

**Written Testimony of Peter Safir
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**U.S. Senate Committee on the Judiciary
Subcommittee on Antitrust, Competition Policy and Consumer Rights
Hearing on the CREATES Act of 2016 (S. 3056)**

June 21, 2016

Chairman Lee, Ranking Member Klobuchar, and Members of the Subcommittee, my name is Peter Safir, and I am senior counsel at Covington & Burling LLP. I was asked to testify by the Pharmaceutical Research and Manufacturers of America (“PhRMA”), but the views I express are my own. I have represented innovative pharmaceutical companies for over twenty-five years and for twenty-two years I have been a Professorial Lecturer in Food and Drug Law at George Washington University Law School. Thank you for the opportunity to participate in this hearing and to provide the perspective of innovative companies on the CREATES Act.

I am here to provide a perspective on the bill and FDA’s oversight of risk evaluation and mitigation strategies (“REMS”), which were created to enhance patient safety.

I. Overview of the Safety Considerations and Legislative History Underlying FDA’s Risk Evaluation and Mitigation Strategies and Current Law

A. Development of FDA’s Current Approach to Risk Management

The Food and Drug Administration Amendments Act of 2007 (“FDAAA”) amended the Federal Food, Drug, and Cosmetic Act (“FDCA”) to give the U.S. Food and Drug Administration (“FDA” or “the Agency”) substantial new authority to regulate the safety of marketed drugs. As part of this expanded authority, FDA may require drug companies to propose and implement REMS for certain drugs whose risk-benefit profiles warrant the adoption of additional safety measures.

FDAAA’s enactment codified a new approach to risk management reflecting “the understanding [that] a drug’s risk-benefit profile necessarily evolves over the drug’s life cycle.”¹ Effective risk management is now understood to require “interaction and cooperation between regulatory agencies and the company, as well as communication of benefit-risk information in a timely and transparent manner to healthcare providers and ultimately to patients.”²

¹ Institute of Medicine Committee on the Assessment of the U.S. Drug Safety System, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* at S-2 (Sept. 22, 2006).

² Statement of Dr. Adrian Thomas, Vice-President for Benefit-Risk Management, Johnson & Johnson, *Building a 21st Century FDA: Proposals to Improve Drug Safety and Innovation: Hearing Before the S. Comm. on Health, Education, Labor and Pensions*, 109th Cong. (Nov. 16, 2006).

Although FDA developed risk management programs for several prescription drugs on an informal basis in the 1980s and 1990s,³ the Agency had not formalized its approach to risk management beyond the prescribing information for approved prescription drugs. The Agency finalized a set of guidance documents in March 2005, each addressing one of the primary aspects of risk management: risk assessment, risk minimization, and pharmacovigilance practices.⁴ Consistent with evolving risk management principles, the agency stressed that risk management should be “continuous throughout a product’s life cycle.”⁵ FDA defined risk management as a four-part, “iterative process of (1) assessing a product’s benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance.”⁶

Even while recognizing that the FDA-approved labeling (the “routine risk minimization measure”) was sufficient for most products, the Agency noted that for certain products “a strategic safety program designed to meet specific goals and objectives in minimizing known risks of a product while preserving its benefits” (a “risk minimization action plan” or “RiskMAP”) may be necessary.⁷ This recognition was consistent with the emerging risk management principle that in some cases, “proactive steps to safeguard against preventable risks” were needed.⁸ The “tools” that might be required in a RiskMAP included targeted education and outreach (such as healthcare practitioner letters), training programs for healthcare practitioners or patients, continuing education for healthcare practitioners, prominent professional or public notifications, patient labeling such as Medication Guides and patient package inserts, and other techniques such as direct to consumer advertising that highlighted appropriate patient use or product risks. RiskMAP tools also included what FDA referred to as “performance-linked access systems,” which the Agency suggested be considered “only when (1) products have significant or otherwise unique benefits in a particular patient group or condition, but unusual risks also exist, such as irreversible disability or death, and (2) routine risk minimization measures, targeted education and outreach tools, and reminder systems are known or likely to be insufficient to minimize those risks.”⁹ Examples of “performance-linked access systems” included prescription only by specially-certified healthcare practitioners, limiting a

³ Jamie Wilkins Parker, Pharm.D., FDA Division of Risk Management, *Risk Management in the United States* (slide deck), at 15.

⁴ FDA, Guidance for Industry – Premarketing Risk Assessment (Mar. 2005); FDA, Guidance for Industry – Development and Use of Risk Minimization Action Plans (Mar. 2005); FDA, Guidance for Industry – Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Mar. 2005).

⁵ Guidance for Industry – Development and Use of Risk Minimization Action Plans, at 2.

⁶ *Id.*

⁷ *Id.* at 5.

⁸ Eleanor M. Perfetto et al., *Evidence-Based Risk Management: How Can We Succeed?: Deliberations from a Risk Management Advisory Council*, 37 DRUG INFO. J. 127 (2003).

⁹ Guidance for Industry – Development and Use of Risk Minimization Action Plans, at 10.

product's dispensing to pharmacies or practitioners that elect to be specially certified, and dispensing a product only to patients with evidence or other documentation of safe-use conditions.¹⁰ By February 2007, 30 drugs had some sort of a RiskMAP in place.¹¹

B. FDCA's Statutory Framework for REMS

FDAAA's legislative history confirms that Congress intended to codify FDA's shift in approach to risk management, referring to "the need to extend drug safety consideration from premarket through postmarket approval."¹² Moreover, Congress viewed legislation as necessary to address "cultural issues within FDA and gaps in the agency's authorities hamper[ing] the ability to take swift and effective action when problems arise."¹³ The legislation thus amended the FDCA to establish an integrated, systematic approach to risk management.

Section 505-1 of the FDCA authorizes FDA to require sponsors to propose REMS for a drug if the Agency determines that one is "necessary to ensure that the benefits of the drug outweigh the risks of the drug."¹⁴ FDA may also require a license holder adopt a REMS for an approved drug if the Agency "becomes aware of new safety information and makes a determination that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug."¹⁵

Under section 505-1, FDA may require that a drug's REMS include "elements to assure safe use," which are commonly known as "ETASU," because of "[the drug's] inherent toxicity or potential harmfulness."¹⁶ FDA may require a drug to have REMS with ETASU if the Agency determines that the drug has been shown to be effective "but is associated with [such] a serious adverse drug experience" that it "can be approved only if, or would be withdrawn unless, such elements are required" as part of the REMS.¹⁷ For drugs that must be approved with ETASU, FDA also must determine that other REMS elements "are not sufficient to mitigate such serious risk."¹⁸ The statute sets forth specific examples of ETASU that may be required:

¹⁰ *Id.*

¹¹ FDA Office of Surveillance and Epidemiology, *An Overview of RiskMAPs* (slide deck) (June 25, 2007).

¹² H.R. Rep. 110-225, at 12 (2007).

¹³ *Id.*

¹⁴ FDCA § 505-1(a)(1).

¹⁵ *Id.* § 505-1(a)(2).

¹⁶ *Id.* § 505-1(f)(1).

¹⁷ *Id.* § 505-1(f)(1)(A).

¹⁸ *Id.* § 505-1(f)(1)(B).

- Healthcare providers who prescribe the drug have particular training or experience or are specially certified;¹⁹
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified;²⁰
- The drug may be dispensed to patients only in certain healthcare settings, such as hospitals;
- The drug may be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results;
- Each patient using the drug is subject to certain monitoring; or
- Each patient using the drug is enrolled in a registry.²¹

Section 505-1 of the FDCA also provides that a drug that is the subject of an abbreviated new drug application must use a single, shared REMS system with the listed drug's manufacturer.²² This requirement explicitly applies only to generic drugs, which are submitted to FDA for approval under section 505(j) of the FDCA, and not to follow-on drug products submitted for approval under section 505(b)(2) or biosimilars submitted for licensure under section 351(k) of the Public Health Service Act.²³ FDA may waive the shared REMS requirement if the Agency determines either that (1) the burden of creating a single, shared REMS outweighs the benefit; or (2) an aspect of the drug's ETASU is covered by an unexpired patent or is otherwise subject to protections as a trade secret.²⁴

C. Enforcement of REMS Requirements

A company's failure to maintain compliance with the requirements of the approved REMS may subject it to enforcement action. As an initial matter, failure by the "responsible person" (i.e., a drug's sponsor or license holder) for a drug to comply with a REMS requirement renders the drug misbranded,²⁵ which can become the basis for an enforcement action under the FDCA's

¹⁹ The opportunity to obtain such training or certification with respect to the drug must be available to any willing provider from a frontier area in a widely available training or certification method (including an on-line course or via mail) as approved by FDA at reasonable cost to the provider.

²⁰ The opportunity to obtain such certification must be available to any willing provider from a frontier area.

²¹ FDCA § 505-1(f)(3).

²² *Id.* § 505-1(i)(1).

²³ *See id.*

²⁴ *Id.* § 505-1(i)(1)(B)(ii).

²⁵ *Id.* § 502(y).

injunction, seizure, and criminal penalty provisions.²⁶ Also, a person may not introduce a REMS drug into interstate commerce if that person fails to comply with all of the drug’s REMS requirements.²⁷ A “responsible person” is also subject to steep civil monetary penalties for violating a REMS requirement.²⁸

II. Safety Concerns with the CREATES Act

The CREATES Act uses a blunt instrument to address a narrow issue. Congress and FDA have long recognized the risks associated with drugs requiring REMS—and particularly the products whose REMS must also include ETASU in order to receive or maintain FDA approval. Examples of such serious safety issues associated with currently approved drugs with ETASU include risks of shortened overall survival, increased risk of tumor progression or recurrence, increased risks of first trimester pregnancy loss and congenital malformations, and central nervous system depression.

Despite the serious safety risks of drugs with REMS with ETASU, the CREATES Act does not establish robust criteria that eligible product developers seeking to obtain such a drug must satisfy in order to protect patients and other individuals who come into contact with the drug during its distribution. The bill requires eligible product developers to obtain an “authorization” from FDA before they can sue an innovator to force the transfer of drugs subject to an ETASU, and the Agency “shall” issue such an authorization within 90 days. An eligible product developer may elect, but is not required, to submit a clinical trial safety protocol that sets forth its plan for testing a drug in humans. The bill provides that an eligible product developer need only show that such protocols and other documentation provide safety protections “comparable to those” provided by the innovator’s REMS—rather than equivalent to the existing REMS—or “otherwise satisf[y] [FDA] that such protections will be provided.” This standard creates the distinct possibility that an eligible product developer will adopt less rigorous safety protections than the REMS with ETASU that was implemented by the innovator following careful discussions with and review by FDA.

The CREATES Act gives FDA limited recourse for situations in which it finds an eligible product developer’s proposed safety measures to be insufficient—or, even more significantly, if the Agency discovers that an eligible product developer has failed to implement or comply with its own proposed safeguards. The bill provides that FDA “shall . . . authorize” the eligible product developer within 90 days, without providing express authority for FDA to deny the request or to extend the timeframe. Moreover, the CREATES Act requires that the Agency issue an authorization based only on the documentation submitted by an eligible product developer, without taking into account the developer’s qualifications and compliance history, even where the company has a recent history of violating good clinical practices. The bill also does not account for the fact that the risks posed to healthy volunteers in a clinical study will, at a

²⁶ *Id.* § 301, 302, 303(a).

²⁷ *Id.* § 505(p)(1)(B).

²⁸ *Id.* § 303(f)(4)(A).

minimum, be different and may even be greater than the risks for patients with the disease or condition intended to be treated by a drug.

If a developer obtains samples but conducts its clinical trials without adhering to its own safety protections, the CREATES Act provides FDA with no authority to rescind its authorization. Indeed, because the bill does not require an eligible product developer have submitted an investigational new drug (“IND”) application, FDA also would not have at its disposal the enforcement authority wielded by the Agency in the IND context. For example, FDA may impose a “clinical hold” on an IND sponsor, ordering a delay or suspension of a clinical study due to “unreasonable and significant” safety issues or because of concerns relating to the study’s administration.²⁹

Under the bill, safety concerns instead would be addressed in detail in litigation before federal courts; however, the courts lack the specialized knowledge and expertise that FDA has developed over several decades of honing risk management strategies. The CREATES Act therefore undermines the authority that Congress granted the Agency in FDAAA for the express purpose of enhancing FDA’s role in risk mitigation.

In addition to the safety concerns outlined above, the bill introduces uncertainty for innovators about whether providing samples of a drug with REMS with ETASU to an eligible product developer—should a court order an innovator to do so—would constitute a violation of the REMS. As noted above, the FDCA sets forth a number of both civil and criminal penalties that can be brought for the violation of a single REMS requirement. The CREATES Act attempts to address this issue by requiring “[a] covered product authorization issued under this clause [to] state that the provision of the covered product by the license holder under the terms of the authorization will not be a violation of the REMS for the covered product.” The bill does not amend the FDCA to this effect, however, and leaves innovators with conflicting statutory obligations that could expose them to enforcement.

III. The Provisions on Single, Shared REMS Also Raise Concerns

The CREATES Act establishes a cause of action for an eligible product developer to sue an innovator once “120 days have elapsed since the developer first initiated an attempt to reach an agreement with the license holder that would allow the product developer to participate in a single, shared system of [ETASU].”

This provision of the bill overlooks the reality that negotiations over a single, shared REMS are complicated—in large part because they deal with important safety issues and a complex healthcare system. The 120-day deadline established under the CREATES Act reflects an unreasonable length of time for parties to reach agreement on the range of concerns that must be addressed (e.g., REMS design, adverse event reporting protocols, collective standard operating procedures, cost sharing, decision-making authority about REMS administration, assessments, and modification, and associated legal issues such as intellectual property and product liability). Moreover, the bill generally assumes that these negotiations involve only two parties—the

²⁹ See 21 C.F.R. § 312.42(b).

innovator and the eligible product developer—when, in actuality, they typically involve multiple parties with competing interests and positions. The negotiations may sometimes involve one innovator and multiple developers, or multiple innovators and multiple developers, or a single developer who seeks to join a shared REMS that has already been agreed to by different parties. Because of these different permutations, the threat of litigation is not an appropriate measure for these negotiations and may only complicate the discussions.

Despite these complexities, the bill includes no limitations on the 120-day deadline, such as a requirement that the eligible generic product developer negotiate in good faith before it may bring a lawsuit. A lawsuit may be brought even if the launch of a generic drug is years away (e.g., due to patent or approvability issues). Thus, the CREATES Act could create a new layer of litigation beyond Hatch-Waxman patent litigation prior to generic entry. Indeed, the provision may even result in the unintended consequence of encouraging an eligible generic product developer not to engage in good faith negotiations given the possibility that the monetary reward from liability and damages that it could receive at trial may exceed any actual losses without any actual delay to its product approval and launch.

For example, the bill starts the clock when “the developer *first initiate[s] an attempt* to reach an agreement.” The italicized language could be interpreted as referring to any point in an eligible product developer’s communications—the date on which the parties first meet to negotiate an agreement, the date on which a developer sends a letter to an innovator, the date on which a developer places a phone call with an employee of the innovator, etc. Given the bill’s ambiguity, an eligible generic product developer enjoys broad discretion in how it chooses to reach out to an innovator without facing any risk that attempts that are not made in good faith would prevent the developer from bringing a cause of action.

IV. Conclusion

In conclusion, I urge the Committee to give careful consideration to the serious safety risks that the CREATES Act may introduce for patients and other individuals who come into contact with an ETASU drug during a clinical trial. The existing statutory framework recognizes the need for specific and precise safeguards—REMS with ETASU—for certain drugs whose toxicity and risk potential warrant the adoption of such measures. I also recommend that the Committee assess the described implications of the bill’s shared REMS provisions, which may encourage rather than resolve disputes over participation in shared REMS.