
Waivers of the Single, Shared System REMS Requirement Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact the Center for Drug Evaluation and Research (CDER) at 301-796-2089 or the Office of Communication, Outreach and Development (CBER), 800-835-4709 or 240-402-8010.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Drug Evaluation and Research (CBER)**

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Waivers of the Single, Shared System REMS Requirement Guidance for Industry¹

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes how FDA intends to consider granting a waiver of the requirement in section 505-1(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355-1(i)) that the applicant for an abbreviated new drug application (ANDA) and its reference listed drug (RLD) use a single, shared system (SSS) for a required risk evaluation and mitigation strategy (REMS) with elements to assure safe use (ETASU).²

This guidance is intended for ANDA applicants that reference a drug with a REMS with ETASU and the applicants³ for such referenced new drug applications (NDAs). It is intended to explain the factors FDA will consider in evaluating a request for a waiver of the SSS requirement, and provide recommendations to ANDA applicants regarding the submission and content of waiver requests. The guidance also addresses FDA's interpretation of what constitutes a different, comparable aspect of the ETASU as described in section 505-1(i)(1)(B) of the FD&C Act. This guidance does not provide recommendations on the development of a shared system REMS for multiple prescription drug products.⁴ FDA issued a separate guidance that addresses the development of shared system REMS generally, whether between ANDA applicant(s) and the referenced NDA applicant or between applicants for multiple prescription drug products.⁵

¹ This guidance has been prepared by the Office of Regulatory Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² FDA has already granted three waivers of the SSS requirement. *See* <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/CDERFOIAElectronicReadingRoom/ucm521456.htm>. Some of the factors we considered in each case were the amount of time taken to negotiate a SSS, the burdens of creating a SSS on various stakeholders, and the benefits of a SSS to various stakeholders.

³ For purposes of this guidance, *applicants* includes any person that holds an application approved under section 505 of the FD&C Act (21 U.S.C. 355) or a license issued under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262) for a drug product, or that submits an NDA or ANDA or a biologics license application (BLA) or an amendment or supplement to an NDA or ANDA or a BLA to obtain FDA approval.

⁴ Shared system REMS can involve multiple NDAs, ANDAs, or BLAs approved under section 505(b)(1), 505(b)(2), and 505(j) of the FD&C Act or section 351(a) or (k) of the PHS Act.

⁵ See the draft guidance for industry, *Development of a Shared System REMS*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page (available at

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33 The scope of this guidance is limited to waivers of the SSS requirement where there is no
34 previously established SSS for the drug product, and no previously approved separate REMS for
35 an ANDA(s) that the pending application can join.

36
37 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
38 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
39 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
40 the word *should* in Agency guidances means that something is suggested or recommended, but
41 not required.

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II. BACKGROUND

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46 The Food and Drug Administration Amendments Act of 2007 (FDAAA)⁶ created section 505-1
47 of the FD&C Act, which authorizes FDA to require a REMS if FDA determines that a REMS is
48 necessary to ensure that the benefits of the drug outweigh its risks.⁷ A REMS is a required risk
49 management strategy that employs tools beyond prescribing information to ensure that the
50 benefits of a drug outweigh its risks. A REMS may require a Medication Guide (or patient
51 package insert) to provide risk information to patients⁸ and/or a communication plan to
52 disseminate risk information to health care providers.⁹ FDA may also require certain ETASU
53 when such elements are necessary to mitigate specific serious risks associated with a drug.¹⁰
54 ETASU may include, for example, requirements that health care providers who prescribe the
55 drug have particular training or experience, that patients using the drug be monitored, or that the
56 drug be dispensed to patients with evidence or other documentation of safe-use conditions.

57

58 Certain REMS with ETASU may also include an implementation system through which the
59 applicant is able to monitor and evaluate implementation of the ETASU and work to improve
60 their implementation.¹¹ Finally, REMS generally must have a timetable for submission of
61 assessments of the strategy.¹²

62

63 An ANDA referencing a drug with a REMS with ETASU is subject to the same ETASU
64 requirements as its reference listed drug. Section 505-1(i)(1)(B) of the FD&C Act requires that
65 the holder of an ANDA approved under section 505(j) use a “single, shared system” with the
66 RLD for any ETASU, unless FDA waives this requirement. The statute permits a waiver of the
67 SSS requirement if FDA finds that (1) “the burden of creating a [SSS] outweighs the benefit of a

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>) or Biologics
guidances web page (available at
<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>).

When final, this guidance will represent FDA’s current thinking on this topic.

⁶ Public Law 110-85.

⁷ Section 505-1(a) of the FD&C Act.

⁸ Section 505-1(e)(2) of the FD&C Act.

⁹ Section 505-1(e)(3) of the FD&C Act.

¹⁰ Section 505-1(f)(3) of the FD&C Act.

¹¹ Section 505-1(f)(4) of the FD&C Act.

¹² Section 505-1(d) of the FD&C Act.

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68 single, system, taking into consideration the impact on health care providers, patients, the
69 applicant for the [ANDA], and the holder of the reference drug product”¹³ or (2) an aspect of the
70 ETASU for the applicable listed drug is claimed by an unexpired patent or is a method or process
71 that, as a trade secret, is entitled to protection, and the ANDA applicant certifies that it sought a
72 license for use of the aspect, but was unable to obtain one.¹⁴ If a waiver of the SSS requirement
73 is granted, the ANDA applicant may use “a different, comparable aspect of the [ETASU],”
74 instead of implementing the ETASU as part of a SSS REMS.
75

76 The Generic Drug User Fee Amendments (GDUFA) was enacted in 2012 to speed access to safe
77 and effective generic drugs to the public and reduce costs to industry. Under GDUFA, FDA
78 committed to review and act on complete electronic ANDAs within 10 months after the date of
79 submission.¹⁵ On August 18, 2017, the President signed into law the Food and Drug
80 Administration Reauthorization Act (FDARA),¹⁶ which includes the reauthorization of the
81 Generic Drug User Fee Amendments through September 2022 (GDUFA II). Under GDUFA II,
82 FDA has committed to continue to review and act on standard ANDAs within 10 months after
83 the date of submission, and to also review and act on certain priority ANDAs within 8 months of
84 the date of ANDA submission.¹⁷
85
86

III. FDA CONSIDERATION OF WAIVERS OF THE SSS REQUIREMENT

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89 In determining whether to grant a waiver of the SSS requirement, FDA will consider each waiver
90 request on a case-by-case basis. As described in section 505-1(i)(1)(B)(i) of the FD&C Act,
91 FDA can grant a waiver if the burden of creating a SSS outweighs the benefit of a single system.
92 As described in section 505-1(i)(B)(ii), FDA can also grant a waiver if an aspect of the ETASU
93 is protected by a patent, or if an aspect is a method or process that, as a trade secret, is entitled to
94 protection, and the ANDA applicant certifies that it sought a license to that aspect and was
95 unable to obtain one. This guidance primarily addresses waivers pursuant to section 505-
96 1(i)(1)(B)(i).
97

98 Under section 505-1(i)(1)(B)(i), FDA will determine whether a waiver is appropriate by
99 analyzing whether the burden of forming a SSS outweighs the benefits of having a SSS in a
100 particular case, taking into account the impact on health care providers, patients, the ANDA
101 applicant(s), and the holder of the RLD. The following sections discuss factors that FDA may
102 consider in evaluating benefit and burden. Additional factors may be relevant to particular cases,
103 including the drug product at issue, the nature of the existing REMS program for the RLD, and
104 circumstances in the health care delivery system.
105

¹³ Section 505-1(i)(1)(B)(i) of the FD&C Act.

¹⁴ Section 505-1(i)(1)(B)(ii) of the FD&C Act.

¹⁵ Generic Drug User Fee Act Program Performance Goals and Procedures, available at <http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>

¹⁶ Generic Drug User Fee Amendments of 2017, Title III, FDA Reauthorization Act of 2017 (Public Law 115-52).

¹⁷ GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022, available at <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

See also CDER’s Manual of Policies and Procedures 5240.3, *Prioritization of the Review of Original ANDAs, Amendments, and Supplements*.

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A. Benefits of Having a SSS

The potential benefits of a SSS generally stem from opportunities for increased efficiencies. In evaluating the potential benefits of a SSS for health care providers, patients, the RLD holder, and the ANDA applicant, FDA will consider a variety of factors, including the following.

Impact on ANDA applicant and RLD holder. Use of a SSS may benefit the applicants by providing opportunities for sharing the cost of developing and implementing the program, analyses of adverse events or other safety data, and periodic assessments to determine whether the REMS is meeting its intended risk management goal(s). A SSS may also make the process of modifying a REMS that encompasses multiple products and adding other applicants to the REMS more efficient.

Impact on health care providers and patients. A SSS REMS generally uses a shared infrastructure for all of the products in the REMS. This generally provides a single portal for REMS participants¹⁸ to engage in and undertake the activities of the program. For example, prescribers and pharmacists can complete certification and other administrative requirements once for multiple drugs, rather than separately for each individual drug. A shared infrastructure can also allow for a single set of REMS materials and information about the program.

B. Burden of Forming a SSS

The formation of a SSS between an RLD holder and an ANDA applicant (or multiple ANDA applicants) can be a complex and time-consuming process. In evaluating the potential burden of forming a SSS on health care providers, patients, the RLD holder, and the ANDA applicant(s), FDA will consider a variety of factors, including the following.

Impact on ANDA applicant(s) and RLD holder. Based on our experience, development of a SSS REMS is dependent on negotiations and establishment of agreements between companies, as well as completion of numerous steps to develop and manage a shared program. These negotiations are carried out between companies that are marketplace competitors and potential adversaries in patent litigation related to the drug product. If negotiations for a SSS are unsuccessful, the ANDA applicant(s) may have to request a waiver from the SSS REMS requirement and begin the REMS development process anew. If the need for a waiver occurs late in the ANDA review cycle, this may delay approval of the generic application.

Impact on health care providers and patients. Health care providers and patients may be disadvantaged to the extent that access to a generic version of the drug is delayed pending the formation of a SSS REMS.

¹⁸ *REMS participants* are stakeholders who participate in the REMS based on their role in clinical assessment; prescribing, dispensing, administering the product; monitoring treatment; or the distribution process. REMS participants can include health care providers who prescribe, patients who receive the drug, health care settings, practitioners, dispensing pharmacies, and distributing wholesalers/distributors.

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IV. TIMING AND PROCESS FOR FDA CONSIDERATION OF A WAIVER

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148 Generally, FDA notifies the applicant of an ANDA that references an RLD with a REMS with
149 ETASU¹⁹ of the requirement for a SSS REMS after the ANDA has been received for review.²⁰

150 At that time, FDA will direct the ANDA applicant to contact the RLD holder to discuss the
151 possible formation of a SSS REMS. The Agency generally holds a meeting with the ANDA
152 applicant(s) and RLD holder to discuss the SSS requirement, the process for developing a SSS,
153 and FDA's expectations, and to answer any questions the companies may have.²¹

154

A. When FDA Will Consider a Request for a Waiver

156

157 While FDA encourages companies to work together to form a SSS, the Agency will consider a
158 waiver at any time (either upon request of the applicant, or on the Agency's own initiative). The
159 statutory provisions governing REMS do not impose time constraints on the Agency's
160 consideration of a waiver.

161

162 The Agency's experience with REMS since the passage of FDAAA in 2007 has demonstrated
163 that the process of forming a new SSS can, in some cases, be lengthy because it is a complex
164 process that is negotiated between marketplace competitors. This length and complexity can add
165 to the burden of forming a new SSS, for example, by contributing to delays in the approval of
166 ANDAs. To the extent such delays occur, they disadvantage health care providers and patients
167 by delaying access to generic versions of drugs.

168

169 Such delay is also counter to FDA's understanding of Congress's intent. FDA must implement
170 the REMS SSS provisions, including section 505-1(f)(8) of the FD&C Act which states that
171 holders of approved applications must not use any ETASU to block or delay approval of another
172 application, as well as the SSS waiver provision, in concert with the generic drug approval
173 provisions. GDUFA is designed to speed the delivery of safe and effective generic drugs to the
174 public and improve upon the predictability of the review process. Delay in the approval of
175 ANDAs is counter to this fundamental goal.

176

B. Process for Requesting a Waiver and Review of Separate REMS

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179 An ANDA applicant may either submit a SSS REMS (if agreed to with the RLD holder) or a
180 proposed separate REMS with a request for a waiver of the SSS requirement. Whichever REMS
181 the ANDA applicant submits, FDA will review it as part of the application for approval. In
182 either case, FDA recommends that the proposed REMS be submitted to the Agency by the
183 midpoint of the pending application review cycle to allow sufficient time for Agency review.

184

185 If the ANDA applicant chooses to submit a proposed REMS that is separate from the REMS of
186 the RLD, it should also submit a request for a waiver (the recommended content of which is

¹⁹ A comprehensive list of drug products subject to a REMS is located at <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

²⁰ 21 CFR 314.101(b).

²¹ See the draft guidance for industry *Development of a Shared System REMS*. When final, this guidance will represent FDA's current thinking on this topic.

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187 described below). The Agency will consider the waiver request and proposed separate REMS
188 simultaneously, and does not intend to grant or deny a waiver until its review of the proposed
189 separate REMS is complete.

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C. Content of a Waiver Request

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193 While a waiver request is not required for FDA to grant a waiver of the SSS requirement, an
194 ANDA applicant is strongly encouraged to submit a written waiver request in conjunction with
195 its separate REMS submission, as this will assist the Agency in determining whether the
196 statutory criteria for a waiver have been met. In addition, the RLD holder is welcome to submit
197 its views on the appropriateness of a waiver at any time.

198

199 The ANDA applicant's waiver request should include the following, in addition to any other
200 information the Agency should consider:

201

- 202 • Discussion of the benefit of having a SSS with the RLD in this case;
- 203 • Discussion of the burden of forming a SSS with RLD in this case, including attempts at
204 negotiation, if any, and any other ways in which formation of the SSS creates burden;
- 205 • Analysis of why the burden of forming a SSS outweighs the benefits of having a SSS in
206 this case, taking into account the impact on health care providers, patients, ANDA
207 applicant(s), and RLD holder;
- 208 • Description of the ANDA applicant's plans to include additional applicants in its REMS
209 program;²²
- 210 • Analysis of how the proposed separate program is different from the RLD program,
211 including explanations of how aspects of the required ETASU are comparable to those of
212 the RLD REMS;
- 213 • If applicable, discussion of the attempts made by the ANDA applicant to obtain a license
214 to an aspect of the ETASU that is protected by an unexpired patent or, alternatively, is a
215 method or process that, as a trade secret, is entitled to protection.

216

217

V. COMPARABILITY OF SEPARATE REMS

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220 The statute authorizes FDA to waive the SSS requirement and permit the ANDA applicant to use
221 a “different, comparable aspect of the [ETASU].” Accordingly, FDA will conduct an in-depth,
222 case-specific analysis of any proposed separate REMS to determine whether the proposed
223 separate REMS uses an aspect of the ETASU that is comparable to that of the RLD REMS and
224 achieves the same level of safety. FDA interprets this standard to mean that a separate system
225 for ETASU with a waiver of the SSS requirement must include the same ETASU as described in
226 the statute. For example, if the RLD's ETASU consist of prescriber certification (under section
227 505-1(f)(3)(A) of the FD&C Act) and dispensing of a drug only in certain health care settings
228 (under section 505-1(f)(3)(C) of the FD&C Act), the ANDA's separate REMS must include
229 those elements as well.

²² Note that FDA has only granted waivers in instances where the ANDA applicant has agreed to share its REMS system with any concurrent or subsequent applicants.

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FDA further interprets “different, comparable aspect of the [ETASU]” to allow a separate REMS for ANDA applicants to use different methods or operational means to effectuate a REMS requirement, provided the program achieves the same level of safety. The ANDA applicant should explain and justify any operational differences from the RLD REMS in its waiver request.

Generally, FDA expects to assess any separate REMS for ANDAs at the same intervals and with the same metrics as the RLD REMS to ensure that the separate REMS is meeting its goals.