A Look Back at Risk Evaluation and Mitigation Strategies at the Food and Drug Administration in 2020: Year in Review

by David S. Shotlander and Tiffany Jang

Risk Evaluation and Mitigation Strategies (REMS) faced significant developments on multiple fronts in 2020 as the life science and pharmaceutical industries responded to the global coronavirus pandemic and the impact of long-awaited legislation to expand access to brand samples subject to REMS. As the pandemic took hold in March, the U.S. Food and Drug Administration (FDA or Agency) announced its intent to temporarily suspend enforcement of certain REMS requirements in the interest of maintaining social distancing. More recently, the U.S. Department of Health and Human Services Office of Inspector General (OIG) provided a pessimistic evaluation of FDA's ability to provide effective REMS oversight of opioid misuse and abuse. In this article, we provide an overview of some of the major REMS news from the past year.

REMS is a drug safety program that restricts access to pharmaceutical products that present safety risks. The Food and Drug Administration Amendments Act of 2007 (Pub. L. 110- 85) provided FDA with authority to require REMS[1] when the Agency determines they are necessary to ensure that the benefits of a drug sufficiently outweigh its risks. Examples of REMS include Medication Guides, package inserts for patients, communication plans, and packaging and safe disposal technologies. Certain REMS programs include additional Elements to Assure Safe Use (ETASU), which may be required for drugs proven to be effective while also being associated with a specific serious risk listed on the drug label. Examples of ETASU include special training, experience, or certification requirements for health care providers prescribing a drug; special certifications for pharmacies, providers,

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or health care settings dispensing a drug; and monitoring requirements for patients who are administered a drug.[2]

As of November 2020, there were fifty-nine approved individual and shared system REMS programs in existence, including fifty-one with ETASU.[3]

CREATES Act Is Signed into Law, Remains Unasserted in Legislation's First Year

On December 20, 2019, President Trump signed into law H.R. 1865, one of two year-end comprehensive appropriations bills for fiscal year 2020.[4] Buried within § 610 of that massive bill[5] was the "Creating and Restoring Equal Access to Equivalent Samples Act" (CREATES Act), which expanded generic and biosimilar access to reference drug samples.[6] The CREATES Act responds to long-standing allegations that innovator drug and biologic companies have attempted to block generic or follow-on competition and thereby extend their market exclusivity by refusing to provide product samples to generic or biosimilar drug manufacturers seeking to develop lower-cost follow-on drug products.

Follow-on drug manufacturers require drug samples from an innovator company to conduct bioequivalence/biosimilarity testing. While there is a statutory prohibition against using ETASU to prevent the approval of an application under Sections 505(b)(2) or (j) of the FDCA,[7] FDA does not have authority to compel the provision of reference product samples to follow-on drug or biosimilar manufacturers. Instead, private litigants have brought antitrust actions against innovator companies for withholding reference product samples, alleging such "REMS abuse" amounts to anticompetitive conduct. To date, however, FTC has only threatened,[8] but not taken action against, innovator companies allegedly withholding reference product samples on the basis of a REMS program.

The CREATES Act provides a private right of action to "eligible product developers,"[9] including manufacturers of follow-on drugs or biosimilars, allowing them to sue the "license holder"[10] of a "covered product"[11] for refusal to provide sufficient quantities of reference product samples on "commercially reasonable, market-based terms."[12] The CREATES Act defines "commercially reasonable, market-based terms" to include:

1. a nondiscriminatory price no greater than the covered product's most recent wholesale acquisition cost;
2. a schedule for delivery that entails transfer within 31 days following receipt of request for a covered product, unless the reference drug is subject to REMS with ETASU, in which case the sample must be provided within 31 days following the later of the date of receipt of request for the covered product or the date on which the license holder received a copy of the covered product authorization from the Secretary of Health and Human Services (with some additional requirements attached); and
3. no additional conditions imposed on the sale of the covered product.[13]

To defend against a claim brought under the CREATES Act, a license holder may plead any of the following affirmative defenses:

1. upon request by the eligible product developer, neither the license holder nor any of its agents, wholesalers, or distributors was engaged in the manufacturing or commercial marketing, or otherwise had access to inventory, of the covered product to supply to the eligible product developer on commercially reasonable, market-based terms;
2. the license holder sells the covered product through agents, distributors, or wholesalers with no restrictions against selling the covered products to eligible product developers, and an eligible product developer can purchase the product in sufficient quantities on commercially reasonable, market-based terms from such agents, distributors, or wholesalers; or
3. the license holder made an offer to sell sufficient quantities of the covered product on commercially reasonable market-based terms (i) if the covered product is not subject to REMS with ETASU, within fourteen days after receiving the eligible product developer's request, and the eligible product developer did not accept the offer within seven days, or (ii) if the covered product is subject to a REMS with ETASU, within twenty days after receiving the eligible product developer's request, and the eligible product developer did not accept the offer within ten days.[14]

An eligible product developer that succeeds in a claim under the CREATES Act is entitled to injunctive relief for sufficient quantities of a covered product under commercially reasonable, market-based terms as well as attorney's fees and costs.[15]

Under some circumstances, an eligible product developer may also receive a monetary award intended as a punitive measure against the license holder, where the license holder either delayed providing sufficient quantities of the covered product to the eligible product developer without a legitimate business

justification or failed to comply with an order of injunction previously issued by the court in the same action.[16] This monetary award can be quite significant. For a covered product not subject to REMS with ETASU, the award can be as great as the revenue earned by the license holder between thirty-one days following receipt of request for the covered product to when the eligible product developer received sufficient quantities of the covered product.[17] For a covered product subject to REMS with ETASU, the award can be as great as the revenue earned by the license holder, calculated from thirty-one days following the later of (i) receipt of request for the covered product or (ii) receipt of the covered product authorization from the Secretary of Health and Human Services, to when the eligible product developer received sufficient quantities of the covered product.[18]

Along with creating a private right of action to eligible product developers suing license holders for drug samples, the CREATES Act also streamlines the drug approval process for eligible product developers by providing a new REMS approval process for "subsequent filers." Previously, eligible product developers would sometimes engage in protracted negotiations with license holders to develop a single, shared system of REMS with ETASU for all versions of an approved product. The CREATES Act empowers the Secretary of Health and Human Services to modify approved REMS with ETASU in order to "accommodate different, comparable aspects of the elements to assure safe use for a drug that is the subject of an application under section 355(j) of this title, and the applicable listed drug."[19] The CREATES Act also eliminates the general requirement that eligible product developers and license holders use a single, shared system of REMS with ETASU, allowing eligible product developers to implement "a different, comparable aspect of the elements to assure safe use."[20] A single, shared system of REMS with ETASU may only be required "if the Secretary determines that no different, comparable aspect of the elements to assure safe use could satisfy the requirements of" Section 505-1(f) of the FDCA.[21]

Passage of the legislation in December 2019 was much-anticipated since its 2016 introduction, and though an eligible product developer has yet to bring a claim under the new law, the impact of the legislation is likely reflected in less restrictive access to REMS, which cannot be publicly tracked. Since a section of the CREATES Act expressly states that nothing in the legislation "shall be construed to limit the operation of any provision of the antitrust laws,"[22] moving forward, we continue to anticipate the first claims by private litigants brought pursuant to the CREATES Act—possibly in conjunction with federal or state antitrust claims. There have been no new antitrust actions filed in 2020 over REMS restraints, which is consistent with the CREATES Act easing access to REMS for generic manufacturers. In assessing antitrust claims challenging REMS as anticompetitive or exclusionary conduct, there is now a risk that a court or factfinder may deem a violation of the CREATES Act to constitute anticompetitive conduct.

FDA Provides Discretionary Suspension of Certain REMS Requirements During the COVID-19 Public Health Emergency

Shortly after the country went into lockdown in response to the COVID-19 outbreak, FDA published a Guidance for Industry and Health Care Professionals on March 22, 2020, titled *Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency* (Guidance). The Guidance communicated FDA's temporary policy for certain REMS requirements during the public health emergency (PHE) declared by the Secretary of the U.S. Department of Health and Human Services on January 31, 2020.

The Guidance discussed the impact of COVID-19 on certain REMS with ETASU that may require laboratory testing (e.g., liver enzyme testing) or imaging studies (e.g., magnetic resonance imaging) under § 505-1(f)(3)(d) or (e) of the FDCA (21 U.S.C. § 335-1(f)(3)(d) or (e)).[23] FDA acknowledged that during the COVID-19 pandemic, such laboratory testing or imaging studies in order to obtain a drug subject to REMS may be unfeasible and unsafe for patients and others.[24] For drugs subject to such REMS requiring laboratory testing or imaging requirements, FDA noted that health care providers "should consider whether there are compelling reasons not to complete these tests or studies during the PHE, and use their best medical judgment in weighing the benefits and risks of continuing treatment in the absence of laboratory testing and imaging studies."[25] Furthermore, health care providers should engage patients in a dialogue regarding the risks associated with such laboratory testing and imaging studies.[26]

While REMS requirements remain in effect during the PHE, FDA announced its intent to not take enforcement action when discretionary accommodations are made related to laboratory testing or imaging study requirements imposed under § 505-1(f)(3)(d) or (e) of the FDCA (21 U.S.C. § 335-1(f)(3)(d) or (e)).[27] However, FDA asked that drug manufacturers "document and summarize" in upcoming REMS Assessment Reports the steps

they took to accommodate patient access to such drugs during the PHE.[28] It should be noted that while the Guidance was implemented immediately without prior public comment based on FDA's determination that prior public participation was neither feasible nor appropriate,[29] it was subject to comment pursuant to FDA's good guidance practices.[30]

U.S. Department of Health and Human Services Office of Inspector General Examines FDA Oversight of Opioid REMS Programs

The U.S. Department of Health and Human Services Office of Inspector General (OIG) published a report on September 25, 2020, titled *FDA's Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness in Addressing the Opioid Crisis* (OIG Report). The purpose of the OIG Report and its underlying study was to examine how and whether FDA has been able to hold drug manufacturers accountable for opioid misuse and abuse through REMS programs aimed at "mitiga[ing] the risk of misuse, abuse, addiction, accidental overdose, and death, while maintaining patient access to these medications."[31] The OIG Report, however, uncovered several possible shortcomings in FDA's oversight of opioid REMS programs that may undermine the programs' objectives.

How OIG Conducted its Review of TIRF and ER/LA Opioid REMS Programs

To conduct its review, OIG examined drug manufacturer-submitted and FDA documents pertaining to shared system REMS programs for transmucosal immediate-release fentanyl (TIRF)[32] and extended-release/long-acting (ER/LA) opioid[33] analgesics from between 2011 to 2017.[34] Specifically, OIG studied drug manufacturer-submitted assessments related to the manufacturers' implementation and compliance with the two REMS programs, such as updates on efforts to educate prescribers and other stakeholders about risks associated with the relevant drugs, surveillance and other patient outcome data, survey and audit results, and any other metrics defined in a REMS assessment plan.[35] OIG also reviewed FDA assessment reviews, inspection reports, and other analyses and correspondence.[36] Additionally, OIG interviewed FDA staff regarding the Agency's oversight of TIRF and ER/LA opioid REMS programs.[37]

OIG Findings Respecting TIRF and ER/LA Opioid REMS Programs

FDA reviewed assessments submitted by drug manufacturers following institution of the TIRF REMS. FDA's conclusion was that the TIRF REMS did not meet the program's overarching goal of "mitigat[ing] the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors."[38] Additionally, of the four subgoals set by FDA for the TIRF REMS, none were fully met.[39]

In reviewing the manufacturer assessments, FDA "consistently raised concerns about some of the data that manufacturers had submitted, which sometimes made it difficult for FDA to determine whether manufacturers were meeting the REMS' overarching goal and subgoals."[40] Problems in the manufacturer assessments included, among others, disorganized data, data that did not directly address the REMS goals, data indicating a lack of prescriber knowledge as to appropriate prescribing, concerning data about opioid tolerance, and data suggesting an *increase* in adverse events over time.[41]

Following a public advisory meeting held in August 2018 to discuss potential improvements to the TIRF REMS, FDA announced in March 2019 that it would be moving forward and modifying TIRF REMS with new goals and processes.[42] However, these new goals and processes were not part of OIG's review.

Similarly, FDA reviewed assessments submitted by manufacturers from the ER/LA opioid REMS.[43] FDA was unable to conclude, after each of four assessment reviews, whether manufacturers attained the overarching ER/LA opioid REMS goal of reducing serious adverse events from inappropriate prescription, misuse, or abuse of ER/LA analgesics.[44]

Furthermore, FDA found in many of their assessment reviews that manufacturers of ER/LA opioid analgesics had not achieved even half of the REMS targets for training prescribers on safe prescribing habits for opioids.[45] FDA was also late to review REMS assessments submitted by drug manufacturers between 2015 to 2018, resulting in manufacturers being unable to timely address deficiencies noted by the Agency.[46]

In 2018, FDA modified the focus of the ER/LA opioid REMS program from reducing serious adverse outcomes caused by inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics to educating prescribers and healthcare providers on concepts of pain management and how to counsel patients on safe opioid use.[47] Again, the effectiveness of these modifications was not part of OIG's review.

OIG Conclusions and Recommendations

Following its review of FDA's implementation and oversight of REMS for TIRF and ER/LA opioid analgesics between 2011 and 2017, OIG concluded that REMS may not be a particularly efficient vehicle for effecting change in the opioid crisis.[48] The TIRF and ER/LA

opioid REMS relied heavily on educating prescribers about risks associated with the drugs, but it takes time to meaningfully change prescribing habits.[49] OIG also speculated that pharmaceutical marketing campaigns aimed at increasing prescribing may have countered the effects of the REMS programs.[50] To improve oversight of the two opioid REMS programs going forward, OIG provided the following recommendations to FDA:

1. Implement a new TIRF REMS patient registry for monitoring identified risks, such as inappropriate conversions between different TIRF drugs and off-label prescriptions.[51]
2. Strengthen REMS for opioid analgesics by requiring providers to complete mandatory training.[52]
3. Improve the REMS assessment review process by timely completing reviews and requesting information on opioid promotion and inappropriate prescribing trends from FDA's Office of Prescription Drug Promotion.[53]
4. Seek additional authority to hold manufacturers accountable as appropriate.[54]

FDA concurred with the first and third recommendations, did not concur with the second recommendation, and is considering the fourth recommendation.[55] OIG and FDA have continued to work together to address OIG's recommendations, including recommendations that FDA did not explicitly concur with.[56]

Conclusion

While enactment of the CREATES Act was arguably the biggest REMS development of the past several years, let alone the last year, the new legislation remains unasserted in its first year despite being widely anticipated. Time will tell whether enactment of the CREATES Act will have a deterrent effect on the targeted behavior and quash the filing of antitrust claims against innovator drug and biologic companies allegedly withholding reference product samples to deter follow-on competition, or whether parallel claims filed under the CREATES Act and antitrust laws will gradually become a matter of course. While the year draws to a close, interesting new developments are already beginning to appear on the REMS front: FDA has solicited and is currently evaluating comments directed to whether patents associated with an established REMS should be listed in the Orange Book.[57] As the world gradually recovers from the disruption to ordinary life caused by the COVID-19 pandemic, clarity from stakeholders on new legislations and regulations concerning REMS may gradually emerge.

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1. *See* § 505-1 of the Federal Food, Drug & Cosmetic Act (FDCA) (21 U.S.C. § 355-1).
2. *See* § 505-1(f)(3) of the FDCA (21 U.S.C. § 355-1(f)(3)).
3. *See* Approved Risk Evaluation and Mitigation Strategies (REMS), FDA, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm (last visited Nov. 1, 2020).
4. Further Consolidated Appropriations Act, H.R. 1865, 116th Cong.
5. § 610 is codified at 21 U.S.C. § 355-2.
6. CREATES Act, S. 340, 116th Cong. (2019).
7. 21 U.S.C. § 355-1(f)(8).
8. *See* Joint Statement of the Food & Drug Administration and the Federal Trade Commission Regarding a Collaboration to Advance Competition in the Biologic Marketplace, FTC (Feb. 3, 2020), https://www.ftc.gov/system/files/documents/public_statements/1565273/v190003fdaftcbiologicsstatement.pdf.
9. An "eligible product developer" pursuant to § 610(a)(4) of the CREATES Act is an entity developing a product for approval pursuant to § 505(b)(2) or § 505(j) of the FDCA or for licensing pursuant to § 351(k) of the Public Health Service Act (PHSA).
10. A "license holder" pursuant to § 610(a)(5) of the CREATES Act includes the holder of an application approved under § 505(c) or 505(j) of the FDCA, or the holder of a license pursuant to §§ 351(a) or 351(k) of the PHSA.
11. A "covered product" pursuant to § 610(a)(2) of the CREATES Act includes, *inter alia*, a drug, a biological product, and combinations of a drug or biological product.
12. § 610(b)(1).
13. *Id.* § (a)(1).
14. *Id.* § (b)(3).
15. *Id.* § (b)(4)(A)(i), (ii).
16. *Id.* § (b)(4)(A)(iii).
17. *Id.* § (b)(4)(B).
18. *Id.*
19. § 610(f)(1); 21 U.S.C § 355-1(g)(4)(B)(iii).
20. § 610(f)(2); 21 U.S.C § 355-1 (i)(1)(C).
21. § 610(f)(2); 21 U.S.C § 355-1 (i)(1)(C)(ii).
22. § 610(e)(2).
23. Policy for Certain REMS Requirements During the COVID-19 Public Health Emergency: Guidance for Industry and Health Care Professionals, U.S. Dep't of Health & Human Servs. 7 (Mar. 2020), https://www.fda.gov/media/136317/download [hereinafter Guidance].
24. *Id.*
25. *Id.*
26. *Id.*
27. *Id.*
28. *Id.*
29. *See* § 701(h)(1)(C)(i) of the FDCA (21 U.S.C. § 371(h)(1)(C)(i)); 21 C.F.R. 10.115(g)(2).
30. Guidance, *supra* note 23, at 5.
31. FDA's Risk Evaluation and Mitigation Strategies: Uncertain Effectiveness in Addressing the Opioid Crisis, U.S. Dep't of Health & Human Servs., Off. of Inspector General 2 (Sept. 2020), https://oig.hhs.gov/oei/reports/OEI-01-17-00510.pdf.

32. TIRF drugs are potent opioid analgesics used for the management of breakthrough pain in cancer patients who routinely take opioid pain medication and have become opioid-tolerant. Examples of TIRF drugs are fentanyl sublingual and buccal tablets, lozenges, and nasal sprays, as well as buccal-soluble films. TIRF drugs are both potent—up to 100 times more powerful than morphine—and exhibit a wide range of different pharmacokinetic profiles, meaning prescribers must be especially careful when converting patients from one TIRF to another to prevent overdose. *See id.* at 3–4.
33. ER/LA drugs are also strong opioid analgesics, but they are used for long-term, 24/7 treatment of severe pain for which there are few adequate alternative treatments. Examples of ER/LA opioid analgesics include morphine, oxycodone, methadone, and fentanyl. *See id.* at 5.
34. *Id.* at 6.
35. *See id.* at 6–7; *id.* at 3 (for explanation of manufacturer assessment reports).
36. *See id.* at 6.
37. *See id.* at 7.
38. *See id.* at 8–9.
39. The four subgoals included prescribing/dispensing TIRF drugs to only the right patients, which includes only opioid-tolerant patients; preventing inappropriate conversion of patients between different TIRF drugs; limiting exposure of TIRF drugs to only appropriate patients; and educating stakeholders on misuse, abuse, addiction, and overdose of TIRF drugs. *Id.* at 9.
40. *Id.* at 10.
41. *Id.* at 10–12.
42. *Id.* at 13.
43. *Id.* at 14–15.
44. *Id.* at 15.
45. *Id.* at 15–16.
46. *Id.* at 16.
47. *Id.* at 17.
48. *Id.* at 20.
49. *Id.*
50. *Id.*
51. *Id.* at 20–21.
52. *Id.* at 21–22.
53. *Id.* at 22.
54. *Id.*
55. *Id.* at 23–24.
56. *Id.*
57. *See* Listing of Patent Information in the Orange Book, 85 Fed. Reg. 33,169 (June 1, 2020).