

Intellectual Property

A SECOND LOOK AT THE CREATES ACT: WHAT'S NOT BEING SAID

By Erika Lietzan

Note from the Editor:

This article critically discusses the CREATES Act, which is currently pending in the Senate.

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- Written Submission of Robin Feldman, *Hearing on the CREATES Act: Ending Regulatory Abuse, Protecting Consumers and Ensuring Drug Price Competition*, Senate Committee on the Judiciary, Subcommittee on Antitrust, Competition Policy, and Consumer Rights (June 21, 2016) [*Hearing*], available at <https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Feldman%20Testimony.pdf>.
- Statement of Senator Patrick Leahy, *Hearing*, available at <https://www.leahy.senate.gov/press/statement-of-senator-patrick-leahy-hearing-on-the-creates-act-ending-regulatory-abuse-protecting-consumers-and-ensuring-drug-price-competition>.
- Ameet Sarpatwari, Jerry Avorn, Aaron S. Kesselheim, *Using a Drug-Safety Tool to Prevent Competition*, 370 NEW ENG. J. MED. 16 (2014), available at <http://www.nejm.org/doi/pdf/10.1056/NEJMp1400488>.
- 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), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2555791.
- Rachel Sachs, *Thoughtful CREATES Act May Help Speed Generic Drug Approvals*, BILL OF HEALTH (2016), available at <http://blogs.harvard.edu/billofhealth/2016/06/17/thoughtful-creates-act-may-help-speed-generic-drug-approvals/>.

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In the late 1950s and early 1960s, a German pharmaceutical company marketed a new medicine in Europe that contained thalidomide.¹ Thalidomide was sold—over the counter, for a while, in West Germany—for a variety of uses including the treatment of morning sickness in pregnant women. As it turns out, thalidomide is a powerful “teratogen,” meaning it causes severe malformation of embryos and sometimes fetal death. In particular, it leads to phocomelia (in which the hands or feet are attached close to the torso and the limbs are significantly underdeveloped) and amelia (in which the limbs are absent altogether). The U.S. Food and Drug Administration (FDA)—which rejected a new drug application (NDA) for thalidomide at the time—estimates that more than 10,000 children in 46 countries were born with deformities as a result of thalidomide use.²

In 1998, FDA finally approved a drug for the U.S. market containing thalidomide. Celgene’s Thalomid® was initially approved for treatment of moderate to severe erythema nodosum leprosum, a complication of leprosy. Today, Thalomid is also approved to treat multiple myeloma, a cancer that forms in the white blood cells. FDA conditioned approval on the implementation of rigorous restrictions on distribution of the drug, and Celgene responded with a novel program aimed to achieve zero fetal exposure.³ Today, pursuant to an FDA-approved “risk evaluation and mitigation strategy” (REMS), Celgene distributes Thalomid through a network of certified pharmacies (which are required to, among other things, counsel patients about the risk) and only in response to prescriptions from specially trained and certified prescribers, who in turn must counsel patients, provide contraception, and administer pregnancy tests. The protocol is enforced through a secure database and assignment of unique authorization codes; the codes are provided once all the steps have been completed, and they are required before a prescription can be filled.⁴ Celgene holds patents covering the use of thalidomide to treat multiple

- 1 For an excellent account of the thalidomide story, see Daniel Carpenter, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 213–297 (2010).
- 2 Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, FDA CONSUMER MAGAZINE (2001), available at http://permanent.access.gpo.gov/lps1609/www.fda.gov/fdac/features/2001/201_kelsey.html.
- 3 See 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) (“Celgene Brief”), at 7–8.
- 4 See generally REMS, Thalomid (Apr. 2016); see also Celgene Brief, *supra* note 3.

myeloma and also holds patents on Thalomid's formulation and the REMS.⁵

Notwithstanding the rigorous REMS protocol, Celgene has provided Thalomid to generic drug companies that want to develop and test generic copies of the drug and that agree to Celgene's risk mitigation policies. Celgene has done so when those companies provided documentation and information confirming steps and safeguards that would not only prevent fetal exposure but also minimize the risk for Celgene's business and reputation, such as risk from products liability litigation.⁶ Mylan—one of the generic companies—has declined to provide information requested by Celgene, however, and instead filed an antitrust suit that is still pending in federal court.⁷

The story of thalidomide provides helpful context for a bill recently introduced by Senator Patrick Leahy and three colleagues: the "Creating and Restoring Equal Access to Equivalent Samples Act" or CREATES Act. This bill would require innovative drug companies like Celgene to manufacture and sell their products to their competitors, and it would also require these companies to share with these same competitors the use and distribution arrangements they developed to manage the risks of the products.⁸ These requirements would apply even if this meant requiring the company to practice its patents for the benefit of its competitors (in the first case) or requiring it to license its patents to or share its trade secrets with the competitors (in the second case).

Earlier proposals relating generally to the same topic, but differing in approach, were introduced in 2014 and 2015 but failed to move forward.⁹ Several high profile drug pricing controversies in 2015 and 2016 have placed the biopharmaceutical industry in the congressional and media spotlight, however, and momentum for the CREATES Act has picked up somewhat in the second session of the current Congress.¹⁰ Supporters describe the bill as the latest remedy for the "regulatory abuse" and "predatory delay tactics" of the innovating biopharmaceutical companies and thus part of a broader program to address "high" drug prices.¹¹

This article aims to add balance to public discussion of the CREATES Act. It explains some of what is *not* being said—about use and distribution restrictions associated with new medicines, about the underlying complaints from the generics industry, and about the design and likely effect of

the bill. Part I discusses pharmaceutical risk management and FDA's decades-old practice of requiring use and distribution restrictions for certain drugs to manage risk. Part II assesses the complaints levied against the research-based companies and the proposals offered to address those complaints. Part III suggests possible practical effects of the proposed legislation and broader implications for innovation policy.

I. UNDERSTANDING USE AND DISTRIBUTION RESTRICTIONS

The heart of the case for the CREATES Act is a complaint that innovative biopharmaceutical companies adopt distribution restrictions for new medicines in bad faith, that is, with the goal and effect of making it more difficult for generic drug companies to develop and market copies—or that the companies, regardless of their motivation in adopting distribution restrictions, misuse those restrictions to the same end. These distribution restrictions generally take the form of REMS, which were authorized under a 2007 amendment to the Federal Food, Drug, and Cosmetic Act (FDCA). The complained-of behavior is often referred to as "REMS abuse," and it is also said to be increasing substantially.

There are some common misperceptions about use and distribution restrictions, which may be coloring the current debate over and whether and why the CREATES Act is necessary. As explained below, new medicines always require post-approval risk management, and FDA has been requiring distribution restrictions in exceptional cases for more than 25 years. The current REMS authority is narrow, limiting the types of restrictions that can be imposed as REMS, as well as the basis for their imposition. Establishing and maintaining a REMS under this authority can also be extremely burdensome. There are fewer REMS with distribution restrictions than people may realize, and many of them are legacy arrangements, imposed by the agency long before the 2007 amendment was passed.

A. Post-Approval Risk Assessment and Management

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 benefits of the product outweigh its risks when it is used as labeled, meaning for the indicated population and purpose. Safety and effectiveness are not absolutes; they are always relative. Moreover, every approved medicine has risks. These include *known* risks; for instance, 5% of people in the clinical trials may have experienced a particular side effect (such as nausea) which can now be expected in about 5% of real world patients. Another type of known risk might be a more significant clinical consequence in a very small percentage of patients, which will 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. These known risks are captured in the product's approved labeling for healthcare professionals. There is also a possibility of *unknown* risks; this is because no premarket clinical program of reasonable length can detect extremely rare side effects, nor can controlled testing identify

5 Celgene Brief, *supra* note 3, at 9.

6 *Id.*

7 *Id.*

8 S. 3056 (114th Cong.) (introduced June 21, 2016).

9 H.R. 2841 (114th Cong.) (introduced June 19, 2015); H.R. 5657 (113th Cong.) (introduced Sept. 19, 2014).

10 The Antitrust subcommittee of the Senate Judiciary Committee recently held a hearing on the bill at which five witnesses spoke in support of the legislation and one witness spoke in opposition.

11 See Statement of Senator Patrick Leahy, Hearing on "The CREATES Act: Ending Regulatory Abuse, Protecting Consumers, and Ensuring Drug Price Competition" (June 21, 2016).

all of the consequences that might stem from use in real-world conditions.

As a result of this uncertainty, the “sponsor” of a new medicine—the company that develops the medicine and brings it to market with FDA approval—engages in risk assessment and risk minimization after product approval. The primary way that FDA and a company *assess* the risk of an approved drug or biologic is through pharmacovigilance: the company files quarterly safety reports for the first three years after approval and has a permanent obligation to report individual adverse events that are both serious and unexpected.¹² The primary ways that FDA and a company *manage* the risks of a new drug or biologic are through the approval decision itself and through the labeling that FDA approves for healthcare professionals. This labeling synthesizes all of 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 use of the product to treat (or diagnose or prevent) a particular illness, with a particular dosing regimen, and 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).¹³

In some instances, these standard means of risk assessment and minimization may be insufficient. With respect to risk mitigation, FDA therefore sometimes requires sponsors to disseminate special labeling for patients that focuses on the risks associated with the products. This practice dates to 1968 and began in earnest in 1970 when FDA required a patient package insert regarding blood clot risk for oral contraceptives.¹⁴ Today, patient labeling often takes the form of a Medication Guide, or “MedGuide.” FDA introduced MedGuides in 1995, after it grew concerned that “inappropriate use of prescription medications” was “resulting in serious medical injury.”¹⁵ The agency will require a MedGuide for any product that poses a “serious and significant public health concern” such that distribution of FDA-approved patient information is “necessary for the product’s safe and effective use.”¹⁶

B. The Development of Use and Distribution Restrictions

In some instances, despite a compelling public health need for a particular product, physician and patient labeling may be insufficient to ensure that the benefits of the product outweigh its risks. For decades, therefore, FDA has imposed use

and distribution restrictions on drugs with unusually significant toxicity profiles.

Initially, the agency extracted agreements to restrictions as part of the drug approval process. For example, clozapine, used to treat schizophrenia, can cause agranulocytosis, a deficiency in absolute neutrophils—a type of white blood cell—that can lead to serious infection and death.¹⁷ FDA approved Clozaril® (clozapine) in 1989 only after the sponsor agreed to make distribution of the drug contingent on weekly blood monitoring.¹⁸ The agency similarly extracted an agreement for distribution restrictions when it approved Tikosyn® (dofetilide) in 1999, due to life-threatening arrhythmia.¹⁹ In other cases, safety issues arose after approval, and FDA obtained an agreement to distribution restrictions by threatening to initiate withdrawal proceedings. After approval of the antibiotic Trovan® (trovafloxacin) in 1998, for instance, the agency received reports of over 100 cases of liver toxicity, including 14 reports of acute liver failure, many of which were fatal or required a liver transplant. As an alternative to market withdrawal, FDA issued a public health advisory that “effectively restricted use of this drug to hospitalized patients with certain serious life or limb-threatening infections,” and the sponsor agreed to restrict distribution to pharmacies in hospitals and long-term nursing care facilities.²⁰

After 1992, the agency sometimes invoked its new “subpart H” regulations.²¹ These regulations apply only to products for treatment of serious or life-threatening conditions that provide meaningful benefit over existing treatments.²² But in addition to authorizing approval on the basis of surrogate endpoints, they authorize approval of a product “shown to be effective” subject to use or distribution restrictions.²³ Although the regulations offer two examples—restricting distribution to particular facilities or physicians with specific training or experience and conditioning distribution on the performance of particular medical procedures—they assert broad authority to impose whatever “postmarketing restrictions” are necessary “to assure safe use.”²⁴ FDA rejected the argument that the statute authorized only an “up or down” decision on an application and that the agency consequently lacked statutory authority to

12 21 C.F.R. §§ 314.80, 600.80.

13 See 21 C.F.R. § 201.57.

14 35 Fed. Reg. 9001 (June 11, 1970).

15 60 Fed. Reg. 44182, 44199 (Aug. 24, 1995).

16 21 C.F.R. § 208.1; see 63 Fed. Reg. 66378 (Dec. 1, 1998). A Medication Guide will be required if: (1) patient labeling could help prevent serious adverse effects; (2) the product has serious risks relative to its benefits, and information concerning the risks could affect patient decisions to use the product; or (3) the product is important to health, and patient adherence to directions for use is crucial to its effectiveness. 21 C.F.R. § 208.1(c).

17 See GAO, FDA Approval of Mifeprex: GAO-08-751 (Aug. 2008), at 44.

18 See FDA’s Accelerated Drug Approval Proposal Would Permit Restricted Distribution of Highly Toxic, Beneficial Products, THE PINK SHEET (Oct. 28, 1991).

19 GAO Report, *supra* note 17.

20 See FDA, Risk Assessment and Risk Mitigation Review, NDA 22406 (rivaroxaban), Appendix on Drug-Induced Liver Injury (Feb. 13, 2009) at 25, 34–35 (describing this as an instance “where regulatory action prompted by concern about severe [drug-induced liver injury] included risk management actions which stopped short of market withdrawal”).

21 21 C.F.R. part 314, subpart H. The biologics regulations contain parallel authority. 21 C.F.R. part 601 subpart E.

22 21 C.F.R. § 314.500, § 601.40.

23 21 C.F.R. § 314.520, § 601.42.

24 *Id.*

impose restrictions as a condition of approval.²⁵ This question was never resolved by a court, and amendment of the statute in 2007 mooted the issue.

In the years leading up to the 2007 amendments, FDA embarked on additional initiatives to strengthen its drug safety program. These initiatives included the development of detailed guidance documents on risk assessment and minimization.²⁶ The guidance on risk minimization, released in draft in 2004 and finalized in 2005, introduced the “Risk Minimization Action Plan,” or RiskMAP.²⁷ FDA identified numerous processes and systems that a drug’s sponsor might adopt to minimize its known risks. These included the following:

- Targeted education and outreach to communicate risks and appropriate safety behaviors to healthcare professionals or patients. This might involve training programs for physicians or patients, patient labeling, and patient–sponsor interaction programs like disease management or patient access programs.
- Reminder systems, processes, or forms to foster reduced–risk prescribing and use. This might involve consent forms; healthcare provider training programs (for instance with testing); enrollment of physicians, pharmacies, or patients in data collection systems that reinforce appropriate product use; specialized product packaging that enhances safe use of the product in

certain patients; and specialized systems or records to attest that safety measures have been followed.

- Performance–linked access systems that guide prescribing, dispensing, and use of the product to the population and condition of use most likely to confer benefits and minimize risks. This might involve limiting prescription to specially certified prescribers, limiting product dispensing to pharmacies that are specially certified, and limiting dispensing to patients who have evidence or documentation of safe use conditions (for instance, lab results).
- If the goal was ultimately to impose direct conditions on healthcare professionals and patients, the sponsor agreed with FDA that it would impose those conditions itself through appropriate measures. These could include contractual arrangements with individual physicians or pharmacists, pharmacies, and distributors.²⁸

By mid–2007, FDA had restricted distribution of nine drugs via subpart H: Actiq® (fentanyl citrate), Accutane® (isotretinoin), Lotronex® (alosetron hydrochloride), Mifeprex® (mifepristone), Plenaxis® (abarelix), Revlimid® (lenalidomide), Thalomid® (thalidomide), Tracleer® (bosentan), and Xyrem® (sodium oxybate).²⁹ The nature of the safety problems that triggered distribution restrictions varied. Actiq, for instance, is associated with a risk of misuse, abuse, addiction, overdose and serious complications due to medication errors.³⁰ Thalomid, Revlimid, and Accutane are associated with serious birth defects in developing embryos.³¹ Lotronex is associated with the risk of ischemic colitis and serious complications of constipation, resulting in hospitalization, blood transfusion, surgery, and death.³² Tracleer is teratogenic and also associated with liver failure.³³ The nature of the restrictions also varied.³⁴ For seven of the nine products, FDA required that distribution be limited to authorized distributors and pharmacies. For eight, FDA required that dispensing or distribution of the drug be contingent on verification that physicians and others had enrolled or registered in the distribution program, or that patients had complied with certain safety measures. For five, the agency required a formal registry of all prescribers and patients. For all nine products,

25 Those who made this argument cited *American Pharmaceutical Association (APhA) v. Weinberger*, 377 F. Supp. 824, 829 n. 9 (D.D.C. 1974), *aff’d sub nom.* *APhA v. Mathews*, 530 F.2d 1054 (D.C. Cir 1976) (“As outlined in the Court’s opinion, FDA’s discretion under the Act’s NDA provisions is limited to either approving or denying NDAs and nowhere is FDA empowered to approve an NDA upon the condition that the drug be distributed only through specified channels.”). The *Weinberger* case involved methadone, a controlled substance approved as an analgesic and antitussive but not, at the time, for detoxification treatment of opioid addiction. FDA had permitted investigational use for heroin addiction, but grew concerned about diversion and misuse and rescinded this permission. The agency also initiated withdrawal of approval of the eight NDAs and published a regulation that purported to treat the drug as approved for opioid detoxification or maintenance subject to distribution restrictions. *See* 37 Fed. Reg. 26790 (Dec. 15, 1972); 21 C.F.R. § 130.44 (1973). Several commenters argued that the new drug provisions of the FDCA did not authorize the approach in question but gave FDA only three options: distribution controls in connection with investigational status, new drug approval with unrestricted and uncontrolled distribution, or withdrawal from use. The district court found that the regulation exceeded FDA’s statutory authority, but appeared to limit the scope of its holding to drugs that are controlled substances, the permissible distribution of which is “clearly within the jurisdiction of the Justice Department.” 377 F. Supp. at 831. The case was clearly relevant to the question whether FDA’s 1992 accelerated approval regulations were permissible, but it was not directly on point.

26 FDA committed to providing this guidance when Congress reauthorized user fees for the agency in 2002. *See* PDUFA III Reauthorization Performance Goals and Procedures, at § VIII.e.

27 FDA, *Guidance for Industry, Development and Use of Risk Minimization Action Plans* (March 2005); 69 Fed. Reg. 25130 (May 5, 2004).

28 Scott Gottlieb, *Drug Safety Proposals and the Intrusion of Federal Regulation into Patient Freedom and Medical Practice*, HEALTH AFFAIRS 26, no. 3 (2007): 664–677.

29 *See* GAO Report, *supra* note 17, at 5. FDA originally approved Accutane in 1982, long before it promulgated subpart H. In 2005, however, and with the company’s agreement, the agency placed Accutane under subpart H pursuant to a supplemental new drug application.

30 REMS, *Transmucosal Immediate–Release Fentanyl Products* (Dec. 2014).

31 REMS, *Thalomid* (Apr. 2016); REMS, *Revlimid* (Apr. 2016); REMS, *Isotretinoin* (July 2016).

32 REMS, *Lotronex* (Apr. 2016).

33 REMS, *Tracleer* (Dec. 2015).

34 *See generally* GAO Report, *supra* note 17.

FDA required the sponsor to implement an educational program for patients, prescribers, and/or pharmacists.

Also by mid-2007, various products that had not been approved under subpart H were subject to use or distribution restrictions embodied in RiskMAPs. One example was the multiple sclerosis drug, Tysabri® (natalizumab).³⁵ Biogen Idec had withdrawn Tysabri from the market in 2005 due to cases of progressive multifocal leukoencephalopathy, an opportunistic infection of the brain cells.³⁶ FDA and Biogen Idec developed a RiskMAP that would allow the drug to be reintroduced a year later.³⁷ All patients, prescribers, pharmacies, and infusion centers involved in distribution and use of Tysabri were registered and tracked. Distribution was limited to a dozen specialty pharmacies, and administration was limited to around 4500 infusion centers and physician offices. Patients were required to complete a checklist (for instance, confirming that they had not started taking any immunosuppressants) before each infusion to verify continuing eligibility. Baseline MRIs were also recommended.³⁸ Another example was Accutane® (isotretinoin), an acne medication associated with severe birth defects; FDA did not approve the product under subpart H, and in fact the product was initially marketed only with labeling information about the risk. The education-only approach failed, leading to restricted distribution under a RiskMAP and placement of the drug under subpart H.³⁹

C. The Narrow REMS Authority

Following these many years of discussion of risk management, Congress amended the FDCA in 2007 to authorize FDA to impose a REMS with respect to any new drug or biological product. Four points about the new REMS authority are important to understanding the CREATES Act.

First, the standard for imposition of a REMS is high; these strategies were intended to be rare. When it initially approves a product, FDA may require a REMS only if it concludes that the REMS is necessary to ensure the benefits of the drug outweigh its risks.⁴⁰ Put another way, the agency may require a REMS only if the drug would not be approvable without the REMS in place.⁴¹ This leads directly to the *second* point, that if the standard for a REMS is understood and applied correctly, enactment of the REMS authority should lead to approval of

more drugs than before. If a REMS can be imposed only when necessary to ensure the benefits of the drug outweigh its risks, then the REMS will always make an otherwise unapprovable drug approvable. This could create a perception that more new drugs have REMS after 2007 than had risk management plans prior.

Third, the statute limits the elements in a REMS. Whenever the REMS standard is met, FDA may require: (1) a MedGuide, (2) a patient package insert, or (3) planned communications with healthcare providers.⁴² Although the agency had required these tools previously, codification gave it additional enforcement authorities. But FDA may impose use and distribution restrictions only if an *additional* standard is met. Specifically, these restrictions may be imposed only to mitigate a specific serious adverse drug experience identified in the product's labeling, and only if a MedGuide, patient package insert, and plan for communications with healthcare providers are insufficient to mitigate that risk.⁴³ Moreover, the statute permits only six types of restriction: (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 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.⁴⁴ The statute refers to these restrictions as "elements to assure safe use," and they are known more generally by the acronym ETASU.

Fourth, a REMS is a significant undertaking.⁴⁵ Designing and developing a REMS and associated tools takes time, and it is an iterative process in which FDA is heavily engaged.⁴⁶ The REMS submission must identify the goals of the strategy and lay out pragmatic, specific, and measurable objectives that will lead to processes or behaviors that in turn will lead to achievement of

35 *The Risk of Risk Management*, THE PINK SHEET (Jan. 1, 2007).

36 *Tysabri Withdrawn Pending Analysis of Safety Signal in Long Term Trial*, THE PINK SHEET (March 7, 2005); *Tysabri Return to Market with Expanded Indication Backed by Committee*, THE PINK SHEET (March 13, 2006).

37 See Biogen Idec, Form 10-K (Feb. 21, 2007), at 7.

38 *Tysabri Out of Remission; Returns with Updated Indication, Risk Management*, THE PINK SHEET (June 12, 2006).

39 *Managing Risk Management: FDA Wants to Gauge Effectiveness of RiskMAPS*, THE PINK SHEET (Apr. 3, 2006). See also *supra* note 29.

40 21 U.S.C. § 355-1(a)(1).

41 After a product's initial approval, the agency may impose a REMS only if this standard is met (the REMS is necessary to ensure the benefits outweigh the risks) and the agency is acting on new safety information *Id.* § 355-1(a)(2)(A).

42 *Id.* § 355-1(e).

43 *Id.* § 355-1(f)(1).

44 *Id.* § 355-1(f)(3).

45 See generally FDA, Draft Guidance for Industry, Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications (Sept. 2009). Indeed, this was the goal; as a key health staffer on the Senate HELP Committee explained in early 2007, they "require a lot of work." Managing Risk Management, *supra* note 39.

46 Much of the regulatory history of each REMS—including sometimes the timeline relating to submissions, meetings, and calls with the agency about the proposal, the materials reviewed and informing the review, and evolution in the proposed elements—can be pieced together from the "Administrative Correspondence" and FDA's formal "Risk Assessment and Risk Mitigation Review," both available through the Drugs@FDA database on the agency website. Despite redactions for confidential commercial information, the latter amply illustrate the agency closely reviewing and frequently changing, or dictating, all aspects of REMS with ETASU, from the goals, to elements, to scope (for instance, definitions that effectively dictate which patients are monitored), to design and functionality of written materials.

the goals. (To clarify the distinction: a goal might be to eliminate a particular risk associated with drug–drug interactions, and the objectives might be lowering co–prescribing rates and co–dispensing rates.) Goals and objectives must be explained and justified. If the REMS imposes distribution restrictions, the sponsor must describe the restrictions and any tools (processes or systems) used to implement the restrictions. This may require providing evidence of the effectiveness of the restriction or tool, including results from testing. The sponsor must explain how the restrictions correspond to the risk in question, explain how they will mitigate the risk, verify that the restrictions are not unduly burdensome on patient access to the drug, describe the burden on the healthcare system, explain how the restrictions compare with those required for other drugs with similar risks, and explain how the restrictions are designed to be compatible with established distribution, procurement, and dispensing systems.

FDA must approve every aspect of the REMS, including the restrictions themselves, the tools used to implement the restrictions, and all associated materials—survey documents, methodologies, attestations for physicians to sign, procedures, consent forms, patient education materials, and so forth. The sponsor must establish and follow a timetable for regular assessment of the REMS and must monitor and evaluate the implementation of any distribution restrictions. This can require development and maintenance of a validated and secure database of certified entities, for instance, or creation of a tool and protocol for audits of pharmacies. If the sponsor fails to comply with a requirement of its REMS, the drug is deemed “misbranded” under the FDCA. This gives FDA the ability to seize the product, prosecute the company criminally, and seek injunctive relief.⁴⁷ Failure to comply with a REMS requirement can also give rise to civil money penalties.⁴⁸

Since enactment of the REMS provision, FDA has approved several drugs and biologics with REMS that include elements to assure safe use. In 2013, for instance, it approved Adempas[®] (riociguat) for treatment of chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension. These are serious and disabling lung conditions, but the drug is teratogenic, which leads to distribution restrictions to minimize the risk of fetal exposure.⁴⁹ FDA also approved Opsumit[®] (macitentan) for treatment of pulmonary arterial hypertension, though this drug, too, is teratogenic.⁵⁰ Kynamro[®] (mipomersin sodium) was approved to treat patients with homozygous familial hypercholesterolemia, a rare genetic lipid disorder that can lead to low density lipoprotein (LDL, the “bad” cholesterol) levels up

to 1000 mg/dL and that is associated with a significantly reduced life expectancy. Kynamro is associated with hepatotoxicity.⁵¹

The 2007 legislation also imposed REMS requirements, retroactively, on products approved before its effective date.⁵² Any already approved drug or biological product with use or distribution restrictions that qualified as ETASU under the statute was deemed to have an approved REMS. In 2008, the agency listed the 18 approved products to which this pertained.⁵³ Many of the drugs that appear to be a focal point of the current “REMS abuse” controversy—such as Thalomid and Revlimid—were on this list.

D. Other Use and Distribution Restrictions

It is possible for a new drug or biological product to 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. To give an example, Genentech limits distribution of Avastin[®] (bevacizumab), approved for treatment of a half dozen different types of cancer, due to extensive counterfeiting.⁵⁴ The product may be purchased only from a list of authorized distributors contractually committed to the company to purchase only from Genentech and not to distribute to secondary wholesalers.⁵⁵ Counterfeit versions in circulation outside the closed distribution network have lacked the active ingredient, putting patients at risk.⁵⁶ Other drugs

47 21 U.S.C. §§ 331, 332, 333(a), 352(y).

48 21 U.S.C. § 333(f)(4)(A).

49 REMS, Adempas (Dec. 2015).

50 REMS, Opsumit (Feb. 2016).

51 REMS, Kynamro (July 2015).

52 Pub. L. No. 110–85, § 908(b).

53 These were: Plenaxis (abarelix), Lotronex (alosetron), Letairis (ambrisentan), Tracleer (bosentan), Clozaril (clozapine), Fazaclor ODT (clozapine), Tikosyn (dofetilide), Soliris (eculizumab), Ionsys (fentanyl PCA), Actiq (fentanyl citrate), Accutane (isotretinoin), Revlimid (lenalidomide), Mifeprex (mifepristone), Tysabri (natalizumab), ACAM2000 (smallpox vaccine), Xyrem (sodium oxybate), and Thalomid (thalidomide). 73 Fed. Reg. 16313, 16314 (Mar. 27, 2008).

54 See TK Mackey et al., *After counterfeit Avastin[®]—what have we learned and what can be done?*, NAT. REV. CLIN. ONCOL. 2015 May; 12(5): 302–308; Jack McCain, *Connecting Patients with Specialty Products: The Future of Specialty Drug Distribution*, BIOTECHNOLOGY HEALTHCARE 2012 Fall; 9(3): 13–16.

55 See Avastin Distribution, <https://www.genentech-access.com/hcp/brands/avastin/learn-about-our-services/product-distribution.html>.

56 See FDA, Counterfeit Version of Avastin in U.S. Distribution (July 10, 2012).

may be subject to distribution restrictions in connection with resolution of manufacturing compliance issues.⁵⁷

II. EXPLORING THE COMPLAINTS RELATING TO GENERIC DRUGS AND BIOSIMILAR BIOLOGICS

This part explores the concerns that have been raised about the impact of use and distribution restrictions—including REMS with ETASU—on approval of generic drugs and biosimilar biologics. It begins by describing the relationship between abbreviated approval of generic drugs and biosimilar biologics and innovator intellectual property. It then analyzes the complaints that the CREATES Act purports to address and the solutions that the bill offers.

A. Abbreviated Approvals and Innovator Intellectual Property

An innovator's new drug or biologics license application typically contains data from dozens of laboratory, animal, and clinical trials, gathered over as many as ten or twelve years. Abbreviated applications generally propose a copy (or near-copy in the case of a biosimilar) and rely on this research. Although they may rely on this research (after an appropriate period of time), generic drug and biosimilar applicants are always required to respect the innovator's intellectual property.⁵⁸

The biopharmaceutical industry is highly dependent on patent protection. A variety of different inventions associated with a particular new drug or biologic may be patented. The Patent Act protects the property right of an inventor in "any new and useful process, machine, manufacture, or any composition of matter, or any new and useful improvement thereof."⁵⁹ In the case of a new drug or biologic, this could include the drug substance itself (active ingredient), the formulation (a particular combination of active ingredient and inactive ingredients), as well as numerous methods and processes—such as a method of using the product, or a method of manufacturing the product. It could also include how the company implements, monitors, or assesses any particular distribution restrictions, or associated tools, to mitigate the drug's risks. Provided the invention satisfies the statutory requirements of novelty, non-obviousness, and utility, and provided the patent application adequately describes and distinctly claims the invention, federal law protects the inventor's property right for 20 years from the date of the patent application.⁶⁰ This in turn means the inventor may exclude—generally for 20 years—any other person from making, using,

selling, offering to sell, or importing the invention. Patent law allows a generic or biosimilar applicant to develop its product and submit its application prior to patent expiry, but it does not require the patent holder to assist the applicant in carrying out this activity.⁶¹ Any resulting application during the patent term is deemed an artificial act of patent infringement, facilitating evaluation of patent issues prior to product launch.⁶² There is no change to the underlying patent law. The patent owner may therefore exclude, for the term of the patent, the generic or biosimilar applicant from making, using, selling, offering to sell, or importing its invention, whatever that invention might be.

New drug and biologic innovators are also heavily dependent on trade secret protection. Generally speaking, trade secret law protects ideas, inventions, and knowledge that are kept mostly secret by a company (aside from, for instance, disclosure to FDA in a marketing application) and that are valuable to the company because of the secrecy.⁶³ New drug applications and biologics license applications contain extensive trade secrets and confidential commercial information—including detailed "chemistry, manufacturing, and controls" information about their manufacturing processes, and extensive data from and information relating to years of laboratory, preclinical, and clinical testing.⁶⁴ Various materials and processes associated with a use or distribution restriction could be trade secret, including, for instance, internal company protocols associated with auditing third party compliance. Although generic and biosimilar applicants may rely (indirectly) on the research performed by the pioneer *after* a period of "data exclusivity" has expired, they do not have access to the innovator's trade secrets, nor may FDA consider those trade secrets when approving their products.

B. First Complaint: Sale of Reference Products for Testing Purposes

Generic drug and biosimilar applications are comparative applications. An abbreviated new drug application (ANDA) for a generic drug must demonstrate that the proposed generic drug is the same as, and bioequivalent to, an innovator's drug, also known as its reference drug or reference listed drug.⁶⁵ The

57 For example, a medically necessary drug might be subject to limited distribution as part of a consent decree that otherwise requires the company to stop manufacture and distribution of its products while it addresses compliance issues. This was the case for Celestone[®] Soluspan[®] (betamethasone sodium phosphate and betamethasone acetate) injection and Celestone[®] (betamethasone sodium phosphate) injection. See 71 Fed. Reg. 2047 (Jan. 12, 2006).

58 In addition to patents and trade secrets, discussed in the text, innovators also hold trademarks and, in some cases, may hold copyrights that are relevant.

59 35 U.S.C. § 101.

60 35 U.S.C. §§ 102, 103, 112, 154. In the case of a divisional, continuation, or continuation-in-part patent, the 20-year term begins with the date of the parent patent application.

61 35 U.S.C. § 271(e)(1) (deeming it not an act of infringement to make, use, offer to sell, sell, or import a patented product "solely for uses reasonably related to the development and submission of information under a federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products").

62 35 U.S.C. § 271(e)(2) (deeming it an act of infringement to submit an ANDA or biosimilar application during the patent term if the applicant seeks to market prior to patent expiry—i.e., if the applicant challenges the patent in question).

63 *E.g.*, RESTATEMENT (FIRST) OF TORTS § 757 cmt. b (1939); Uniform Trade Secrets Act § 1(4) (amended 1985); RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39 (1995).

64 See generally 39 Fed. Reg. 44602 (Dec. 24, 1974); 21 C.F.R. §§ 314.430, 601.51.

65 21 U.S.C. § 355(j)(2)(A)(iv). The proposed generic must have the same active ingredient, route of administration, dosage form, and strength, although FDA will permit deviations if no clinical data are necessary to establish its safety and effectiveness. 21 U.S.C. § 355(j)(2)(C). The agency may not require clinical data in a generic application, apart from pharmacokinetic data needed to show bioequivalence. 21 U.S.C. § 355(j)

generic applicant therefore conducts comparative analytical testing to show that the active ingredients are the same, and it conducts modest bioequivalence testing. The latter might entail a comparative pharmacokinetic study in a few dozen healthy volunteers. An abbreviated application for a biosimilar biologic must demonstrate that the proposed biosimilar is highly similar to its reference product and that there are no clinically meaningful differences between the two.⁶⁶ A biosimilar applicant conducts comparative analytical testing as well as comparative preclinical and clinical testing; the approvals to date indicate this might entail administration of both products to 500 or even 1000 patients, in some cases for months or even perhaps over a year.

To obtain the reference product for purposes of comparative testing, the 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 the innovator to sell its product to anyone for purposes of comparative testing (or for any other reason); the underlying premise of both schemes, in fact, is that a medicinal product is sold specifically for use in treating, preventing, or mitigating a disease. FDA does not have the authority to require such a sale, nor has it ever asserted that it did. Moreover, there is no statutory exception from the penalties for non-compliance with the REMS provision for sales to a competitor.

1. Generic Companies Unable to Purchase Reference Products

The first cause of action that the CREATES Act would establish responds to a claim that these comparative applications are now sometimes impossible because distribution restrictions make it impossible to acquire restricted drugs from third parties and because the innovators themselves also decline to sell the restricted drugs to their competitors.

It may help to understand how many innovative products could plausibly be at issue. The vast majority of new drugs and biologics are available through normal distribution channels. With the notable exception Daraprim[®] (discussed in the conclusion), the public controversy over “abuse” of distribution restrictions appears to relate to products distributed under REMS. This is why it is generally called “REMS abuse.” There are, however, only 42 REMS with use or distribution restrictions (ETASU).⁶⁷ Of these, six are REMS with ETASU shared by innovators and generic companies, and another REMS with ETASU belongs to a generic company.⁶⁸ In other words, the drugs with these seven REMS already have approved generic copies. As a practical matter, therefore, there are 35 new molecular entities with REMS that include ETASU as to which there is no approved generic or biosimilar. To put this number in perspective, FDA generally approves 30 to 40 new molecular entities every year, and more than 1,500 total have

been launched in the U.S. market.⁶⁹ Further, it appears that generic and biosimilar companies have in fact been able to purchase the reference product in many of these instances. For instance, there are pending ANDAs for 10 of the 26 drugs.⁷⁰ Of the nine approved biologics that have REMS with ETASU, there is already a pending biosimilar application for one,⁷¹ and readily available information indicates clinical trials of several others.⁷² In the end, much of the public controversy seems to relate to only a few products—Thalomid[®], Revlimid[®], Tracleer[®], and Letairis[®]—and there are pending generic applications citing these products.⁷³

This is not to say that innovators always provide products to their competitors when requested; they have sometimes refused sale. In some situations, innovators have grounded their refusal in concerns that the requesting company did not have adequate safeguards in place to address the special risks presented by the drug in question.⁷⁴ FDA can provide a letter assuring the innovator that the generic applicant’s bioequivalence study protocol contains safety protections comparable to the innovator’s ETASU,⁷⁵ but it is not clear this letter provides the

69 Michael S. Kinch, *An overview of FDA-approved new molecular entities: 1827–2013*, 19 DRUG DISCOVERY TODAY (Aug. 2014) (concluding that FDA had approved a total of 1453 new molecular entities by the end of 2013); FDA, Novel Drug Approvals for 2014 and Novel Drug Approvals for 2015 (noting another 86 in 2014 and 2015 combined).

70 See Paragraph IV Certifications (Aug. 4, 2016).

71 *Pending Biosimilars*, THE PINK SHEET (Mar. 7, 2016).

72 For example, Amgen is developing a biosimilar version of Soliris[®] (eculizumab). See Gareth MacDonald, *Amgen developing Soliris biosimilar*, BIOPHARMA REPORTER (June 21, 2016). To give another example, Merck was developing a biosimilar of Aranesp[®] (darbepoietin alfa) but reportedly stopped its program after FDA requested extensive cardiovascular outcomes data. See, e.g., NCT00968617 and NCT00924781 (clinicaltrials.gov identifiers for trials of MK2578 in comparison with Aranesp); *Merck’s Ditching of Aranesp Biosimilar Highlights Follow-On-Biologics Pitfalls*, SEEKING ALPHA (May 16, 2010).

73 Dr. Reddy’s filed a citizen petition in 2009 relating to purchase of Celgene’s Revlimid. Docket No. FDA-P-0266. Lannett brought suit against Celgene in 2008 relating to purchase of Thalomid, and Mylan brought suit in 2014 relating to purchase of both products. Lannett Co., Inc. v. Celgene Corp., No. 08-cv-3920 (E.D. Pa. Aug. 15, 2008); Mylan Pharmaceuticals, Inc. v. Celgene Corporation, Case No. 2:14-CV-2094-ESMAH (D.N.J. Apr. 3, 2014).

In 2012, Actelion brought suit to establish that it had no obligation to sell Tracleer to generic applicants. Actelion Pharms. Ltd. v. Apotex, Inc., No. 12-cv-5743 (D.N.J. Sept. 14, 2012). In 2014, Natco brought suit against Gilead regarding purchase of Letairis. Natco Pharma Ltd. v. Gilead Sciences, Inc. and Express Scripts Holding Co., No. 14-cv-3247 (SD. Minn. Aug. 22, 2014). The court dismissed the complaint. *Court Dismisses Natco’s REMS-Based Antitrust Suit*, BNA PHARMACEUTICAL LAW & INDUSTRY REPORT (Sept. 30, 2105).

The Mylan case is still pending; the other cases settled or were dismissed.

74 See Brief in Support of Defendant Celgene Corporation’s Motion to Dismiss, Mylan v. Celgene (noting that the company had sold Thalomid to competitors that satisfied its “safety, reputational, business, and liability concerns”).

75 See FDA, Draft Guidance for Industry, How to Obtain a Letter from FDA Stating that Bioequivalence Study Protocols Contain Safety Protections Comparable to Applicable REMS for RLD (Dec. 2014).

(2)(A)(last sentence). For the sake of simplicity, I have omitted from discussion a third type of abbreviated application, filed under section 505(b)(2) of the FDCA.

66 42 U.S.C. §§ 262(i), 262(k).

67 See REMS@FDA. The agency maintains a spreadsheet of approved REMS, which can be downloaded.

68 *Id.*

innovator with a defense in court if use of the innovator's product causes an injury. Consequently, an innovator might refuse sale if safety protocols do not seem adequate in its own judgment, if it lacks confidence in the competitor's commitment to the protocols, if it has doubts about the coverage of the competitor's liability insurance, or if it cannot agree to terms about liability. But it is not clear a reason is needed.⁷⁶ The Supreme Court wrote nearly 100 years ago that the antitrust laws generally protect the right of a manufacturer to decide with whom it will deal.⁷⁷ The Department of Justice and Federal Trade Commission cited this ruling as recently as August 2016, noting that "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."⁷⁸

More significant than whether innovators may refuse to sell their products to competitors is whether lack of access to the reference product is truly an impediment to generic approval. Innovators stop marketing their products all the time and for all sorts of reasons. Since 1984, the generic drug provisions have contemplated the possibility that the reference product might have been withdrawn from the market, and FDA regulations dating to 1992 provide a mechanism for determining whether a product that is no longer commercially available may nevertheless serve as a reference product.⁷⁹ Typically in these situations, a generic applicant petitions FDA to determine whether the listed drug was withdrawn for reasons of safety or effectiveness. If the agency confirms that it was not withdrawn for those reasons, the generic applicant may cite the drug in its application. These petitions are commonplace, and FDA publishes its responses in the Federal Register. The agency 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."⁸⁰ 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."⁸¹

FDA has thus indicated that it has the flexibility to work with generic applicants where the reference listed drug is no longer available. This is likely grounded in the agency's view that it has wide discretion with respect to the data needed to establish bioequivalence.⁸² Although the statute requires proof of bioequivalence and defines the term, it does not specify how bioequivalence must be shown.⁸³ For instance, it might be possible to demonstrate that the rate and extent of absorption of the two drugs are identical by testing the proposed generic and comparing the results with robust published pharmacokinetic data on the reference drug. As the agency commented in response to a citizen petition ten years ago:

It is well-accepted that FDA has wide discretion to determine how the bioequivalence requirement is met. FDA's discretion need only be based on a reasonable and scientifically supported criterion, whether [the agency] chooses to do so on a case-by-case basis or through more general inferences about a category of drugs.⁸⁴

The agency's own 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."⁸⁵

Concerns relating to reference biological products may be more speculative than real at this point. To begin with, FDA has authorized applicants to perform at least some of the comparative testing with foreign versions of the reference product.⁸⁶ Biosimilar sponsors may be able to purchase some of

76 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); but compare Michael Carrier, et al., *Using Antitrust Law to Challenge Turing's Daraprim Price Increase*, 31 BERKELEY TECH. L. J. ___ (2016) (arguing that in the case of Daraprim, the elements of a monopolization claim under the Sherman Act—monopoly power and exclusionary activity—were established).

77 *United States v. Colgate*, 250 U.S. 300, 307 (1919).

78 U.S. Department of Justice and Federal Trade Commission, *Antitrust Guidelines for the Licensing of Intellectual Property* (Proposed Update, Aug. 12, 2016), at 13. Some of the support for the CREATES Act stems from this very fact—that antitrust law may not provide generic applicants with the relief they seek. One former FTC official testified in favor of the bill in June, supporting it in part because antitrust law has a "general presumption against requiring a firm to assist a competitor." Alden Abbott, *The CREATES Act: Ending Regulatory Abuse, Protecting Consumers, and Ensuring Drug Price Competition of 2016*, Testimony before the Subcommittee on Antitrust, Competition Policy, and Consumer Rights, Committee on the Judiciary, U.S. Senate (June 21, 2016), available at <https://www.judiciary.senate.gov/imo/media/doc/06-21-16%20Abbott%20Testimony.pdf>.

79 *E.g.*, 21 C.F.R. §§ 314.92(a)(1), 314.122.

80 *E.g.*, 79 Fed. Reg. 60852 (Oct. 8, 2014) (Lupron Depot); 79 Fed. Reg. 49327 (Aug. 20, 2014) (Lupron Depot-Ped); 76 Fed. Reg. 7219 (Feb. 9, 2011) (Decaspray); 71 Fed. Reg. 2047 (Jan. 12, 2006) (Celestone Soluspan); 75 Fed. Reg. 36419 (June 25, 2010) (Delalutin).

81 *E.g.*, 76 Fed. Reg. 7219 (Feb. 9, 2011); 75 Fed. Reg. 36419 (June 21, 2010); 71 Fed. Reg. 2047 (Jan. 12, 2006).

82 In a 2009 response to a citizen petition on this very issue, FDA noted its "considerable flexibility in determining the appropriate method" of showing bioequivalence. It added that "with limited exceptions, bioequivalence studies involve the potential applicant obtaining supplies of the RLD in order to conduct the required comparisons." FDA Citizen Petition Response, Docket FDA-2009-P-0266-0001 (August 7, 2013), at 4. This sentence seems to concede the legal and regulatory possibility of ANDA approval without use of the reference listed drug.

83 21 USC §§ 355(j)(2)(A)(iv) (requiring bioequivalence), 355(j)(8)(B) (defining it).

84 Letter from Janet Woodcock, Director, CDER, to Christopher V. Powala, CollaGenex Pharmaceuticals, Inc., Re: Docket Nos. 2003P-0315/CP1 and PSA1, 2003P-0372/CP1, and 2004P-0517/PSA1 (May 13, 2005), at 2, *citing* Bristol-Myers Squibb Co. v. Shalala, 923 F. Supp. 212, 218 (D.D.C. 1996) (*quoting* Schering v. Sullivan Corp., 782 F. Supp. 645, 651 (D.D.C. 1992), *vacated as moot sub nom*, Schering Corp. v. Shalala, 995 F.2d 1103 (D.C. Cir. 1993)).

85 21 CFR § 320.24(b)(6).

86 FDA, Guidance for Industry, *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and*

their needed supplies from foreign affiliates and subsidiaries of the U.S. license holders. Further, although the PHSA presumes that a biosimilar application will contain preclinical and clinical data, it authorizes FDA to waive any element of the application that is not “necessary” in the application.⁸⁷ The agency may have the flexibility to develop alternative approaches for applicants unable to acquire large supplies.

2. The CREATES Act’s Proposed Cause of Action

Under the pending legislation, a generic or biosimilar applicant would be empowered to bring suit in federal court alleging that the innovator “declined to provide sufficient quantities” of the reference product on “commercially reasonable, market-based terms” within 31 days of request. There are two affirmative defenses: that the innovator does not manufacture, market, or have access to the product, or that the innovator has not imposed any restrictions on sale to generics and the product can therefore be purchased from distributors and wholesalers. Put another way, if the innovator manufactures and markets the product, it *must* sell the product to generic or biosimilar companies or permit its distributors to do so. If it refuses to sell the product, the court must order it to do so *and* award attorney’s fees and costs to the complainant. Moreover, if the court concludes that the innovator acted “without a legitimate business justification,” it must award the generic/biosimilar company “a monetary amount sufficient to deter the [innovator] from failing to provide . . . sufficient quantities” to other generic companies, up to the amount of all actual revenue from the reference product from 31-day mark to the day the product was actually provided. This cause of action is available whether or not the innovator’s drug is under a REMS.

If the 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.”⁸⁸ 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. Assuming the innovator intends to continue supplying current patients with the medicine, it will have to make additional lots specifically for its competitors—for as

many competitors as ask, for as many studies as are necessary to obtain approval, even if the competitors face regulatory obstacles and run their studies over and over, even if the competitors have significant compliance problems precluding application approval, and even if the product is protected by patent so that the generic applicant has no reasonable prospects of approval for years. In the case of a biological product, this could entail manufacturing enough product for several companies to run year-long trials in hundreds or thousands of patients. Absent a national defense emergency, however, it is hard to identify a compelling public policy justification for a law that effectively compels the manufacture of goods for sale.⁸⁹

C. Second Complaint: Sharing of System to Implement REMS-with-ETASU

If a reference listed drug has ETASU under a REMS, federal law generally requires that the innovator and generic companies use a “single, shared system” to implement the restrictions.⁹⁰ In these situations, all companies work with the same REMS documents, tools, and procedures. This requirement applies only to generic drugs, however, not to biosimilar biologics.

1. Inability to Reach Agreement on a Shared System

The statute allows FDA to waive the requirement of a “single, shared system” for any generic applicant, if the burden of creating the shared system outweighs the benefit of creating a shared system, taking into account the impact on the generic drug applicant and the innovator (new drug application—or NDA—holder), among others.⁹¹ The agency may separately waive the requirement for a generic applicant if an aspect of the restrictions is protected by patent or is trade secret.⁹² 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.⁹³ But the statute *expressly* contemplates the possibility that a shared system might unduly burden the generic applicant. This might be true, for instance, if arm’s length negotiations did not result in terms that were acceptable to the generic applicant. Moreover, that the NDA holder holds intellectual property in its REMS is a *separate* reason to excuse the generic applicant from the obligation to use a shared system, presumably reflecting the fundamental rule that a property owner may lawfully choose not to license or share its property at any price. In either case, FDA is free to relieve the generic applicant of the presumptive obligation to use the NDA holder’s system.

The complaint that a particular innovator will not agree to a “single, shared system” for implementation of use and

Innovation Act of 2009 (April 2015), at 8.

87 42 U.S.C. § 262(k)(2)(A)(ii).

88 *Continental Paper Bag Co. v. Eastern Paper Bag Co.*, 210 U.S. 405, 429 (1908). A ruling from the Second Circuit in 2015 departed sharply from the well-established principle that a patent owner has an unfettered right to make (or not make) and sell (or not sell) its invention and from the guidance in the Patent Act, 35 U.S.C. § 271(d)(4), that refusal to make a patented product should not give rise to antitrust liability. *New York ex rel. Schneiderman v. Actavis PLC*, 787 F.3d 638 (2d Cir. 2015) (affirming injunction that required pharmaceutical company to continue manufacturing and distributing its patented product for an additional 238 days, so that in the final 30 days patients would receive the generic by virtue of state automatic substitution laws).

89 The Defense Production Act of 1950 empowers the President to compel manufacturers to perform contracts deemed necessary to the national defense. 50 U.S.C. § 2071.

90 21 U.S.C. § 355-1(i)(1)(B); FDA, *Guidance for Industry, Risk Evaluation and Mitigation Strategies: Modifications and Revisions* (Apr. 2015).

91 21 U.S.C. § 355-1(i)(1)(B).

92 *Id.*

93 *Id.*

distribution restrictions is therefore, at bottom, a complaint that the negotiation did not go favorably for the generic applicant, or that the innovator declined to license its property to the generic applicant. Because FDA has explicit authority to approve a generic drug with a use and distribution system of the generic company's own creation, however, this complained-of situation has no legal significance. Put another way, there is no legal impediment to approval of the generic drug. As a matter of public policy, we may well prefer shared distribution systems because they are more efficient, or less confusing to third parties, or for other reasons. This could provide good reason to consider incentivizing the companies to find agreeable terms. But the law is clear that FDA may approve generic drugs with their own systems.

Further, there is no reason to think that generic applicants are unable to design and support REMS, including with use and distribution restrictions. Many generic companies today also market innovative products under NDAs and have the resources and experience to design sophisticated risk assessment and risk mitigation programs. FDA has already approved a separate REMS. Roxane Laboratories has a REMS, with use and distribution restrictions, in connection with its generic alosetron product.⁹⁴ This includes the company's own Patient Acknowledgment Form, Patient Follow-Up Survey, program stickers (for affixing to written prescriptions), Prescriber Enrollment materials (letter, form, education slide deck), a special website, and a database for certified enrolled prescribers. The reference listed drug, Lotronex, originally developed by GlaxoSmithKline, is now marketed by Sebelo Pharmaceuticals under its own REMS and implementation system.⁹⁵ FDA also granted a waiver in connection with Suboxone® (buprenorphine hydrochloride; naloxone hydrochloride) when the innovator and generics could not reach agreement.⁹⁶

2. The CREATES Act's New Cause of Action

Under the pending legislation, a generic applicant could bring suit in federal court alleging that the innovator failed to reach an agreement with it regarding a single, shared system of use and distribution restrictions. The new cause of action is also available to biosimilar applicants, even though neither the FDCA nor the PHSA suggests that biosimilar biologics and their reference products should have single, shared systems in the first instance. There are no affirmative defenses.

As a result, liability would follow provided the applicant "initiated an attempt" to negotiate terms, 120 days passed without any agreement reached, and the agency did not waive

the requirement for a shared system. The applicant would have no obligation to ask for a waiver, however, and FDA would have no obligation to grant one. As a practical matter, therefore, the bill would entitle a generic or biosimilar applicant to a court order requiring an innovator to agree to a shared system or use of the innovator's own system on what the court determines to be "commercially reasonable terms" (as opposed to negotiated terms). It also entitles the applicant to attorney's fees and costs. If the court concluded that the innovator had declined to agree "without a legitimate business justification," it would award the generic or biosimilar company a "monetary amount sufficient to deter the [innovator] from failing to reach agreements" with other companies, up to the amount of all actual revenue from the reference product from the 121-day mark to the day the agreement was actually reached.

If the innovator owned patents or other intellectual property in connection with the program it had established, the court order would effectively require it to share the intellectual property with its competitors. It would no longer be possible for arm's length negotiations to result in a realization that no set of terms was mutually agreeable. Depending on the nature of the program and the nature of the intellectual property, therefore, the innovator might be required to practice the patent for the benefit of its competitors, or it might be required to license the patent for the competitor's use, on terms of the court's choosing.

III. CONSEQUENCES AND IMPLICATIONS

At first blush, this bill seems to steer private parties towards use of the courts to achieve their business goals. As noted in the prior section, there might be good reason to incentivize innovators and generic/biosimilar companies to find mutually agreeable terms for shared distribution systems. Rather than incentivizing agreements, however, the bill makes the negotiation phase perfunctory at best and may encourage generic and biosimilar applicants to negotiate in bad faith, as explained below.

First, it is unrealistic to think that 31 days would be enough time to negotiate all terms relevant to sale of a restricted product for analytical and clinical testing (and to deliver all of the product needed, which is also required under the plain terms of the bill). To begin with, the parties would need to settle on basic contractual terms (quantities, time and place of delivery, and consideration). They would need to discuss essential matters such as the adequacy of the applicant's safety protocols and the handling of liability in the event a subject in the trial experienced an injury (including a process for determining whether the applicant's protocol, or compliance with that protocol, was to blame). The innovator might want to address the risk of shareholder suits—perhaps grounded in having shared its product too hastily or without adequate assurances of liability protection—in the event of product liability exposure. Unexpected events during the applicant's studies could raise new questions about the product's risk-benefit profile, and the innovator might need the agreement to address how those questions would be explored. A mutually satisfactory deal might

⁹⁴ REMS, Alosetron Tablets (Mar. 2016).

⁹⁵ REMS, Lotronex (Apr. 2016).

⁹⁶ Compare REMS, Suboxone (July 2016) with REMS, Buprenorphine-containing Transmucosal Products for Opioid Dependence (July 2016); FDA, Citizen Petition Response, Docket No. FDA-2012-P-2028 (Feb. 22, 2013) at 12 n.45 (noting waiver). Negotiations apparently failed when the innovator requested that the generic companies (1) commit to patient safety; (2) agree to cost-sharing; and (3) agree to sharing of product liability costs. See Comments of Amneal Pharmaceuticals, Docket No. FDA-2012-P-1028 (Feb. 4, 2013), at 4 n.3 (listing the terms requested by the innovator).

never be reached, and a mutually satisfactory deal within 31 days might be impossible.

So too with the 120 days to develop a shared REMS for the innovative drug and its generic equivalents. This misunderstands the complexity of the process.⁹⁷ Typically, more than one generic applicant submits an ANDA referring to a particular innovative product. The innovator and generic companies form a working group that develops the new shared REMS, which means developing and sharing responsibility for every aspect of the REMS. Consider, by way of illustration, the REMS shared by nine companies marketing clozapine to address the risk of low absolute neutrophil count (ANC).⁹⁸ These companies agreed to roughly 250 pages worth of common documents (REMS, patient enrollment form, two different pharmacy enrollment forms, two prescriber enrollment forms, knowledge assessment for healthcare providers, guide for healthcare providers, and ANC lab reporting form). They share responsibility for ensuring that healthcare providers and pharmacies are certified; for maintaining validated secure databases of certified healthcare providers, enrolled patients, and certified pharmacies; for ensuring that certified prescribers have access to the databases of certified pharmacies and enrolled patients; and for ensuring that distributors have processes and procedures to verify pharmacy certification. They share responsibility for monitoring distribution data, and auditing wholesalers, distributors, and pharmacies. They maintain a single contact center to support prescribers and pharmacies, and they maintain a shared REMS website. In short, a group of companies that may have diverging business models and different levels of risk tolerance must work out a wide range of issues, from the actual procedures and tools used and the content of all written materials, to cost-sharing (with attendant contractual complications, such as how cost will be determined, how the sharing will be allocated, and how disputes will be handled), insurance, and liability. A deadline for this process that is both arbitrary and unrealistic sends a clear signal that the negotiation phase is a sham.

Second, even if negotiation on these timetables were realistic, generic and biosimilar applicants are given no incentive to negotiate in good faith. The bill imposes on innovators the obligation to manufacture and sell their products to their competitors in every case without exception or defense, as well as the obligation to reach agreement on a shared REMS (or share their own REMS) in every case without exception or defense. And the remedies provided are mandatory. If a court will in every case order the innovator to provide “sufficient quantities” of the product “without delay” and on “commercially reasonable, market-based terms”—and order the innovator to negotiate a shared system or share its own system “on commercially reasonable terms”—there is no reason for a generic or biosimilar applicant to attempt negotiation before going to court. Further, the penalty provision may encourage unscrupulous companies to stonewall even where the innovator offers terms that are reasonable. After all, if the court concludes that the innovator’s

refusal lacked “legitimate business justification,” it will award to the generic company all of innovator’s revenue on the product from the deadline (day 31 or 121) until the day the innovator complies with the court’s mandate. The revenue for the generic company during this time—actual revenue from all of the innovator’s sales of the product in question—could significantly exceed any revenue the generic company could realize from an eventual approved product. It is not unreasonable to worry that unprincipled companies might seek to delay judicial proceedings to extend that financial windfall.

All of this said, the court cases may be a red herring. Although some innovators may stand their ground and litigate, the design of the bill suggests it is not really intended to shift responsibility to the courts. In fact, the bill may discourage litigation. Take the cause of action for manufacture and delivery of products, for instance. As noted, from the perspective of a generic or biosimilar applicant, there is no reason to negotiate in good faith, because a court order with attorney’s fees is assured, and an award of innovator revenues is possible. From the perspective of an innovator, proceeding to court means a federal judge will decide the quantities of product that are “sufficient” for its competitor, as well as the timing for delivery and the terms that are “commercially reasonable” and “market-based.” The statute does not define these phrases, leaving a wide range of outcomes possible.⁹⁹ Proceeding to court may also mean loss of all revenue from the product in question, if the judge determines the innovator lacked a “legitimate business justification” for its position in the negotiations—another phrase that is left to the courts to interpret.

Thus, the basic approach of the bill is to incentivize the generic applicant to refuse terms offered by the innovator, while threatening the innovator with unpredictable penalties for failing to agree to terms requested by the generic applicant. It is not unreasonable to expect innovators to agree to almost any terms suggested, and generic companies to refuse almost all terms proposed. The legislation may force innovators into acceding to unreasonable demands at the outset. An innovator would proceed to court, presumably, only if the deal requested by the generic company was *worse* than whatever rate a hostile court would set, plus all of the company’s revenue for the interim period. This potential outcome is profoundly troubling, given the strong possibility that, in refusing sales, innovators are acting in full compliance with antitrust law.¹⁰⁰

IV. CONCLUSION

The CREATES Act has gained traction this year in part because some supporters have linked it to the pricing

97 For a description, see generally FDA, Citizen Petition Response, Docket No. FDA-2013-P-0572 (Oct. 7, 2013), at 5–6.

98 See generally Clozapine Shared System REMS (Sept. 15, 2015).

99 Indeed, there might not be “commercially reasonable, market-based terms” for directly assisting one’s competitors.

100 An NDA holder may not “use” an ETASU to “block or delay” approval of an ANDA or to prevent “application” of an element in an ETASU to the generic drug in question. 21 U.S.C. § 355-1(f)(8). FDA can enforce this prohibition through civil money penalties. *Id.* § 333(f)(4)(A). There is no evidence in the statute or legislative history, however, that Congress meant to override the bedrock principle of antitrust law that a company has no duty to deal with its competitor, or the bedrock principle of patent law that a company has no duty to practice its patent. Indeed, there is evidence to the contrary. Congress rejected earlier proposals that would

controversy associated with Martin Shkreli and his company, Turing Pharmaceuticals. In August 2015, Turing acquired the rights to a decades-old, off-patent drug for toxoplasmosis, Daraprim® (pyrimethamine). Turing maintained a closed distribution system that had been established in June 2015, and it increased the price from \$13.50 per tablet to \$750 per tablet.¹⁰¹ The distribution program was not linked to any particular safety issue, however, and company documents suggested it was intended specifically to “create a barrier and pricing power.”¹⁰² Outrage over the price increase, and Shkreli’s seeming indifference to criticism, took over mainstream media and social media for months. Although earlier bills addressing REMS predated the Daraprim controversy, the incident now features prominently in discussion of the legislation.

The problem is that it is analytically unsound to equate Daraprim—a drug without significant safety concerns—with drugs like Thalomid and Adempas, which present serious risks of embryo-fetal toxicity, which are subject to FDA-mandated distribution restrictions because of (and tailored to reduce) those risks, and which are associated with intellectual property.¹⁰³ While the legislation would have forced Shkreli to sell his product to aspiring generic applicants, the drug had been marketed since the 1950s, and there had not previously been significant interest in generic applications. Had Shkreli not also increased the price, it is unlikely there would have been any meaningful interest in generic applications in 2015. The *real* issue with Daraprim was the sudden and dramatic price hike, coupled with Shkreli’s combativeness. Deep frustration with the cost of medicine in this country cannot, however, justify a failure to differentiate analytically between Turing Pharmaceuticals and the research-based, innovating biopharmaceutical industry. The cost of innovation is a period of high prices without competition; that is the nature of intellectual property. The intellectual property clause of the original U.S. Constitution of 1788 enshrines the bargain that we make as a society: protection of exclusive rights for limited times, with all this entails, in order to ensure continuing progress and innovation.¹⁰⁴ While the cost

of innovation may be frustrating at times, it is exceptionally short sighted to direct this frustration towards companies that are developing new medicines, own intellectual property, and have a right to choose with whom they will do business.

have imposed a duty of sale. *E.g.*, H.R. 2900, 110th Cong. § 901 (2007). And the statute plainly contemplates the possibility that a deal cannot be reached on a shared system.

101 See Andrew Pollock, *Drug Goes From \$13.50 a Tablet to \$750, Overnight*, THE NEW YORK TIMES (Sept. 20, 2015).

102 See Memorandum to Democratic Members of the Full Committee, from Democratic Staff, re: Documents Obtained by Committee from Turing Pharmaceuticals (Feb. 2, 2016), at 3.

103 The vast majority of the 35 products under REMS-with-ETASU are protected by data exclusivity, patents, or both. Of the 35 innovative products under REMS-with-ETASU, six of the nine biologics have unexpired data exclusivity, seven of the 26 drugs have unexpired new chemical entity exclusivity, four of the latter also have orphan drug exclusivity, and several other drugs have three-year exclusivity. All but four of the drugs have patents listed in the Orange Book. See Approved Drug Products with Therapeutic Equivalence Evaluations (36th ed., 2016); List of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations (CDER List, Aug. 30, 2016).

104 U.S. Const. Art. I, § 8, cl. 8.

