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before the

Committee on the Judiciary's Subcommittee on Regulatory Reform, Commercial, and Antitrust Law  
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“Antitrust Abuses and the FDA Approval Process”

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Chairman Marino, Ranking Member Cicilline, and Members of the Subcommittee,

Thank you for the opportunity to testify today. I am a law professor at the University of Missouri in Columbia, Missouri, where I teach FDA law, intellectual property law, and administrative law. Before joining academia, I practiced law in Washington, DC, focusing on FDA regulation of pharmaceutical and medical device companies. I have more than two decades of experience studying and writing about the intersection of this country's intellectual property rights system and the regulatory framework in which pharmaceutical companies operate.

Various scholars and policymakers have voiced concern over the years that pharmaceutical companies often operate in ways that are inconsistent with norms of fair competition and may violate antitrust law — in particular that, despite complying with the regulatory framework and the intellectual property framework, these companies invoke or employ these frameworks inappropriately. Among scholars, however, these concerns are not uniformly shared. I was asked by subcommittee staff to provide my perspective on three aspects of the regulatory paradigm of particular interest: citizen petitions, use and distribution restrictions, and FDA's unapproved drugs initiative. The views that I present below are my own; I do not speak for my employer or any other organization or entity.

**I. Citizen Petitions**

**A. The Open Government Philosophy**

In the 1970s, responding to complaints that national policy was set by administrative agencies without public knowledge or participation, Congress re-examined the way that administrative agencies did their work. The legislation resulting from this effort took two forms. The first was a series of general laws applicable to all administrative agencies, and the second was reflected in amendments to the statutes governing specific agencies. The overarching goal of the reforms was to make administrative agencies more accessible to the public, to make their decisionmaking more transparent, and to make them publicly accountable.

Congress did not amend the Federal Food, Drug, and Cosmetic Act (FDCA) as part of this process. Instead, FDA embraced the open government philosophy on its own initiative. In the early 1970s, the agency embarked on a comprehensive program of procedural reforms, which were released for public comment in 1975 and mostly finalized in 1977.<sup>1</sup> These reforms embraced the themes central to the open government philosophy: transparency, access, and accountability. The Commissioner of Food and Drugs told Congress in 1975 that the new policies — “stressing

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<sup>1</sup> 40 Fed. Reg. 40682 (Sept. 3, 1975); 42 Fed. Reg. 4680 (Jan. 25, 1977).

openness and public participation” — would “strengthen the agency, and increase public confidence in the integrity of [its] decisions.”<sup>2</sup>

Among other things, FDA adopted methods for issuing formal advisory opinions and committed to publishing comprehensive preambles to proposed and final regulations, the latter of which would summarize and respond to every type of comment received. The agency also split its decisionmaking roles from its litigation roles, defined the administrative record for purposes of judicial review, and instituted several new types of informal hearing. FDA also adopted a formal process for members of the public to petition the agency to take, or stop taking, action — the “citizen petition” process.<sup>3</sup>

The citizen petition regulation exemplified FDA’s commitment to open government. The agency had “come to recognize the benefits of opening up [its] decisionmaking to public scrutiny and of broadened involvement by interested persons and experts outside the agency.”<sup>4</sup> The regulation therefore allowed any person to request that FDA issue, amend, or revoke a regulation or order, or take or refrain from taking any other administrative action. The agency envisioned petitioners raising the full range of factual, policy, and legal issues relevant to the agency’s many administrative activities.<sup>5</sup> By specifying a format and procedural requirements for these petitions, the new approach allowed members of the public to signal to FDA staff that a particular communication was a formal request requiring response. Any member of the public could file written comments on the petition; after all, the agency’s activities “directly affect all members of the public.”<sup>6</sup> The agency would respond to a petition within 180 days of receipt, and its response would constitute final agency action subject to court review.<sup>7</sup>

## **B. Section 505(q) of the FDCA**

FDA receives petitions from many interested parties. Members of Congress have submitted citizen petitions. So have hospitals, national professional organizations, state and local government entities, nonprofit advocacy groups, and academics. Companies regulated by FDA file petitions, as well. Some relate to products marketed by their competitors or pending applications submitted by their competitors. Within this latter category are petitions filed by drug innovators concerning pending generic drug applications. Like other citizen petitions, these petitions raise a variety of legal, scientific, and policy issues. For instance one might argue that FDA appears poised to misinterpret the statute or that the Constitution precludes an action that a generic applicant has requested the agency take. Another might argue that as a scientific matter one particular approach to assessing bioequivalence is better than another for a particular drug.

A petition pertaining to a pending generic drug application may delay approval of the generic drug in question, and the concern arises in situations where the petition is ultimately denied. As early as 1993, concerns were raised that some innovator petitions were improper — essentially, that they

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<sup>2</sup> Congressional Oversight of Administrative Agencies (Food and Drug Administration and Environmental Protection Agency, Hearings before the Subcomm. on Separation of Powers of the Comm. On the Judiciary, United States Senate, 94th. Cong., 1st Sess. 9 (July 21 & 23, 1975) (statement of Alexander M. Schmidt, Commissioner of Food and Drugs).

<sup>3</sup> 42 Fed. Reg. at 4700, adopting 21 C.F.R. § 2.7, now 21 C.F.R. § 10.30; *see also* 21 C.F.R. § 10.3 (definition of “petition”).

<sup>4</sup> Schmidt Testimony, *supra* note 2, at 5.

<sup>5</sup> 40 Fed. Reg. at 40686.

<sup>6</sup> *Id.* at 40683.

<sup>7</sup> *Id.* at 40686.

were known to be frivolous, that they were held back until they would inevitably delay generic drug approval, or both.<sup>8</sup>

Responding to these concerns, Congress enacted section 505(q) of the FDCA in 2007.<sup>9</sup> As amended in 2012, this provision states that FDA may not delay approval of a pending abbreviated new drug application (ANDA), 505(b)(2) application, or biosimilar application because of a request to take an action relating to the application unless the request takes the form of a formal petition to the agency and the agency determines that delay is necessary to protect the public health. The petitioner must also state the date on which it first became aware of the information on which it bases its petition and certify that it did not “intentionally delay” submission of the document. FDA must take final agency action within 150 days, and in the case of a generic or 505(b)(2) application the agency is considered to have taken final agency action if the 150 days expire without a decision. The deadline was originally 180 days, but Congress shortened it to 150 days in 2012. FDA may at any time deny a petition “submitted with the primary purpose of delaying the approval of an application,” provided the petition does not on its face raise valid scientific or regulatory issues.

### C. Continuing Criticism

Enactment of section 505(q) has not silenced critics of the petitioning process, who appear to believe that most innovator petitions are meritless and filed with the purpose, and perhaps effect, of delaying generic drug approval. Recently, in its first attempt to use the antitrust laws to address petitions it views as improper, the Federal Trade Commission (FTC) filed a complaint charging Shire ViroPharma with violating section 5(a) of the FTC Act. Shire ViroPharma allegedly violated section 5(a) through “repetitive, serial, and meritless petitioning” that “harmed competition and consumer welfare by obstructing and delaying the FDA approval process for a generic version of Vancocin Capsules.”<sup>10</sup> Also recently, scholars have published empirical studies of drug industry petitions, offering the results to support the claim that companies “frequently” raise “frivolous or questionable claims in a last-ditch effort to hold off competition”<sup>11</sup> (the “Hastings study”) and the claim that these petitions “play an increasingly important role in delaying generic competition” and “bear a dangerous potential to extend brand monopolies . . . at a potential cost of millions of dollars per day” (the “Rutgers study”).<sup>12</sup>

These studies — which worked from different datasets and investigated slightly different questions — represent a significant amount of work and make an important contribution to our thinking about the nature of petitioning to FDA. But it is important to separate the factual findings from any inferences that might be urged. The findings on their own do not support making changes to the statute or the regulations governing petitions.

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<sup>8</sup> The FTC raised concerns as early as 1993, and FDA at one point considered eliminating the option to file a petition regarding a pending application. *See* 64 Fed. Reg. 66822, 66822 (Nov. 30, 1999). *See also* Lars Noah, *Sham Petitioning as a Threat to the Integrity of the Regulatory Process*, 74 N.C. L. REV. 1 (1995).

<sup>9</sup> 21 U.S.C. § 355(q).

<sup>10</sup> Federal Trade Commission v. Shire ViroPharma Inc., Case 1:17-cv-00131-RGA (D. Del.) (filed Feb. 7, 2017). A motion to dismiss is pending.

<sup>11</sup> Robin Feldman & Connie Wang, *A Citizen’s Pathway Gone Astray — Delaying Competition from Generic Drugs*, 376 NEW ENG. J. MED. 1499, 1499 (2017).

<sup>12</sup> Michael A. Carrier & Carl Minniti, *Citizen Petitions: Long, Late-Filed, and At-Last Denied*, 66 AM. UNIV. L. REV. 305, 307, 352 (2016); *see also* Michael A. Carrier & Daryl Wander, *Citizen Petitions: An Empirical Study*, 34 CARDOZO L. REV. 249 (2012).

First, there is little evidence of delay in generic drug approvals due to petitions. Over the eight years for which we have data from FDA, approval of **five** generic drug applications — out of 4008 ANDAs and 505(b)(2) applications approved during this time — was delayed because the agency needed additional time to resolve issues raised in a petition.<sup>13</sup> Three quarters of the petitions received by the drug center do not even relate to a pending ANDA, 505(b)(2) application, or biosimilar application in the first instance.<sup>14</sup> Of the 175 petitions that related to a pending application, only five resulted in delays of generic drug approval that were not necessary to protect the public health. These five may raise concerns,<sup>15</sup> but if the delay stemmed from timing of the petitions we should know more of the underlying facts before rushing to judgment.<sup>16</sup> In any event they result from a very small percentage of the petitions and relate to an exceptionally small percentage of the total number of generic drugs approved.

The authors of the Rutgers Study suggest that FDA’s resolution of a citizen petition on the same day (or in the same month) as its approval of the relevant ANDA means that FDA waited to approve the ANDA until it was prepared to deny the petition.<sup>17</sup> An alternative explanation, however, is that FDA waited to issue its petition denial until it needed to make a final decision on the ANDA.<sup>18</sup> This would, for instance, avoid committing to a course of action before the decision was final. The timing of ANDA approval, in turn, may be dictated by a 30-month stay arising automatically out of patent litigation. Or it may be dictated by a patent that the generic applicant chose not to challenge. In the alternative, it may be governed by an action date set by the agency pursuant to the Generic Drug User Fee Act (GDUFA). The authors of the Hastings study found a clear trend in favor of petitions filed shortly before final ANDA approval; since 2007 more than half have been filed in the final 18 months.<sup>19</sup> They note more cautiously that this “potentially extends the

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<sup>13</sup> These numbers were calculated from FDA’s annual reports to Congress on delays in approvals of applications related to petitions. The reports are required under section 505(q) and available on the agency’s website.

Out of 4008 approved applications, FDA identified only ten as to which approval was delayed due to a citizen petition. Of these, two were delayed by a petition filed by one of the ANDA applicants, and one was enjoined from market entry anyway on account of patent infringement. The remaining five ANDAs and two 505(b)(2) applications were delayed an average of 39 days while FDA resolved issues that had been raised by the petitioners.

<sup>14</sup> FDA’s statistics exclude suitability petitions and petitions relating to OTC monographs. If these were included, far fewer than one in four petitions would relate to a pending ANDA, 505(b)(2) application, or biosimilar application.

<sup>15</sup> See, e.g., note 29, *infra*.

<sup>16</sup> An innovator may not learn all of the facts necessary to file a thorough and well-supported petition until after the relevant ANDA has been filed. Moreover if we prefer that petitions be supported by thorough research and, perhaps, testing data, we need to understand that performing the research and tests will require some time. In other words, there may be an inevitable tradeoff between timing and thoroughness.

<sup>17</sup> Carrier & Minniti, *supra* note 12, at 41-43.

<sup>18</sup> The authors concede this possibility but seem to prefer their own inference, adding immediately that simultaneous resolution “can still raise the suspicion that the FDA delayed approval until it dealt with the petition.” *Id.* at 44.

<sup>19</sup> Robin Feldman et al., *Empirical Evidence of Drug Pricing Games — A Citizen’s Pathway Gone Astray*, 20 STAN. TECH. L. REV. 39, 75 (2017). The 18-month window may not be surprising or concerning. An innovator may not learn about a potential generic competitor until it receives notice of a paragraph IV certification (patent challenge), and it may not know the facts that give rise to scientific and regulatory concerns until it learns of the ANDA. In the case of a new chemical entity, this necessarily means its citizen petition can be filed no sooner than the final 12 months before data exclusivity expires. In the further event of a 30-month litigation stay, a petition filed after the data exclusivity expires will arrive in the final 18 months before the stay ends (permitting ANDA approval).

length of the generic approval process,” but we know from FDA’s annual reports to Congress that an exceptionally small number of generic approvals are actually delayed.

Second, neither study examined whether innovator petitions are actually meritless or frivolous. Rather, we know that petitions are generally denied. Several years ago the Rutgers team found that FDA denied 81 percent of the petitions filed between 2001 and 2010, and the recent Rutgers Study found that the agency denied 92 percent of the petitions filed from 2011 through 2015.<sup>20</sup> The authors imply that denial is a signal that the petition was not legitimate.<sup>21</sup> The authors of the Hastings Study report that their study “reveals” that petitions are “frequently” filed by companies raising “frivolous or questionable claims.”<sup>22</sup> In fact, though, the Hastings Study did not evaluate the strength or merit of the issues presented in the petitions.<sup>23</sup> The claim that petitions are frequently frivolous appears based on the timing of petitions and denial rate, not the substance, of the petitions.<sup>24</sup>

The statistics on denial are important, and the denial rate is worth reflecting on. But FDA has pointed out to Congress that a petition may raise valid scientific and regulatory concerns even if it lacks persuasive power.<sup>25</sup> As the agency pointed out when it published its citizen petition regulation, issues before the agency “rarely turn on definitive or uncontradicted evidence.”<sup>26</sup> Scientific issues always involve inference and prediction on the basis of a finite amount of data. When considering new drugs and biologics in particular, the agency and applicants are almost always laboring with an imperfect understanding of the relevant disease process and the drug’s mechanism of action and effects in the body. Approval decisions may require difficult judgment calls about the appropriate regulatory policy in the face of scientific uncertainty, as well as tough decisions about the flexibility of the law to accommodate new or unclear factual situations. This is why, as FDA has noted, differences in opinion and perspective are “expected” in scientific and regulatory processes.<sup>27</sup> Consequently, FDA has told Congress that it “welcomes the submission of material information that can help inform its decision on the appropriate standards to employ in the review of a particular ANDA or 505(b)(2) application.”<sup>28</sup> Petition denial may simply mean that the scientists, regulatory

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<sup>20</sup> Carrier & Minniti, *supra* note 12, at 26, 27.

<sup>21</sup> *Id.* at 35.

<sup>22</sup> Feldman & Wang, *supra* note 11, at 1499.

<sup>23</sup> *See* Feldman et al., *supra* note 19, at 62 (“[N]o attempt was made to judge the merits of the issues raised in the petition.”).

<sup>24</sup> *Id.* at 70-71.

<sup>25</sup> FDA, REPORT TO CONGRESS, ENCOURAGING EARLY SUBMISSION OF CITIZEN PETITIONS AND PETITIONS FOR STAY OF AGENCY ACTION 6 (Feb. 2009) [hereafter “FDA 2009 REPORT”] (“Although a petition may not raise persuasive scientific or regulatory issues when those issues have been reviewed by FDA, a petition can easily raise valid scientific or regulatory issues.”).

<sup>26</sup> 42 Fed. Reg. at 4686. The agency relied on this observation for the decision that it would accept all types of adverse information in comments, rather than just scientifically backed commentary. *See id.* (commenting that “adverse educated opinion, even if lay opinion, should be included if for no other reason than to permit the agency to explore the matter further if it so desires”).

<sup>27</sup> *E.g.*, CBER SOPP: RESOLUTION OF DIFFERENCES IN SCIENTIFIC JUDGMENT IN THE REVIEW PROCESS (Jan. 15, 2009).

<sup>28</sup> FDA 2009 REPORT, *supra* note 25, at 2.

affairs personnel, and lawyers at a company reached a different conclusion than their counterparts at the agency.

For these reasons, the important empirical work that has been performed could be enhanced with a robust examination of the agency's disposition of the issues presented in petitions, rather than its disposition of the requests stated in the petitions. Focusing on formal outcomes risks missing evidence that the agency's practices and policies in fact changed to conform with the views of a petition, perhaps in connection with broader dialogue about the issues presented in the petition.

The ultimate question, however, is whether any particular petition made claims that were frivolous rather than simply non-persuasive. And this judgment call must be FDA's to make. FDA is a sophisticated and experienced public health agency, and it has been engaged in a public health mission concerning drugs since its inception (under a different name) more than a hundred years ago. Today the agency employs more than 15,000 people, many of whom are scientists — biologists, epidemiologists, pharmacologists, toxicologists, chemists, statisticians, and medical doctors with a wide range of specialties. It also employs many specialists in regulatory affairs and regulatory policy, and it has a sizeable office of highly skilled lawyers. Without a doubt, it has the ability to determine whether claims in a petition were actually frivolous. It also has the power to act. As noted, section 505(q) allows the agency to deny a petition at any point, if the petition was submitted with the primary purpose of delay and does not on its face raise valid scientific or regulatory issues. The agency may also refer a petition to the FTC for further review, which it has done in the past.<sup>29</sup> FDA also has the power of publicity (public shaming) at its disposal, which it has used effectively as well.<sup>30</sup>

#### **D. Recommendations**

FDA's generous approach to citizen petitions serves important public policy goals. To begin with, the agency's mission statement requires that it carry out its tasks of "promoting" and "protecting" the public health — by ensuring that drugs are safe and effective, promptly and efficiently reviewing clinical research, and taking appropriate and timely action on the marketing of regulated products — in consultation with experts and in "cooperation" with consumers, manufacturers, and others.<sup>31</sup> In addition, the basic principles of open government call for the public to have access to the agency and a role in the agency's policymaking, just as they call for an appropriate level of transparency in decisionmaking — all of which are furthered by citizen petitions, including those filed by industry. And the First Amendment to the U.S. Constitution promises not only the protection of commercial speech but also a right to petition the government, which the Supreme Court has called "among the most precious of the liberties safeguarded by the Bill of Rights."<sup>32</sup> Finally, as FDA works to ensure that new drugs are safe and effective, it must do so in a way that is authorized by and consistent with the statutes it implements (and thus interprets), consistent with the U.S. Constitution, and in full compliance with various procedures and standards

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<sup>29</sup> *E.g.*, FDA Response, Docket No. FDA-2012-P-2028 ("FDA is not denying Reckitt's Petition pursuant to section 505(q) of the FD&C Act. The Agency has, however, referred this matter to the Federal Trade Commission, which has the administrative tools and the expertise to investigate and address anticompetitive business practices.").

<sup>30</sup> For instance, it sharply rebuked the company whose petition led to the delay in approval of two generic versions of Reclast (zolendronic acid). FDA Response, Docket No. FDA-2013-P-0247 (Aug. 1, 2013) ("This Petition represents a particularly egregious misuse of the FDA citizen petition process for what appears to be the purpose of delaying generic competition."). This petition led to two of the five approval delays that FDA has documented since 2008.

<sup>31</sup> 21 U.S.C. § 393(b).

<sup>32</sup> *United Mine Workers v. Illinois State Bar Ass'n*, 389 U.S. 217, 222 (1967).

laid out in the Administrative Procedure Act (APA). The public has a strong interest in ensuring that executive branch agencies work within the constraints of the laws that Congress has written. A robust petitioning practice has the benefit of adding a layer of surveillance to complement the oversight function of the legislative branch and the review function of the judicial branch.

Without empirical evidence that a meaningful number of generic drug approvals are delayed by meritless petitions, the primary issue with citizen petitions — filed by anyone — is the burden they impose on the federal government. The burden may be significant where a petition raises complex scientific issues, and the broader impact of the burden may be concerning if the petition relates to an agency action that must be taken on a particular timetable. Neither issue is exclusive to petitions filed by innovators regarding pending generic drug applications. It is appropriate for policymakers to be concerned about the impact of petitions on resource allocation and other agency programs. Numerous steps could be taken to mitigate the impact of petitions relating to pending generic applications while maintaining FDA’s open door.

First, FDA has complained that Congress’s decision to shorten the deadline from 180 days to 150 days increased the strain on agency resources, requiring the agency to divert resources from other important initiatives.<sup>33</sup> Changing the deadline back to 180 days might be helpful, and it might also be helpful to provide the agency with additional resources for handling petitions. Second, FDA has in the past explored several initiatives to encourage and facilitate the earlier filing of petitions that relate to pending applications, including issuing product-specific bioequivalence guidance documents for public comment.<sup>34</sup> Additional resources would allow FDA to strengthen these initiatives and consider other initiatives. Third, because petitions grounded in scientific concerns are particularly important and also particularly complex, it may be appropriate to incentivize petitioners to generate robust new data to accompany those petitions — that is, to take steps themselves that will reduce the agency’s workload. Where scientific questions are at issue, a robust petitioning practice has the potential to shift some of the workload burden to private parties with deep expertise in the products in question, as well as the resources and incentive to run issues to ground, which is beneficial in an era of shrinking resources. Put another way, policymakers might look for ways to enhance the burden-shifting benefit of petitions.

## **II. Use and Distribution Restrictions**

### **A. Risks Associated with New Drugs and Biological Products**

FDA approval of a new drug under the FDCA or a biological product under the Public Health Service Act (PHSA) represents the agency’s conclusion that the product’s benefits outweigh its risks when it is used as labeled, meaning for the indicated population and purpose. Safety and effectiveness are not, however, absolutes; they are always relative. Every approved medicine has risks. These include known risks, such as a particular side effect (like nausea) that developed in a particular percentage of the patients in clinical trials. Another type of known risk might be a more significant clinical consequence in a very small percentage of patients, which may develop over time but can be prevented if treatment stops when a particular side effect (such as stomach pain) or physiological marker (such as elevated liver enzymes) emerges. There is also a possibility of unknown risks. This is because no premarket clinical program of reasonable length can detect extremely rare side effects or side effects that emerge only after long latency periods. Nor can

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<sup>33</sup> FDA, SIXTH ANNUAL REPORT ON DELAYS IN APPROVALS OF APPLICATIONS RELATED TO CITIZEN PETITIONS AND PETITIONS FOR STAY OF AGENCY ACTION FOR FISCAL YEAR 2013, at 7.

<sup>34</sup> See FDA 2009 Report, *supra* note 25, at 3-6.

controlled testing identify all of the consequences that might stem from use in real-world conditions. Widespread and longer term use may also reveal that a previously identified risk is more severe and more frequent than premarket testing suggested.

The primary way that FDA manages the known risks of a new medicine is through the approval decision and labeling for healthcare professionals. This labeling synthesizes the information presented in the application and describes the conditions under which the benefits of the medicine are currently understood to outweigh its risks. Thus, it describes using the product to treat (or diagnose or prevent) a particular illness, with a specific dosing regimen, subject to various precautions and warnings (such as when not to administer it, what sorts of side effects are expected, what should not be combined with it, which side effects might be more concerning, and so forth). FDA may also require a company to disseminate special labeling for patients that focuses on the risks associated with its product. Risk assessment continues after a product reaches the market. Each company files quarterly safety reports for the first three years after a new drug's approval and has a permanent obligation to report individual adverse events that are both serious and unexpected. These reports can lead to labeling changes, and in some cases FDA may require further study of a drug to assess a known risk or to investigate a signal of a serious risk.<sup>35</sup>

## **B. Access Restrictions**

In some instances, physician and patient labeling may be insufficient to ensure that a product's benefits outweigh its risks. For decades, therefore, FDA has imposed use and distribution ("access") restrictions on drugs with unusually significant toxicity profiles. The agency began by voluntarily extracting agreements. Beginning in 1992, it imposed access restrictions on treatments for serious or life-threatening conditions under its new "subpart H" regulations.<sup>36</sup> In the early 2000s, FDA spent several years exploring ways to strengthen its drug safety program, which culminated in (among other things) a series of detailed guidance documents on risk assessment and minimization. Here, the agency had identified numerous processes and systems that a pharmaceutical company might adopt to minimize the known risks of a drug. During this time, FDA placed several products under access restrictions embodied in Risk Management Action Plans (RiskMAPSs).

Today the agency generally requires a "Risk Evaluation and Mitigation Strategy" (REMS) pursuant to section 505-1 of the FDCA, enacted in 2007. FDA may require a REMS when it approves a new drug or biologic, if the REMS is necessary to ensure the product's benefits outweigh its risks. Put another way, the agency may require a REMS only if the product would not be approvable without the REMS in place. As part of any REMS, FDA may require a Medication Guide or patient package insert (both of which are special labeling for patients), and it may require a plan for communications with healthcare providers. In special circumstances, the agency may also impose access restrictions. The statute allows FDA to require only six types of restrictions, and these may be imposed only to mitigate a specific serious adverse drug experience identified in the product's labeling.<sup>37</sup> The statute refers to these access restrictions as "elements to assure safe use."

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<sup>35</sup> 21 U.S.C. § 355(o).

<sup>36</sup> 21 C.F.R. part 314, subpart H. The biologics regulations contain parallel provisions. 21 C.F.R. part 601, subpart E.

<sup>37</sup> 21 U.S.C. § 355-1. In addition, for FDA to require access restrictions a Medication Guide, patient package insert, and plan for communications with healthcare providers must be insufficient to mitigate the risk. The permitted restrictions are: (1) requiring that prescribers have particular training or experience or are specially certified; (2) requiring that pharmacies and other dispensers have special certifications; (3) requiring that the drug be dispensed to patients only in certain health care settings, such as hospitals; (4) requiring that the drug be dispensed only to patients with evidence or

Some products may have use or distribution restrictions that do not stem from the statutory REMS authority. The narrowness of the REMS provision means that some legitimate issues must be addressed outside the REMS context. For instance, many biological products, including vaccines, require temperature-controlled (“cold chain”) shipping and storage, which may give rise to restricted distribution arrangements. Other products may benefit from distribution restrictions due to an especially high risk of counterfeiting. Some drugs may be subject to distribution restrictions in connection with resolving manufacturing compliance issues.

### C. The CREATES Act

In recent years, generic drug companies and others have alleged that innovators with drugs subject to access restrictions use these restrictions to hinder generic drug approvals.<sup>38</sup> Various bills have been introduced to address this perceived problem, including the Creating and Restoring Equal Access to Equivalent Samples Act of 2017 (“CREATES Act”).<sup>39</sup>

#### 1. Sale of Products

Generic drug and biosimilar applications are comparative applications. To obtain the innovative (“reference”) product for purposes of comparative testing, a generic or biosimilar applicant typically purchases the product from a wholesaler or directly from the innovator. The drug statute (FDCA) and biologics statute (PHSA) do not require an innovator to sell its product to anyone for purposes of comparative testing (or for any other reason); the underlying premise of both schemes is that a medicinal product is sold for use in treating, preventing, or mitigating a disease. Some believe that these comparative applications are now sometimes impossible because distribution restrictions make it difficult to acquire restricted drugs from third parties and because the innovators themselves also decline to sell the restricted drugs to their competitors.

In March 2017, CDER Director Janet Woodcock reported that the agency had received roughly 150 “inquiries” from generic drug companies regarding difficulty accessing an innovator’s product for bioequivalence testing.<sup>40</sup> It is important to understand what this number does and does not mean. It is not clear how many innovator products are at issue, but the number is considerably smaller than 150; indeed, all 150 inquiries could relate to only a handful of drugs.<sup>41</sup> Nor is it clear whether the innovators in question provided the product to other generic companies but — for reasons we do not know — declined to provide the product to the inquiring companies on the terms demanded. Moreover, it is not clear that difficulty purchasing any of these products has

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other documentation of safe-use conditions, such as laboratory test results; (5) requiring that each patient be subject to certain monitoring; and (6) requiring that each patient using the drug be enrolled in a registry.

<sup>38</sup> *E.g.*, Ameet Sarpatwari, Jerry Avorn, Aaron S. Kesselheim, *Using a Drug-Safety Tool to Prevent Competition*, 370 NEW ENG. J. MED. 16 (2014); Jordan Paradise, *REMS as a Competitive Tactic: Is Big Pharma Hijacking Drug Access and Patient Safety?*, 15 HOUS. J. HEALTH L. & POL’Y 43 (2015).

<sup>39</sup> H.R. 2212 (115th Cong.) & S. 974 (115th Cong.).

<sup>40</sup> CRS Report, FDA RISK EVALUATION AND MITIGATION STRATEGIES (REMS): DESCRIPTION AND EFFECT ON GENERIC DRUG DEVELOPMENT (April 11, 2017).

<sup>41</sup> Only 42 drugs have REMS with access restrictions. This includes 10 drugs that have multiple approved generics already as well as shared systems of access restrictions. In fact, only 32 products have innovator-only access restrictions in place. Ten of these — including two that have attracted considerable scrutiny because the innovator declined some sales (Thalomid and Revlimid) — have either approved generics or pending ANDA applications, meaning that the innovator has provided some applicants with products for testing. This leaves only 22 innovative drugs with innovator-only access restrictions.

caused meaningful delays in generic drug approval. Of the 22 drugs with innovator-only access restrictions, 12 still benefit from data exclusivity, which means that FDA cannot lawfully approve a generic or biosimilar anyway.<sup>42</sup> There is no question that some innovators decline to provide generic companies with products that are under access restrictions. But before any legislative action is taken, it would be prudent to determine how many innovative drugs lack generic competition because the innovator declined to sell its product for testing purposes.<sup>43</sup>

Despite weak empirical support for any legislative action, the proposed CREATES Act provides a new federal cause of action against innovators who decline to sell their restricted-access products to their competitors.<sup>44</sup> In brief, a generic company could allege that the innovator had declined to provide sufficient quantities of its product on commercially reasonable, market-based terms. If the generic company made the necessary showing, the court would be required to order the innovator to provide those quantities on those terms. It would also be required to award attorney fees and costs, and it would be required to order the innovator to pay a fine directly to the generic company — up to the total revenue from the product at issue for the contested period.<sup>45</sup>

This proposal raises several concerns.

First, an innovator may have legitimate concerns about the sale of its product to another company. The proposed legislation does not fully address those concerns. In each of these situations, FDA found that a REMS was necessary to ensure the benefits of the drug outweighed its benefits. It also found that the access restrictions at issue were necessary to mitigate a specific serious risk listed in the drug’s labeling. Access restrictions are usually imposed to mitigate severe side effects that are both preventable and life-threatening — teratogenicity (capability of producing fetal malformation) that requires precautions to prevent in utero exposure, for instance, or anaphylaxis (or other immediate life-threatening reactions), or irreversible organ destruction.<sup>46</sup> Even minor lapses at any point by any party to the distribution and administration of the drug could have horrific consequences. This is why virtually every REMS with access restrictions also has an “implementation system” — to monitor and evaluate the healthcare providers, pharmacists, and other parties in the health care delivery system who play a role in implementing the restrictions. A company that manufactures and distributes a drug like this has a special responsibility with respect to the public health. This is why a company might sell its restricted access drug to some generic companies and not others; it may have concerns that the requesting companies do not have

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<sup>42</sup> Another two are monoclonal antibodies, for which FDA is only now beginning to work through biosimilar approval requirements.

<sup>43</sup> Some may lack generic competition for other reasons — for instance because the active ingredient is difficult to manufacture, because demonstrating bioequivalence is difficult, or because the innovator’s sales are insufficient to merit investment in a generic competitor.

<sup>44</sup> It is not clear whether the language in the CREATES Act will be placed in the FDCA. But it would be unprecedented for FDA’s public health statute to provide a private party with a right of action against a regulated entity. 21 U.S.C. § 337(a) (“all such proceedings for the enforcement, or to restrain violations, of this chapter shall be by and in the name of the United States”)

<sup>45</sup> This period would start 31 days after the innovator received the generic company’s request (or an assurance from FDA that the generic company had protocols, informed consent documents, and informational materials providing safety protections comparable to the access restrictions adopted by the innovator). The period would end when the generic company received the product in question.

<sup>46</sup> Scott Gottlieb, *Drug Safety Proposals and the Intrusion of Federal Regulation into Patient Freedom and Medical Practice*, 26 HEALTH AFFAIRS 664, 668 (2007).

adequate safeguards in place to address the special risks presented by the drug.<sup>47</sup> To be sure, FDA may provide a letter assuring the innovator that the generic applicant has protections in place that are comparable to the innovator's access restrictions. What current law lacks, however, is meaningful protection for the innovator in the event that use of its product — after the product has left its control — leads to the very toxicity that it operates a carefully designed program to mitigate.

Section 3(c) of the CREATES Act takes helpful steps toward providing this protection. It insulates an innovator from “any claim” arising from the failure of the generic company to follow adequate safeguards to assure safe use. But this provision would benefit from clarification and strengthening. If FDA has determined that the generic company has safety protocols comparable to the innovator's, might this mean that the innovator is protected only where the generic company failed to comply with its own protocols? It should be clear instead that the innovator receives protection even where FDA had deemed the protocol acceptable. Further, the innovator should be insulated from any claim arising out of the action or inaction of any entity after sale of the drug to the generic company. It would also be helpful to clarify what is meant by “any claim” and to confirm expressly the intent to preempt state law that might otherwise provide a remedy against the innovator. Finally, lack of certainty about the scope of this protection and possible exceptions may invite suits against the innovator which, even if ultimately dismissed due to the protections enacted, take time and money to handle. It may therefore be appropriate simply to preclude suits against the innovator or, in the alternative, to require full indemnification by the generic company.

Second, the proposal is flatly inconsistent with fundamental patent law principles. If an innovator holds patents claiming the drug or the method of manufacturing the drug, the court's order will require the company to practice its patent for the benefit of its competitor, even though it is a bedrock principle of U.S. patent law that a patent owner has no duty to practice its patent at all. As the Supreme Court wrote more than one hundred years ago, “it is the privilege of any owner of property to use or not use it, without question of motive.”<sup>48</sup> Congress did enact a statutory experimental use exception in 1984 so that generic companies could make and test their own otherwise-infringing products.<sup>49</sup> But it requires a staggering leap from this narrow principle to impose on patent owners a duty to practice their patents for the benefit of competitors that wish to experiment.

Enacting this provision will inherently devalue the patents in question. Not only does this invite practical questions about how a court could now determine appropriate “commercially reasonable, market-based terms” for the products in question, but it may harm incentives to innovate. Innovation in medicine over the last century is responsible for profound improvements in public health, both domestically and globally. The United States has been the world leader in the scientific and medical innovation that has produced these breakthroughs. Decades of research confirm that the success of the pharmaceutical sector depends on the availability of meaningful patent protection.<sup>50</sup> By protecting property rights in inventions, the patent system encourages

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<sup>47</sup> *E.g.*, Brief in Support of Defendant Celgene Corporation's Motion to Dismiss, *Mylan Pharmaceuticals, Inc. v. Celgene Corporation*, Case No. 2:14-CV-2094-ESMAH (D.N.J. May 25, 2014) (noting that the company had sold Thalomid to competitors that satisfied its “safety, reputational, business, and liability concerns”).

<sup>48</sup> *Continental Paper Bag Co. v. Eastern Paper Bag Co.*, 210 U.S. 405, 429 (1908).

<sup>49</sup> 35 U.S.C. § 271(e)(1).

<sup>50</sup> *E.g.*, Edwin Mansfield, *Patents and Innovation: An Empirical Study*, 32 MGT. SCI. 173 (1986); Richard Levin et al., *Appropriating the Returns from Industrial Research and Development*, 3 BROOKINGS PAPERS ON ECON. ACTIVITY 783, 796 (1987); Wesley M. Cogen et al., *Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms Patent (or Not)*, NATIONAL BUREAU OF ECON. RESEARCH, WORKING PAPER NO. 7552 (2000); *see also* Rebecca Eisenberg,

companies to make socially valuable investments in research and development that they would not otherwise make. In my view, the evisceration of patent property rights in this proposal is a fatal flaw.

Even in the absence of a patent, the antitrust laws generally protect a manufacturer's right to decide who it will deal with — in part to protect those same incentives.<sup>51</sup> As the Department of Justice and FTC explained less than a year ago, there is generally no “duty to deal,” in part because imposing this liability “may undermine incentives for investment and innovation.”<sup>52</sup> Moreover, the duty to sell adequate amounts of one's product to one's competitors is, effectively, a duty to manufacture these amounts for the competitors. Absent a national defense emergency, it is hard to identify a compelling public policy justification for a law that effectively compels the manufacture of goods for sale. Thus, even where patent rights are not implicated, this proposal's impact on incentives to innovate should be examined closely.

Third, FDA may have the statutory flexibility to adopt a solution itself. Plainly, the agency lacks authority to require a sale, and it has never asserted that it has this authority. But innovators stop marketing their products all the time and for all sorts of reasons. FDA regulations provide a mechanism for determining whether a product that is no longer commercially available may still serve as a reference product. When the agency determines that an unavailable product may serve as a reference product, it sometimes adds that “future applicants are advised that they may not be able to obtain” the reference product and any “ANDA applicant who is unable to obtain” the product “should contact the Office of Generic Drugs for a determination of what is necessary to show bioavailability and same therapeutic effect.”<sup>53</sup> Sometimes it writes that applicants should “contact the Office of Generic Drugs for a determination of what showing is necessary to satisfy the requirements of section 505(j)(2)(A)(iv) of the act.”<sup>54</sup> The agency has thus indicated that it has the flexibility to work with generic applicants when a reference drug is no longer available.<sup>55</sup> It would be appropriate for FDA to explore, with public input, how best to handle those situations and whether the solution would be equally suitable for drugs under access restrictions. The underlying scientific and regulatory challenge appear to be the same.

Finally, the proposal to require the innovator to pay a fine directly to its generic competitor is disturbing. The maximum fine authorized — actual revenue from all of the innovator's sales of

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*The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 350 (2007) (“Biomedical research makes up a large part of overall R&D spending in both the public and private sectors, and it is an area in which empirical studies have found that patents really seem to matter.”).

<sup>51</sup> See Henry N. Butler, *REMS—Restricted Drug Distribution Programs and the Antitrust Economics of Refusals to Deal with Potential Generic Competitors*, 67 FLA. L. REV. 977 (2015) (exploring antitrust jurisprudence in depth and suggesting that the antitrust claims involved do not provide a proper justification for a new exception to a competitor's right to refuse to deal).

<sup>52</sup> U.S. Dept. of Justice and Federal Trade Commission, *ANTITRUST GUIDELINES FOR THE LICENSING OF INTELLECTUAL PROPERTY* 3 (Jan. 12, 2017) (“The antitrust laws generally do not impose liability upon a firm for a unilateral refusal to assist its competitors, in part because doing so may undermine incentives for investment and innovation.”), *citing* *Verizon Commc'ns Inc. v. Law Offices of Curtis V. Trinko, LLP*, 540 U.S. 398, 407-08 (2004); *United States v. Colgate & Co.*, 250 U.S. 300, 307 (1919).

<sup>53</sup> *E.g.*, 79 Fed. Reg. 60852 (Oct. 8, 2014).

<sup>54</sup> *E.g.*, 76 Fed. Reg. 7219 (Feb. 9, 2011).

<sup>55</sup> Although the statute requires proof of bioequivalence and defines the term, it does not specify how bioequivalence must be shown. 21 U.S.C. § 355(j)(8). FDA's regulations state that bioavailability or bioequivalence of a drug product may be determined using “[a]ny other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.” 21 C.F.R. § 320.24.

the product until the product is supplied — could significantly exceed any revenue the generic company might realize from its own eventually approved product. It is not unreasonable to worry that unprincipled companies might seek to delay judicial proceedings to extend that financial windfall.

## 2. Shared System

If an innovative drug has use or distribution restrictions under a REMS, current law generally requires that the innovator and generic companies use a “single, shared system” to implement the restrictions.<sup>56</sup> In these situations, all companies work with the same REMS documents, tools, and procedures.

Current law allows FDA to waive the requirement of a single, shared system for any generic applicant, if the burden of creating a shared system outweighs its benefits. When making this decision, the agency must consider the impact of sharing on both the generic drug applicant and the innovator. Thus the statute expressly contemplates the possibility that a shared system might unduly burden a generic company. This might be true, for instance, if arm’s length negotiations did not result in terms that were acceptable to the generic applicant. FDA may also waive the shared system if an aspect of the access restrictions is protected by patent or is trade secret. The generic company must ask for a license first, and FDA may try to negotiate a voluntary agreement between the innovator and the generic company. But the agency may waive the shared system if the negotiations fail, which presumably reflects the fundamental rule that a property owner may lawfully choose not to license or share its property at any price.

Section 4 of the CREATES Act responds to complaints that some innovators do not agree to a shared system for implementation of access restrictions. It strikes the language just described (laying out the requirement for a single, shared system and providing for waiver authority). In its place, the CREATES Act states that a generic drug may use a single, shared system or “a different comparable aspect of the elements to assure safe use.” This effectively eliminates the default requirement of a shared system as well as the need to ground waiver in the statute (i.e., burden or intellectual property considerations), which could in theory be helpful to FDA. But it may not be needed. Current law may be adequate to address situations where innovators decline to share their systems. The agency has explicit authority to approve a generic drug with access restrictions of the generic company’s own creation. There is no legal impediment to approval of the generic drug in this situation; the law is clear that FDA may approve generic drugs with their own systems, and the agency has already done so.<sup>57</sup>

The significance of section 4 of the CREATES Act lies in the language that follows this, authorizing FDA to “require” a single, shared system if it “determines that no different, comparable aspect of the elements to assure safe use could satisfy the requirements” of the REMS statute. Unlike current law, there would be no provision for waiver if the innovator’s access restrictions were protected by patent. Put another way, FDA would have the authority to order a patent owner to permit a third party to use its patents — simply because the third party’s products would not be safe without them. No principle of patent law permits a federal agency to override one company’s patent

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<sup>56</sup> This requirement applies only to generic drugs, not to biosimilar biologics.

<sup>57</sup> For instance, Jazz Pharmaceuticals has a REMS with elements to assure safe use for Xyrem (sodium oxybate), and it holds several patents associated with the REMS. FDA has separately approved a different “shared REMS” for generic sodium oxybate products. Currently, one generic company holds ANDA approval, and two others hold tentative approvals.

rights simply so that another company may market a safer product. If the patent owner will not license the patent, the third party's options are to seek invalidation of the patent or wait for patent expiry.

#### **D. Recommendations**

The CREATES Act will undermine pharmaceutical patent rights, which are essential to continuing innovation. And it is not clear that any legislative action is required. The alleged problem may be limited to a few innovative drugs, and it may be limited to generic companies that are not willing to provide appropriately robust assurances of liability protection for the companies that have assumed tremendous risk in bringing these tricky drugs to market. FDA may have the authority to address the challenge of preparing generic applications under the circumstances, and it certainly has the authority to permit separate access restrictions.

Congress could take other steps to encourage sales of restricted drugs and sharing of access systems. First, robust liability protections would provide innovators with more confidence that they can safely provide these products to third parties. Second, there may be ways to incentivize innovators to manufacture and sell products under patent protection, so that aspiring generic companies can perform testing. Third and similarly, there may be ways to incentivize innovators to find agreeable terms for shared access systems. This would be appropriate if, as a matter of public policy, we prefer shared systems because they are more efficient, or less confusing to third parties, or for other reasons. An alternative view, however, might be that the obligation to design around an innovator's patented access program will foster creativity and may lead to newer and better approaches to risk mitigation.

### **III. Unapproved Drugs Initiative**

In recent years, concerns have been raised about sudden sharp increases in the prices of drugs that have long been available at low cost. In some cases, the price increase results directly from FDA's "unapproved drugs initiative," which is the agency's approach to removing unapproved new drugs from the U.S. marketplace.<sup>58</sup> It is important to understand that in these cases, nothing untoward has occurred. Although a sudden and significant hike in the price of a long-available medicine is concerning from a public policy perspective, the system is working exactly as designed, and there may not be a better solution to the problem of illegally marketed unapproved drugs.

#### **A. Origins of the Unapproved Drugs Situation**

FDA estimates that there are several thousand drug products marketed in the United States without a required approval.<sup>59</sup> This corresponds to perhaps as few as three dozen (or as many as several hundred) active ingredients. Many of these have been marketed safely for decades or

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<sup>58</sup> We generally refer to the initiative as the unapproved "drugs" initiative, although in fact the only drugs that require approval are "new drugs." Many not-new drugs are lawfully marketed without approval and, in fact, over the counter. Most over-the-counter (OTC) medicines reach the market without an NDA, subject instead to the specifications laid out in a regulation known as an "OTC monograph."

In addition, sometimes new-to-the-market medicines are launched for the first time without NDA approval. This is unlawful. The focus of the unapproved drugs initiative is older medicines that satisfy the definition of "new drug" and are marketed without the required NDA approval.

<sup>59</sup> See generally FDA Guidance for FDA Staff and Industry, *MARKETING UNAPPROVED DRUGS COMPLIANCE POLICY GUIDE* (Sept. 2011).

longer,<sup>60</sup> and some are covered by health insurance.<sup>61</sup> Others have proven to be unsafe as used, causing them to be removed from the marketplace, though sometimes only after serious injuries and deaths.<sup>62</sup>

The presence of unapproved new drugs in the marketplace stems from the piecemeal evolution of the drug approval scheme over the course of the 20th century.

Beginning in 1938, federal law required an effective NDA before any company could introduce a new drug into interstate commerce. A “new drug” was any drug not generally recognized as safe (GRAS) under the conditions described in its labeling. Congress included a grandfather clause, which exempted drugs that had been regulated under the Food and Drugs Act of 1906. If the manufacturer made no changes to this drug or its labeling, the drug would not be deemed a “new drug” that required an NDA. This means that under the 1938 scheme a drug could reach the market lawfully without an NDA if: (1) it fell within the grandfather clause, or (2) it was generally recognized as safe (GRAS). During this time, many unapproved drugs also reached the market essentially as generics; they were copies of drugs with NDAs, and FDA permitted them onto the market without their own NDAs.<sup>63</sup>

In 1962, Congress added an effectiveness requirement to federal law. A drug would require an approved NDA unless it was generally recognized as safe and effective (GRASE) under the conditions described in its labeling.<sup>64</sup> Congress also directed FDA to review the efficacy of drugs that had reached the market pursuant to safety-only NDAs prior to 1962. This process was known as the “Drug Efficacy Study Implementation” (DESI).

- If FDA found a drug effective for its labeled indications, each company marketing the drug under an NDA was required to file a conforming supplement to its NDA. Anyone marketing a purported copy was required to submit an ANDA.
- If FDA found a drug ineffective for its labeled indications, neither the drug nor its copies could be marketed. The pre-1962 NDA would be withdrawn, and all of the drugs were required to be withdrawn from the market.
- Some drugs with pre-1962 NDAs may still be under DESI review. FDA policy permits these drugs (and their copies) to remain on the market until the proceeding finishes.

This process did not examine pre-1938 drugs that had been grandfathered or generic versions of those drugs. Nor did it examine products that reached the market without applications between 1938 and 1962 because they were deemed GRAS.

The 1962 Amendments also included a new grandfather clause. A drug was not subject to the effectiveness requirement if it was marketed prior to 1962 and it was a not-new drug at the time

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<sup>60</sup> See Aaron Kesselheim & Daniel Solon, *Incentives for Drug Development — The Curious Case of Colchicine*, 262 NEW. ENG. J. MED. 2045 (2010) (noting that colchicine in tablet form was widely available in the United States in the 19th century).

<sup>61</sup> One example is Hylira (sodium hyaluronate) 0.2% Gel, which is used to treat dry, scaly skin.

<sup>62</sup> For instance, FDA reports that an unapproved high potency Vitamin E intravenous injection “was associated with adverse reactions in about 100 premature infants, 40 of whom died.” UNAPPROVED DRUGS GUIDANCE, *supra* note 59, at 11.

<sup>63</sup> *Id.*, at 9. These were also known as “identical, related, or similar” (IRS) drugs.

<sup>64</sup> Also, the drug must have been used to a material extent or for a material time under those conditions. 21 U.S.C. § 321(p).

(meaning it was GRAS or grandfathered), provided neither the drug nor its labeling had since been modified.

### **B. Unapproved New Drugs on the Market Today**

In theory, there may be some unapproved drugs permissibly on the market today.<sup>65</sup> These would be: (1) drugs genuinely within the 1962 grandfather clause, (2) drugs genuinely GRASE, and (3) any drugs (whether under a pre-1962 NDA or a copy) with ongoing DESI proceedings. FDA takes the position that virtually no prescription drugs fall within the first two categories. Some companies may disagree. Removing these products from the market would require an expensive enforcement action in which the company's claim of grandfather or GRASE status would be litigated.

For the most part, however, unapproved drugs are unlawfully on the market. These are: (1) drugs found effective in DESI but for which no conforming application was filed; (2) drugs found ineffective in DESI but not removed from the market; and (3) drugs that are incorrectly claimed to be grandfathered or GRASE. Drugs in the second and third categories may present more of a health concern than drugs in the first category, provided the latter have not changed since they were reviewed.

### **C. FDA's Approach to Enforcement**

FDA does not have complete information on the drugs that are currently marketed without approval, and it does not have the resources to take enforcement action against every unapproved drug that is marketed unlawfully. It is committed to taking immediate enforcement action against any medicine that is new to the market and shipped without an approved application. With respect to older medicines that are marketed without required approval, however, the agency has adopted enforcement priorities.<sup>66</sup>

First, FDA takes a risk-based approach, prioritizing drugs that present public health concerns. Thus, for instance, it will take enforcement action against potentially unsafe drugs, including those that present a direct risk to health. It will also take enforcement action against drugs that lack evidence of effectiveness, because these drugs can pose an indirect health hazard by causing consumers to delay or discontinue appropriate medical care.

Second, FDA wants to encourage companies to complete the research necessary for approval of an NDA, because this "benefits the public health by increasing the assurance that marketed drugs are safe and effective" and because it "reduces the resources that FDA must expend on enforcement."<sup>67</sup> The agency also takes the position that once a single company has obtained approval of a particular older medicine, the other companies that market unapproved versions "present a direct challenge to the drug approval system."<sup>68</sup> FDA will therefore take enforcement

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<sup>65</sup> As noted *supra* note 58, most OTC (nonprescription) drugs are unapproved. They are deemed GRASE and may be marketed without an approved NDA.

<sup>66</sup> See generally UNAPPROVED DRUGS GUIDANCE, *supra* note 59.

<sup>67</sup> *Id.* at 7.

<sup>68</sup> *Id.*

action against the remaining companies, after providing a grace period for them to bring their products into compliance or remove the products from the marketplace voluntarily.<sup>69</sup>

#### **D. An Intractable Public Policy Problem**

FDA's solution has profound implications for patients and payers.

Approval of an NDA requires submission of safety and efficacy data that satisfy the high standard of approval in section 505 of the FDCA: that the drug is safe for use under the conditions described in the labeling and that there is "substantial evidence" of its effectiveness under those conditions. This generally requires data from two "adequate and well-controlled" clinical trials.<sup>70</sup>

Even if an older unapproved medicine has been marketed for half a century or longer, the company will usually need to generate the data needed to satisfy the substantial evidence standard. Any testing that may have been performed before the 1962 amendments added a formal effectiveness requirement is unlikely to meet today's standards in terms of clinical and statistical design. The statute does not permit approval based on observational data from decades of use. There is no way to avoid the reality that performing this research will cost a significant amount of money. Phase 3 trials — the pivotal trials providing substantial evidence of effectiveness — are usually the most expensive part of the clinical testing process.

Once a single company obtains approval of a previously unapproved older drug, and after FDA takes enforcement action against the other companies that market the drug without approval, the marketplace changes fundamentally. For a time, there will be only one version of the drug on the market, and the company that performed the research will need a way to recover its investment. Ordinarily federal law will permit FDA to approve generic applications after three years, but in the interim the price of a well-known and long-used drug may increase substantially.<sup>71</sup>

The sudden price increase is unquestionably troubling from a public policy perspective. But so is the distribution of unapproved new drugs that may be neither safe nor effective. And there may not be a way to bring unapproved drugs into the NDA framework without a disruption of this sort. No reasonable firm with a medicine that has been marketed for decades will invest hundreds of millions of dollars to support an NDA unless it is either forced or incentivized to do so.

- FDA cannot force these companies to do this research without threatening enforcement action. The threats will be effective only if backed by actual enforcement actions. Not only would this require substantial additional resources from Congress, but it would entail removing from the market medicines that are well-known, frequently used, safe, effective, and inexpensive.
- FDA can offer a modest incentive. Removal of the competing products, combined with a three-year period before generic competition, provides a competitive benefit. Depending on the prices that can be charged in the marketplace, this may enable the

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<sup>69</sup> Removing the unapproved versions also ensures that patients receive the version of the drug that has been subjected to rigorous modern testing and that is labeled in accordance with FDA requirements.

<sup>70</sup> It is possible sometimes to secure approval on the basis of one such trial, provided the applicant submits acceptable confirmatory data from other sources. 21 U.S.C. § 355(d).

<sup>71</sup> The statute gives the first NDA holder three years of exclusivity, during which time no ANDA can be approved. 21 U.S.C. § 355(j)(5)(F)(iii). This was the case with colchicine, for instance. Kesselheim, *supra* note 60, at 2045. If the drug treats a rare disease, the statute may provide seven years of orphan exclusivity, during which time no ANDA or even NDA may be approved for the same drug for the same use. 21 U.S.C. § 360cc.

company to recover its investment and some profit. This may provide the incentive to do the work. But this approach, too, entails removing from the market medicines that are well-known, frequently used, safe, effective, and inexpensive.

#### **E. Recommendations**

Policymakers decided in 1962 that all new drugs should be supported by robust evidence of safety and effectiveness. If we remain committed to that standard, then we must also recognize that the research in question will cost a significant amount of money. With respect to older medicines that lack approval, there is room to argue that this is not the best use of industry research dollars, because the research in question may simply corroborate the safety and effectiveness of a drug that is well-known and has been used safely for decades. For the same reason, it may not be the best use of exclusivity and the corresponding short-term period of higher prices. At the same time, it could be a necessary use of research dollars, if there is good reason to think some of the products present a public health risk.

Creative solutions may require congressional action, but more study and reflection are probably necessary before any proposals would be ripe. In my view, it would be helpful for this issue to be considered carefully by an expert working group comprising not only healthcare professionals (physicians, pharmacists, and others) but also experts from the relevant federal agencies, payers, legal and regulatory specialists, bioethicists, the involved companies, and patient groups.

Some solutions can probably be rejected out of hand. Appropriating funds for FDA to carry out enforcement action against every unapproved new drug on the market can probably be rejected, because it would be extremely expensive and might take important and cheap medicines away from patients. A public shaming campaign, calling out unapproved drugs and discouraging their use, may be problematic for the same reason; some of these drugs are safe, effective, and inexpensive. As a public health matter, we may not want to discourage their use, and there is no way to know which is which without doing the robust testing. Conversely, simply grandfathering all unapproved drugs on the market — exempting them from the NDA requirement — would raise public health concerns, because some of these drugs likely present safety and effectiveness problems. It would also raise fairness concerns, because it would effectively amount to amnesty for the companies that have declined to comply with federal law, after others have paid for and conducted research to bring their drugs into compliance. It may be worth exploring public funding for the research or — more creatively — a program in which the companies involved with respect to a particular ingredient pool their funds and collaborate on research. FDA might then approve all of the applications at the same time, and the drugs could compete on the basis of price in the market. Or it might be possible to perform the research collaboratively and then, on the theory that the drugs have also been marketed for more than half a century, deem the drugs GRASE. All of these proposals would likely have implications for other FDA programs, which would need to be weighed. It may be possible to incentivize the research some other way, but devising an effective, tailored mechanism will require an improved understanding of which drugs are at issue, as well as the business model of the types of companies that market these drugs. Accordingly, one preliminary step should be gathering information about the scope of the situation from all relevant sources — including FDA, but presumably also payers and perhaps data aggregators like IMS Health.

The outcome of any data-driven consultative process may simply be a recommendation that the current approach — in which FDA focuses on the drugs that present a public health risk and provides soft encouragement for preparation of NDAs for the other drugs — is the best solution, even though it is clearly imperfect. If we are truly committed to the current approval standard for

new drugs, perhaps we must tolerate temporarily high prices for older medicines that people have purchased for years inexpensively. If so, an aggressive public education campaign would be helpful to mitigate some of the backlash against FDA when one company secures approval and prices jump. Such a campaign would also be helpful in the interim while any consultative process is underway and recommendations are being prepared.

#### **IV. Conclusion**

The recommendations in this testimony, summarized below, reflect four core values. The first value is the public health mandate embodied in FDA's statutory mission: promotion of the public health through prompt and efficient review of clinical research and timely appropriate action on marketing of regulated products, and protection of the public health by ensuring that drugs are safe and effective. The second value is the open government principle embodied in the petition clause of the First Amendment, the agency's mission statement, the APA, and other federal statutes: transparency, access, and accountability. The third value is the importance of the patent property right to continued innovation in medicine, and the final value is the importance of evidence-based policymaking, both in the legislature and in administrative agencies.

## Recommendations

### Citizen petitions:

- Performing additional empirical work to examine the agency's disposition of the issues presented in petitions, rather than the requests stated in the petitions.
- Changing the statutory deadline back to 180 days for 505(q) petitions.
- Providing FDA more resources to handle petitions.
- Exploring ways to incentivize petitioners to generate robust data to accompany petitions that raise scientific issues.
- Exploring more ways to encourage and facilitate earlier filing of petitions that can be helpful to the agency in its review of applications.

### Use and distribution restrictions:

- Enacting robust protection for innovators from any liability under federal or state law arising out of use or administration of a product under REMS access restrictions once the drug has been sold or provided to a third party for testing purposes.
- Refraining from mandating sales of products that are protected by patents, and refraining from mandating sales of unpatented products pending closer review of the impact on incentives to innovate. Considering ways to incentivize sales.
- Refraining from needless amendments that simply confirm FDA's existing authority to permit separate systems for use and distribution restrictions. Refraining from giving FDA authority to order patent owners to share their patented access systems. Considering ways to incentivize sharing of innovator systems.
- Exploring whether there may be alternative ways for generic and biosimilar companies to obtain approval of their versions of products under access restrictions when those companies are unable to purchase the FDA-approved reference product for testing.

### Unapproved drugs initiative:

- Obtaining robust data on the scope of the situation from all relevant sources.
- Commissioning an expert working group to recommend policy solutions.
- Engaging a public education campaign to mitigate some of the backlash against FDA when it approves an NDA for an older medicine and prices temporarily increase.