico – The Drug Approval Process §13.04." *International Pharmaceutical Law and Practice*.
- 81 Posma, Jeroen. "Generics Commanding Pharmaceutical Market Share." *Salud Mexico*. Aug. 21, 2015.
- 82 Pan American Health Organization. "PAHO recognizes COFEPRIS as a National Regulatory Authority of Regional Reference." July 2, 2012. http://www.paho.org/hq/index.php?option=com_content&view=article&id=6967%3A2012-paho-recognizes-cofepris-as-national-regulatory-authority-regional-reference&catid=1443%3Aweb-bulletins&Itemid=135&lang=en; Pan American Health Organization, "System for Evaluation of the National Regulatory Authorities for Medicines." http://www2.paho.org/hq/index.php?option=com_content&view=article&id=1615%3A2009-sistema-evaluacion-autoridades-reguladoras-nacionales-medicamentos&catid=1267%3Aquality-drug-regulation&Itemid=1179&lang=en.

- 83 Gupta et al. (2016), see n. 37.
- 84 “S.2388 - Reciprocity Ensures Streamlined Use of Lifesaving Treatments Act of 2015.”
<https://www.congress.gov/bill/114th-congress/senate-bill/2388/text>.
- 85 Centers for Medicare and Medicaid Services. “2015 Medicare Drug Spending Data.”
<https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/2015MedicareData.html>.
- 86 QuintilesIMS Institute (2016). See n. 4.
- 87 Theodore Ruger. 2009. “FDA Reform and European Medicines Evaluation Agency.” *Harv. L. Rev* 108: 2009-2026.
(proposing the approval by EU centralized procedure quality as “substantial evidence” under section 355(d) of FDCA).
- 88 Food and Drug Administration. “FDA approval of generic version of cancer drug Doxil is expected to help resolve shortage.” 2013.
- 89 Greene, Anderson, and Sharfstein (2016), see n. 58.
- 90 See generally Linda Horton. 1999. “Pharmaceutical and Medical Harmonization, Mutual Recognition and Harmonization.” *Seton Hall L Rev* 29: 692; Richard A. Merrill. 1998. “FDA and Mutual Recognition Agreements: Five Models of Harmonization.” *Food Drug L.J.* 53: 133.
- 91 “All legislative Powers herein granted shall be vested in a Congress of the United States...” U.S. Const. art. I. 1. See discussion in Ruger (2009), see n. 89.
- 92 The White House Office of the Press Secretary. 2017. “Presidential Executive Order on Reducing Regulation and Controlling Regulatory Costs.” <https://www.whitehouse.gov/the-press-office/2017/01/30/presidential-executive-order-reducing-regulation-and-controlling>
- 93 See discussion in TJ Bollyky, I Cockburn, ER Berndt. “Bridging the Gap: Improving Clinical Development and the Regulatory Pathways for Health Products for Neglected Diseases.” *Clinical Trials* 7(6): 719-734.
- 94 Posma, Jeroen. 2015. “Generics Commanding Pharmaceutical Market Share.” *Salud Mexico*. Aug. 21, 2015.
- 95 Generic Pharmaceutical Association. “A Single Development Pathway Can Improve Patient Access to Generic Drugs.” <http://www.gphaonline.org/media/wysiwyg/PDF/SDP.pdf>.
- 96 Nather, David. “Trump’s health care plan takes (another) page from the Democrats.” *Stat News*. Mar. 6, 2016.
<https://www.statnews.com/2016/03/02/trump-health-care-plan/>.
- 97 Gottlieb, Scott. 2016. “What Trump Should Have Said on Drug Prices.” *Forbes*. Mar, 4 2016.
- 98 Ibid.
- 99 Danzon and Keuffel (2014), see n. 8; J Costa-Font, A McGuire, and N Varol. 2014. “Price regulation and relative

delays in generic adoption.” *Journal of Health Economics* 38: 1-9.

100 Kesselheim, Avorn, and Sarpatwari (2016), see n. 57.

101 Danzon and Keuffel (2014), see n. 8.

102 Directorate General for Internal Policies, Policy Department of Economic and Social Policy, European Parliament. *Differences in Costs of and Access to Pharmaceutical Products in the EU*. (Brussels: European Parliament, 2011).

103 Office of Inspector General, Department of Health and Human Services. “FDA has Made Progress on Oversight and Inspections of Manufacturers of Generic Drugs.” OEI-01-13-00600. May 2015.