
Development of a Shared System REMS Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER), Lubna Merchant, Office of Surveillance and Epidemiology, at 301-796-5162 or (CBER) Office of Communication, Outreach and Development, 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 Biologics Evaluation and Research (CBER)**

**June 2018
Drug Safety**

Development of a Shared System REMS Guidance for Industry

*Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research*

Food and Drug Administration

10001 New Hampshire Ave., Hillandale Bldg., 4th Floor

Silver Spring, MD 20993-0002

Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353

Email: druginfo@fda.hhs.gov

<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

and/or

Office of Communication, Outreach and Development

Center for Biologics Evaluation and Research

Food and Drug Administration

10903 New Hampshire Ave., Bldg. 71, Room 3128

Silver Spring, MD 20993-0002

Phone: 800-835-4709 or 240-402-8010

Email: ocod@fda.hhs.gov

<https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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

**June 2018
Drug Safety**

Contains Nonbinding Recommendations

Draft — Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
A.	Overview of Risk Evaluation and Mitigation Strategies (REMS).....	2
B.	Overview of Shared System REMS.....	3
C.	Benefits of a Shared System REMS.....	3
D.	Required Use of a Single, Shared System REMS for ANDAs and RLD.....	4
E.	Recommended Use of a Shared System REMS in Other Situations	4
III.	DEVELOPING A SHARED SYSTEM REMS PROGRAM	4
A.	Notification From FDA That a Shared System REMS Is Required or Recommended	5
B.	Formation of an Industry Working Group	5
C.	FDA Role	6
IV.	SHARED SYSTEM REMS ASSESSMENTS	6
V.	SUBMISSION PROCEDURES.....	6
A.	General Considerations.....	7
B.	Timing of Initial Shared System REMS Submission.....	7
C.	RLD Submission of a “Bifurcated REMS”.....	8
D.	Submission to FDA Using a Type V Drug Master File.....	8

Contains Nonbinding Recommendations

Draft — Not for Implementation

**Development of a Shared System REMS
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 provides recommendations to industry on the development of a shared system risk evaluation and mitigation strategy (REMS)² for multiple prescription drug (including biological) products.³ This guidance describes some of the possible benefits of a shared system REMS, and provides general principles and recommendations to assist industry with the development of these programs. This guidance does not discuss the process for requesting a waiver of the single, shared system REMS requirement that applies to abbreviated new drug applications (ANDAs) referencing a listed drug with an approved REMS.⁴ FDA issued a separate guidance describing the process for requesting waivers and the criteria FDA applies in considering them.⁵

In general, FDA’s guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of

¹ This guidance has been prepared by the Office of Surveillance and Epidemiology, Office of New Drugs, Office of Generic Drugs, and Office of Regulatory Policy in the Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration.

² A shared system REMS encompasses multiple prescription drug products and is developed and implemented jointly by two or more applicants.

³ For purposes of this guidance, unless otherwise specified, references to “drugs” and “drug products” include prescription drugs submitted for approval or approved under section 505(b) or (j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(b) or (j)) and biological products submitted for licensure or licensed under section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262), other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

⁴ See section 505-1(i)(1)(B) of the FD&C Act (21 U.S.C. 355-1(i)(1)(B)).

⁵ See the draft guidance for industry *Waivers of the Single, Shared System REMS Requirement*. 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 <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>) or Biologics guidance 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.

Contains Nonbinding Recommendations

Draft — Not for Implementation

27 the word *should* in Agency guidances means that something is suggested or recommended, but
28 not required.

29

30

31 **II. BACKGROUND**

32

33 **A. Overview of Risk Evaluation and Mitigation Strategies (REMS)**

34

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

47

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

52

53 FDA can require a REMS before initial approval of a new drug application (NDA) or, should
54 FDA become aware of new safety information¹³ about a drug and determine that a REMS is
55 necessary to ensure that the benefits of the drug outweigh its risks, after the drug has been
56 approved.¹⁴

57

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.

¹³ Section 505-1(b)(3) of the FD&C Act.

¹⁴ Section 505-1(a) of the FD&C Act.

Contains Nonbinding Recommendations

Draft — Not for Implementation

58 **B. Overview of Shared System REMS**

59
60 A shared system REMS encompasses multiple prescription drug products and is developed and
61 implemented jointly by two or more applicants.¹⁵ A REMS that includes more than one product
62 but only a single applicant is not considered a shared system REMS. A shared system REMS
63 can be a program shared by a drug that is the subject of an abbreviated new drug application
64 (ANDA) and the listed drug, as required in section 505-1(i)(1)(B) of the FD&C Act (described in
65 subsection I.D below). It can also involve multiple NDAs or ANDAs, submitted under section
66 505(b)(1), (b)(2), or (j) of the FD&C Act, or multiple biologics license applications (BLAs),
67 submitted under section 351(a) or (k) of the PHS Act, that form a shared system voluntarily
68 (described in subsection I.E below).

69
70 A shared system REMS uses a single REMS document,¹⁶ supporting document, and REMS
71 materials, agreed to by all applicants and approved as part of each application. Applicants
72 generally share in the implementation and maintenance of any database and infrastructure (e.g.,
73 call center) used for the program, and are jointly responsible for carrying out all or most
74 components of the REMS assessments (see section IV below). There may be product-specific
75 materials (e.g., Medication Guide) that will not be shared across applicants.

76 **C. Benefits of a Shared System REMS**

77
78
79 A shared system for REMS with ETASU may offer benefits to drug applicants and stakeholders
80 in the health care delivery system. The benefits may vary, but generally stem from opportunities
81 for increased efficiencies for stakeholders and applicants.

82
83 *Impact on Drug Applicants.* Use of a shared system REMS may benefit the applicants by
84 providing opportunities for sharing the cost of developing and implementing the program,
85 analyses of adverse events or other safety data, and periodic assessments to determine whether
86 the REMS is meeting its intended risk management goal(s). A shared system may also make
87 modifying a REMS that encompasses multiple products and adding other applicants to the
88 REMS more efficient.

89
90 *Impact on Health Care Providers and Patients.* A shared system REMS generally uses a shared
91 infrastructure for all of the products in the REMS. This generally provides a single portal for
92 REMS participants¹⁷ to engage in and undertake the activities of the program. For example,

¹⁵ For the purpose of this guidance, *applicants* includes any person that holds an application approved under section 505 of the FD&C Act or a license issued under section 351 of the PHS Act for such product, or who submits an NDA, an ANDA, a BLA, or an amendment or supplement to an NDA, an ANDA, or a BLA to obtain FDA approval.

¹⁶ See the draft guidance for industry *Format and Content of a REMS Document*. When final, this guidance will represent FDA's current thinking on this topic.

¹⁷ *REMS participants* are stakeholders who participate in the REMS based on their role in clinical assessment; prescribing, dispensing, administering the product; monitoring treatment; or in the distribution process. REMS participants can include health care providers who prescribe, patients who receive the drug, health care settings, practitioners, pharmacies that dispense, and wholesalers/distributors that distribute.

Contains Nonbinding Recommendations

Draft — Not for Implementation

93 prescribers and pharmacists can complete certification and other administrative requirements
94 once for multiple drugs, rather than separately for each individual drug. A shared infrastructure
95 can also allow for a single set of REMS materials and information about the program.

D. Required Use of a Single, Shared System REMS for ANDAs and RLD

96
97
98
99 As noted above, section 505-1(i)(1)(B) of the FD&C Act requires that a holder of an ANDA
100 approved under section 505(j) use a “single, shared system” with the reference listed drug (RLD)
101 for any ETASU, unless FDA waives this requirement and permits the ANDA to use a separate,
102 comparable aspect of the ETASU.¹⁸

E. Recommended Use of a Shared System REMS in Other Situations

103
104
105
106 The requirement under section 505-1(i)(1)(B) regarding a “single, shared system” only applies to
107 ANDAs. However, FDA recognizes that it may be in the interest of public health to have a
108 shared system REMS in other cases because it may increase efficiencies for applicants and
109 stakeholders.

110
111 For example, we recommend the applicants for a product submitted under section 505(b)(2) of
112 the FD&C Act or section 351(k) of the PHS Act work together with the applicant for the product
113 they are referencing to establish a shared system REMS. If an applicant of a product submitted
114 under section 505(b)(2) of the FD&C Act or section 351(k) of the PHS Act seeks to develop a
115 shared system REMS, we encourage the applicant to contact the applicant of the product they are
116 referencing and begin joint development of the shared system REMS as early as possible.

117
118 Additionally, FDA may request that applicants for a class of products with a similar risk profile
119 develop a shared system REMS. Applicants that are interested in developing a shared system
120 REMS for a class of products should seek the advice of FDA.¹⁹

III. DEVELOPING A SHARED SYSTEM REMS PROGRAM

121
122
123
124
125 This section outlines the process and recommendations for developing a shared system REMS
126 program.
127

¹⁸ For more information on waivers of the single, shared system requirement in section 505-1(i)(1)(B), see the draft guidance for industry *Waivers of the Single, Shared System REMS Requirement*. This guidance, when final, will represent FDA’s current thinking on this topic.

¹⁹ See the guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*. See also the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*. When final, this guidance will represent FDA’s current thinking on this topic.

Contains Nonbinding Recommendations

Draft — Not for Implementation

128 **A. Notification From FDA That a Shared System REMS Is Required or** 129 **Recommended**

130
131 FDA will initiate discussions about the formation of a shared system REMS under the following
132 circumstances:

- 134 • When FDA has received an ANDA that references an RLD that has a REMS with
135 ETASU²⁰
- 136
137 • When FDA has received an NDA or a BLA for a product that references an NDA or a
138 BLA that is subject to REMS with ETASU, and has determined that the proposed product
139 also would require the same ETASU²¹
- 140
141 • When FDA has determined for drugs and biologics in a class with similar, serious risks
142 that a shared system REMS may minimize the burden of having multiple unique REMS
143 programs ²²
- 144

145 The Agency will, where appropriate, request that applicants of the pending applications submit
146 an authorization for disclosure that will allow the Agency to hold meetings between multiple
147 applicants. FDA will provide contact information for the product being referenced by the
148 pending applications to facilitate the development of a shared system REMS.

149 **B. Formation of an Industry Working Group**

150
151
152 Applicants may consider forming a working group, commonly referred to as an *industry working*
153 *group* (IWG). Some applicants have used an IWG to facilitate negotiations and agreements
154 among the applicants to develop a shared system REMS on issues such as confidentiality,
155 governance, voting structure, cost-sharing, any potential changes to the drug distribution model,
156 and any other issues that may come up during the collaboration. Some applicants have used
157 third-party vendors to aid in implementation and management of the program. The applicants
158 must comply with the requirements of the REMS regardless of whether they use a third-party
159 vendor.

160
161 If an IWG is formed, the IWG applicants should identify a single point of contact (POC) to
162 represent the IWG in communication with FDA. This POC will facilitate communication
163 between the Agency and the IWG about the status of developing the shared system. FDA
164 generally requests that the Agency receive updates from the IWG POC on the status of
165 negotiations and on any barriers to developing the shared system REMS based on timelines that
166 have been communicated by the Agency early in the process. The updates are typically
167 submitted to each respective application as a REMS correspondence.

²⁰ Section 505-1(i)(1)(B) of the FD&C Act requires that a holder of an ANDA approved under section 505(j) use a “single, shared system” with the reference listed drug (RLD).

²¹ For products submitted under section 505(b)(2) of the FD&C Act or section 351(k) of the PHS Act.

²² If applicants for a class of products have not received a notification from FDA but are interested in developing a shared system REMS, they may seek further advice from FDA.

Contains Nonbinding Recommendations

Draft — Not for Implementation

168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207

C. FDA Role

FDA does not advise on the business arrangements being negotiated or arbitrate substantive disputes about the terms of contracts. FDA will set forth expectations of the applicants for the development of the shared system REMS, which may include suggested timeframes for various milestones in the process of developing the shared system, and the process for submission of the proposed REMS. FDA may facilitate collaborations between applicants when necessary to achieve a shared system REMS. For example, FDA may host teleconferences to encourage communications between applicants.

FDA will identify an Agency POC for a shared system REMS that is under development and will provide this information to the IWG. If obstacles arise that impede the development of a shared system REMS, the Agency POC should be notified.

IV. SHARED SYSTEM REMS ASSESSMENTS

Information about the performance of REMS programs is important in determining whether the program is meeting its intended risk mitigation goals. All approved REMS for NDA and BLA products are required to include a timetable for submission of assessments of the REMS.²³ The proposed REMS assessment plan for a shared system REMS, which specifies the nature and content of the periodic assessments, is generally included in the REMS supporting document.

The assessments for shared system REMS apply collectively to all products that are subject to the REMS. The Agency generally does not require submission of the shared REMS assessment reports for ANDAs that are part of a shared system REMS with an RLD. However, FDA may require that ANDA applicants submit REMS assessment reports when product-specific utilization information or adverse event data is necessary to evaluate whether the program should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the health care delivery system of complying with the REMS.²⁴

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.

V. SUBMISSION PROCEDURES

This section provides an overview of submission procedures that apply to shared system REMS.

²³ See section 505-1(d) of the FD&C Act. Section 505-1(i) states that the only REMS elements to which ANDAs are subject are a Medication Guide or patient package insert and any ETASU. ANDAs are not subject to the requirement for a timetable for submission of assessments.

²⁴ See section 505-1(g)(2)(C) of the FD&C Act.

Contains Nonbinding Recommendations

Draft — Not for Implementation

208 **A. General Considerations**

209
210 In addition to the recommendations provided in this guidance, FDA advises applicants to refer to
211 other relevant FDA resources to help create their REMS submissions, such as the following:
212

- 213 • Guidance for industry on *Providing Regulatory Submissions in Electronic Format —*
214 *Certain Human Pharmaceutical Product Applications and Related Submissions Using*
215 *the eCTD Specifications (Revision 4)*
- 216 • Electronic Common Technical Document (eCTD) web page²⁵
- 217 • Draft guidance for industry *Format and Content of a REMS Document*²⁶
- 218
- 219 • Draft guidance for industry *Risk Evaluation and Mitigation Strategies: Modifications and*
220 *Revisions*
- 221 • Draft guidance for industry *Providing Regulatory Submissions in Electronic Format –*
222 *Content of the Risk Evaluation and Mitigation Strategies Document Using Structured*
223 *Product Labeling*²⁷
- 224 • eCTD Technical Conformance Guide²⁸
- 225
- 226
- 227
- 228
- 229

230 **B. Timing of Initial Shared System REMS Submission**²⁹

231
232 Applicants that are developing a shared system REMS should submit their REMS by application
233 midpoint for pending applications, or another time frame specified by the Agency. To facilitate
234 submission tracking, FDA recommends that shared system REMS applicants work together to
235 coordinate their submissions on the same day, if possible.
236

²⁵ To make sure you have the most recent version of related technical specifications (CDER and CBER), check the eCTD web page at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>.

²⁶ When final, this guidance will represent FDA's current thinking on this topic.

²⁷ When final, this guidance will represent FDA's current thinking on this topic.

²⁸ Includes information to assist applicants on where to place REMS documents under the eCTD Module 1 REMS 1.16 sub-headings using the DTD v3.3 of the us-regional.xml file.

²⁹ Submission includes the REMS document, supporting document, and appended materials.

Contains Nonbinding Recommendations

Draft — Not for Implementation

237 **C. RLD Submission of a “Bifurcated REMS”**

238
239 In some cases, the approval of a single, shared system REMS between an ANDA and its RLD
240 may coincide with tentative approval of the ANDA.³⁰ *Tentative approval* for an ANDA is a
241 notification to an applicant that an ANDA meets the requirements for approval but cannot be
242 approved because of unexpired patents or exclusivity.³¹ A drug product that is granted tentative
243 approval is not an approved drug and will not be approved until FDA issues an approval letter
244 after any necessary additional review of the ANDA. In such cases, it would not be appropriate
245 for the single, shared system to be operational yet, because the generic product would not yet be
246 approved.

247
248 For the Agency to approve the single, shared system but postpone its operation until the approval
249 of the ANDA(s), FDA will request that the RLD holder submit a REMS modification that
250 proposes a single, two-part REMS, sometimes referred to as a "bifurcated REMS." Part A would
251 consist of the current REMS that applies only to the RLD and would be operational before the
252 first ANDA receives approval. Part B would be the single, shared system REMS that would be
253 operational once the first ANDA receives approval. In this circumstance, the approval letter for
254 the RLD holder’s REMS modification, as well as the REMS document itself, would state that the
255 single, shared system REMS (Part B) becomes operational automatically upon approval of the
256 first ANDA. If approval of the single, shared system REMS coincides with approval of the first
257 ANDA, rather than tentative approval, the single, shared system REMS (Part B) would
258 automatically be operational.

259 **D. Submission to FDA Using a Type V Drug Master File**

260
261
262 To improve the efficiency of the submission and review process for shared system REMS, FDA
263 recommends that applicants use a Type V³² Drug Master File (DMF) for their shared system
264 REMS submissions. Using a DMF allows applicants that are part of a shared system REMS to
265 submit one set of files on behalf of the application holders to the Agency and eliminates the need
266 for each applicant to submit identical REMS-related documents to its own application. The DMF
267 holder of the shared systems REMS DMF is jointly designated by the application holders. The
268 DMF holder will make submissions to the DMF on behalf of the application holders.
269

If applicants that are participating in a shared system REMS choose to use a DMF, they should refer to the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*.³³ Additional, and more-detailed, submission instructions are also included in a separate technical guide.³⁴

³⁰ There may also be instances where the approval of a shared system REMS between multiple NDAs may coincide with one or more NDAs receiving tentative approval.

³¹ Section 505(j)(5)(B)(iv)(II)(dd)(AA) of the FD&C Act; 21 CFR 314.3(b) and 314.107.

³² Type V FDA-Reference Information DMF.

³³ When final, this guidance will represent FDA’s current thinking on this topic.

³⁴ To make sure you have the most recent version of the SSR DMF Technical Conformance Guide, check the FDA website at

<https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm535180.htm>.