
Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry

DRAFT GUIDANCE

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**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)**

**October 2019
Drug Safety
Revision 1**

Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry

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1 **Postmarketing Studies and Clinical Trials—Implementation of**
2 **Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act**
3 **Guidance for Industry¹**
4
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6

7
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

14
15
16
17 **I. INTRODUCTION**
18

19 This guidance provides information on the implementation of section 505(o)(3) of the Federal
20 Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(o)(3)),² which authorizes FDA to
21 require certain postmarketing studies and clinical trials³ for prescription drugs approved under
22 section 505(c) of the FD&C Act and biological products approved under section 351 of the
23 Public Health Service Act (the PHS Act) (42 U.S.C. 262).⁴
24

¹ This guidance has been prepared by the Center for Drug Evaluation and Research (CDER) and the Center for
Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

² Added by section 901 of Food and Drug Administration Amendments Act of 2007 (FDAAA).

³ For purposes of implementing section 505(o)(3) of the FD&C Act, we distinguish between studies and
clinical trials for the purposes described in this document.

⁴ For the purposes of this guidance, all references to *drugs* include both human drugs and biological drug
products regulated by CDER and CBER unless otherwise specified.

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25 This guidance describes FDA’s statutory authority to require certain postmarketing studies and
26 clinical trials under section 505(o)(3) of the FD&C Act (i.e., postmarketing requirements
27 (PMRs))⁵ and provides an overview of the types and purposes of such studies and clinical trials.
28 This guidance also describes those types of postmarketing studies and clinical trials that are
29 agreed upon (i.e., postmarketing commitments (PMCs))⁶ between FDA and the applicant.⁷
30

31 This draft guidance is a revision of the guidance for industry *Postmarketing Studies and Clinical*
32 *Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act*
33 published in April 2011. This revised guidance provides information on implementation of
34 sections 505(o)(3)(D)(i) and (ii) of the FD&C Act. This guidance also reflects certain provisions
35 enacted under the Substance Use-Disorder Prevention that Promotes Opioid Recovery and
36 Treatment for Patients and Communities Act as they relate to postmarketing studies and clinical
37 trials.⁸ This guidance does not distinguish between prescription drugs with active ingredients
38 that are controlled substances and other prescription drugs because, at this time, the Agency does
39 not intend to treat controlled substances differently than other prescription drugs under 505(o).
40 Once finalized, this guidance will replace the April 2011 guidance.
41

42 This guidance does not apply to nonprescription drugs approved under a new drug application or
43 to generic drugs approved under section 505(j) of the FD&C Act.
44

45 The Glossary defines many of the terms for purposes of this guidance. Words or phrases found
46 in the Glossary appear in bold italics at first mention.
47

48 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
49 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
50 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
51 the word *should* in Agency guidances means that something is suggested or recommended, but
52 not required.
53
54

⁵ The term *postmarketing requirement* or PMR is used to describe all required postmarketing studies or clinical trials, including those required under FDAAA and those required under subpart H of 21 CFR part 314, subpart E of 21 CFR part 601, the Pediatric Research Equity Act, and the animal efficacy rule (see Appendix A: PMR and PMC Authorities).

⁶ The term *postmarketing commitment* or PMC is used to describe studies and clinical trials that are agreed upon between FDA and the applicant (see Appendix A: PMR and PMC Authorities).

⁷ For the purposes of this guidance, for ease of reference, the term *applicant* refers to a “responsible person” as defined in section 505(o)(2)(A) of the FD&C Act (i.e., the holder of an application for a prescription drug approved under section 505(c) of the FD&C Act, or pending, and biological products licensed under section 351 of the PHS Act (42 U.S.C. 262), or pending).

⁸ See Section 3041 of Public Law 115-271.

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55 **II. BACKGROUND**

56

57 **A. FDA May Require Postmarketing Studies and Clinical Trials**

58

59 FDA approves drugs based upon a demonstration that the drug is safe and effective when used
60 under the conditions specified in the proposed labeling. In some instances, FDA may be aware
61 of information and/or data at the time of approval or become aware of data and/or information in
62 a postapproval setting that necessitates further assessment.

63

64 Under section 505(o)(3) of the FD&C Act, FDA, based on appropriate scientific data including
65 information regarding chemically related or pharmacologically related drugs,⁹ can require at the
66 time of approval that an applicant conduct postmarketing *studies* or *clinical trials*. FDA may
67 also require that an applicant conduct postmarketing studies or clinical trials for a drug product
68 covered under an approved application if FDA becomes aware of *new safety information*.¹⁰

69

70 For example, in some cases, FDA may be concerned about a potential risk associated with the
71 use of a drug and believe that the risk is serious but may not know enough about the risk, through
72 adverse event reporting or otherwise, to determine how to address the risk in labeling and what
73 information would be appropriate to include. In such cases, FDA can require an applicant to
74 conduct a postmarketing study or clinical trial to obtain more information about the risk.

75

76 Postmarketing studies and clinical trials may be required for any or all of the following three
77 purposes:¹¹

78

- 79 • To assess a known *serious risk* related to the use of the drug
- 80
- 81 • To assess *signals of serious risk* related to the use of the drug
- 82
- 83 • To identify an *unexpected serious risk* when available data indicate the potential for a
84 serious risk
- 85

86

86 For the purposes of this guidance,¹² clinical trials and studies are defined as follows:

87

⁹ See section 505(o)(3)(A) of the FD&C Act.

¹⁰ See section 505(o)(3)(C) of the FD&C Act. *New safety information* is defined at section 505-1(b)(3) of the FD&C Act.

¹¹ See section 505(o)(3)(B) of the FD&C Act.

¹² These definitions of postmarketing clinical trial and study do not affect whether the trials or studies are subject to the requirements of Title VIII of FDAAA (Clinical Trial Databases) and section 402(j) of the PHS Act (42 U.S.C. 282(j)).

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- 88 • ***Clinical trials*** are any prospective investigations in which the applicant or investigator
89 determines the method of assigning the drug(s) or other interventions to one or more
90 human subjects.
91
- 92 • ***Studies*** are all other investigations, such as investigations with humans that are not
93 clinical trials as defined above (e.g., observational epidemiologic studies), animal
94 studies,¹³ and laboratory experiments.
95

96 Before requiring a postmarketing study, FDA must find that adverse event reporting under
97 section 505(k)(1) of the FD&C Act and the active postmarketing risk identification and analysis
98 system as available under section 505(k)(3) of the FD&C Act will not be sufficient to meet the
99 purposes described above.¹⁴ Similarly, before requiring a postmarketing clinical trial, FDA must
100 find that a postmarketing study or studies will not be sufficient to achieve these same purposes.¹⁵
101

102 In order to ensure that a study or clinical trial is well designed and adequate to address the
103 serious risk, FDA describes the study or clinical trial to be conducted, including the study
104 population and indication.
105

106 In general, the purposes of a PMR under section 505(o)(3) are related to serious risks. The term
107 *serious risk* is defined for purposes of section 505(o) as a risk of a ***serious adverse drug***
108 ***experience***. This description does not mean that such postmarketing studies and clinical trials
109 are limited to safety endpoints. Rather, in some cases, a postmarketing study or clinical trial
110 with efficacy endpoints may be appropriate, for example, to further assess whether a potential
111 lack of expected pharmacological effect, including reduced effectiveness, may result in a serious
112 adverse drug experience.¹⁶
113

B. Applicants Are Required to Report on the Status of Studies and Clinical Trials

114

115

116

117 Under section 506B of the FD&C Act and 21 CFR 314.81(b)(2)(vii) and 601.70, applicants are
118 required to report annually on the status of certain PMRs and PMCs, including PMRs required
119 under section 505(o)(3) of the FD&C Act. Under sections 506B(c), FDA is required to track
120 these PMRs and PMCs and report on them annually in the *Federal Register*.¹⁷

¹³ We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

¹⁴ See section 505(o)(3)(D)(i) of the FD&C Act.

¹⁵ See section 505(o)(3)(D)(ii) of the FD&C Act.

¹⁶ See sections 505(o)(2)(C) and 505-1(b)(5) of the FD&C Act.

¹⁷ See the Postmarketing Requirements and Commitments web page at <https://www.fda.gov/drugs/postmarket-requirements-and-commitments/postmarketing-requirements-and-commitments-reports>.

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121
122 Section 505(o)(3)(E)(ii) of the FD&C Act further delineates information that is required for
123 PMRs that are issued under section 505(o)(3). This information must include the following:
124

- 125 • A timetable for completion

126
127 A set of milestone dates¹⁸ by which FDA measures progress of studies and clinical trials and
128 compliance with requirements. These goal dates generally include, but are not limited to,
129 final protocol submission date, study or clinical trial completion date, and final report
130 submission date. Section 505(o)(3) of the FD&C Act does not include provisions allowing
131 amendments to change milestone dates for purposes of required reporting.¹⁹ Therefore,
132 status reporting under these regulations will remain based on the *original* schedule.
133

- 134 • Periodic reports on the status of the study, including whether any difficulties in
135 completing the study have been encountered
- 136 • Periodic reports on the status of the clinical trial, including the following:
 - 137 – Whether enrollment has begun
 - 138 – The number of participants enrolled
 - 139 – The expected completion date
 - 140 – Whether any difficulties completing the clinical trial have been encountered
 - 141 – Registration information with respect to the clinical trial under section 402(j) of the
142 PHS Act (42 U.S.C. 282(j)).²⁰
 - 143
 - 144
 - 145
 - 146
 - 147
 - 148
 - 149

150 In addition, section 505(o)(3)(E)(ii) of the FD&C Act requires that applicants submit a report on
151 each study and clinical trial “otherwise undertaken by the responsible person to investigate a
152 safety issue,” including postmarketing studies or clinical trials that are neither required by FDA
153 nor agreed upon between FDA and the applicant. The studies and clinical trials may include
154 investigations initiated by an applicant for many reasons without prior discussion with or

¹⁸ For purposes of this guidance, milestone dates are a series of goal dates (e.g., final protocol submission, study or clinical trial completion date, final report submission) by which FDA measures progress of studies and clinical trials and compliance with requirements.

¹⁹ 21 CFR 314.81(b)(2)(vii)(a)(8)(ii-iii) and 21 CFR 601.70(b)(8)(ii-iii).

²⁰ Section 402(j) requires that certain clinical trial information, including information regarding results of clinical trials, be submitted to the clinical trials data bank (<https://www.ClinicalTrials.gov>). Registration information for clinical trials required under section 505(o)(3) should include documentation that the PMR is registered in accordance with Title VIII of FDAAA. See the guidance for sponsors, industry, researchers, investigators, and FDA staff *Form FDA 3674 — Certifications to Accompany Drug, Biological Product, and Device Applications/Submissions* (June 2017).

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155 notification to FDA. These studies and clinical trials may be summarized in a section of the
156 annual report (drugs) or annual status report (biologics).

157
158 **III. IMPLEMENTATION OF POSTMARKETING STUDY AND CLINICAL TRIAL**
159 **REQUIREMENTS UNDER SECTION 505(o)(3) OF THE FD&C ACT²¹**
160

161 As discussed in section II.A, FDA May Require Postmarketing Safety Studies and Clinical
162 Trials, FDA can require postmarketing studies and clinical trials for the following purposes: to
163 assess a known serious risk or signals of serious risk related to the use of the drug, or to identify
164 an unexpected serious risk of a drug when available data indicate the potential for a serious risk.
165 This determination will be based on scientific data deemed appropriate by FDA, including
166 information regarding chemically related or pharmacologically related drug use.

167
168 Before requiring a postmarketing study or clinical trial under section 505(o)(3), FDA must find
169 that the adverse event reporting under section 505(k)(1) of the FD&C Act and the analysis
170 system under section 505(k)(3) of the FD&C Act (active risk identification and analysis (ARIA))
171 will not be sufficient to meet the aforementioned purposes. Further, before requiring a
172 postmarketing clinical trial, FDA must find that a postmarketing study or studies will not be
173 sufficient to meet those purposes.

174
175 FDA's determination of whether the information available under subsections (k)(1) and (k)(3) is
176 sufficient is based on analysis of multiple factors, including the following: the nature of the
177 serious risk, the appropriate type of investigation to assess or identify the particular serious
178 risk(s), the strengths and limitations of electronic health data and adverse event report data to
179 assess the specific serious risk, the scientific tools available to evaluate this data, and the extent
180 to which the available data informs the serious risk.

181
182 Certain types of questions related to serious risk may only be answerable through specific types
183 of studies or clinical trials, and the information available under subsections (k)(1) and (k)(3)
184 would generally be considered insufficient to address those questions. For example, animal
185 studies or clinical pharmacokinetic and pharmacodynamic trials may be the only means of
186 determining whether a drug is carcinogenic or has the potential for interaction with other drugs,
187 respectively.

188
189 **A. Determining Whether Reports Under Section 505(k)(1) Are Sufficient**
190

191 *1. Postmarketing Adverse Event Reports and the FDA's Adverse Event Reporting*
192 *Systems*
193

²¹ Applicants conducting postmarketing studies and clinical trials must continue to comply with 21 CFR parts 312 and 58 when applicable and Health and Human Services (HHS) and FDA human subject protection regulations at 45 CFR part 46 and 21 CFR parts 50 and 56 when applicable.

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194 Section 505(k)(1) of the FD&C Act describes data that the applicant must report to FDA relating
195 to clinical experience and other data or information associated with drugs.²² The regulations
196 implementing section 505(k)(1) include, among other things, a requirement for applicants to
197 submit adverse event information, electronically, to FDA. The FDA Adverse Event Reporting
198 System (FAERS) and Vaccine Adverse Event Reporting System (VAERS) databases²³ contain
199 individual case safety reports (ICSRs) that applicants submit based on information provided by
200 consumers, patients, and health care providers. These systems also contain ICSRs submitted
201 directly to FDA by these reporters and ICSRs of adverse events reported in scientific literature
202 and postmarketing studies. FAERS and VAERS data include reports of medication errors
203 or drug quality problems when these are associated with adverse events.

204
205 2. *FDA Considerations in Determining Whether FAERS and VAERS Are Sufficient*
206 *for the Purposes Under Section 505(o)(3)(B) of the FD&C Act in a Specific*
207 *Circumstance*
208

209 The determination of the FAERS's and VAERS's sufficiency to meet the purposes described in
210 section 505(o)(3)(B) of the FD&C Act is based, in the context of the serious risk related to the
211 use of the particular drug, on considerations of the strengths and limitations of adverse event
212 reports as information sources and on the particular data characteristics of the FAERS and
213 VAERS systems. Therefore, FDA determines the FAERS's and VAERS's sufficiency for the
214 purposes of whether to require a postmarketing study or clinical trial on a case-by-case basis for
215 each serious risk.

216
217 Adverse event reports may be sufficient for identifying and assessing new (e.g., unexpected,
218 unlabeled), serious adverse drug events that occur rarely and are closely linked in time to
219 initiation of the drug and for which the background rate of events is low. Examples include
220 Stevens-Johnson syndrome and toxic epidermal necrolysis.

221
222 Limitations of adverse event report data include the following:
223

- 224 • Cannot be used to calculate the actual incidence rate of an adverse event, including the
225 incidence with a particular drug or to conduct comparisons between drugs on the rate of
226 occurrence of an adverse event based on the total number of people exposed to the drug
227 who experienced an adverse event (numerator) and the total number of people exposed to
228 the drug (denominator). For example:
229
 - 230 – There is no certainty that a reported adverse event is due to the drug because FDA
231 does not require a causal relationship between the drug and event be proven as part of
232 the reporting requirements

²² The requirements for postmarketing adverse event reporting are described in 21 CFR 310.305, 314.80, 314.81, 314.98, and 600.80.

²³ The regulations implementing section 505(k)(1) of the FD&C Act also refer to periodic adverse drug experience reports for approved drugs. Periodic safety reports summarize postmarket safety experience with a drug during a defined period of time and largely comprise listings and summary analyses of the adverse event reports submitted to the FAERS and VAERS. Consequently, FDA's determination of the sufficiency of the FAERS and VAERS encompasses the information that would generally be included in periodic safety reports.

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- 233
234 — Lack of adequate detail on adverse events reported to FDA
235
236 — Underreporting of adverse events to FDA
237
238 — Stimulated reporting of adverse events (e.g., after significant publicity of a potential
239 drug risk)
240
241 — The FAERS and VAERS databases do not collect information about the total number
242 of people exposed to the drug
243
244 • Frequently have incomplete or missing information that affects the following:
245
246 — Assessment of potentially relevant risk factors and confounders necessary to
247 determine whether a causal relationship exists between a drug and an adverse event
248
249 — Identification of patient subpopulations (e.g., elderly patients, patients with specific
250 comorbidities) and evaluation of potential differential risk of the adverse event
251
252 — Evaluation of potential drug interactions
253

B. Determining Whether the Active Postmarket Risk Identification and Analysis System Available Under Section 505(k)(3) Is Sufficient

1. The Sentinel System and the Active Postmarket Risk Identification and Analysis System

254
255
256
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259
260 FDA established the Sentinel System (Sentinel), a comprehensive active surveillance system, to
261 complement FDA’s existing postmarket capabilities and to monitor the safety of approved drugs
262 using large sets of electronic health care data.²⁴ Sentinel’s analytic capabilities are broad and
263 range from simple, rapid queries (e.g., counts of exposures) to sophisticated traditional
264 pharmacoepidemiologic studies that include medical record validation.
265

266 Within Sentinel, the ARIA system comprises predefined, parameterized, reusable routine
267 querying tools combined with the electronic data in the Sentinel Common Data Model.^{25, 26}

²⁴ See the FDA’s Sentinel Initiative Background web page at <https://www.fda.gov/safety/fdas-sentinel-initiative/fdas-sentinel-initiative-background>.

²⁵ Information about the ARIA analytic tools is available on the FDA’s Sentinel web page at <https://www.sentinelinitiative.org/active-risk-identification-and-analysis-aria>.

²⁶ The Sentinel Common Data Model is the standardized data structure employed by all the Sentinel participants (Data Partners). The Data Partners transform the data in their local existing environments according to the Common Data Model, which enables them to execute standardized computer programs that run identically at each Data Partner site. Information about the Common Data Model is available at <https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model>.

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268 FDA considers the ARIA system to be the “active postmarket risk identification and analysis
269 system” for the purposes of section 505(k)(3) of the FD&C Act.

270

271 *2. FDA Considerations in Determining Whether the ARIA System Is Sufficient*

272

273 The determination of the ARIA system’s sufficiency to meet the purposes described in section
274 505(o)(3)(B) of the FD&C Act, is based on an assessment of the capabilities of the system (i.e., a
275 combination of the electronic health care data available in the Sentinel Common Data Model and
276 analytic methods) that exist at the time of the sufficiency assessment. This determination is
277 made on a case-by-case basis and takes into consideration multiple factors, some of which may
278 be uncertain at the time of the sufficiency assessment (e.g., the future uptake of a newly
279 approved drug, subsequent exposure of patients to a drug).

280

281 a. ARIA data characteristics needed to assess or identify a serious risk

282

283 With respect to the electronic health care data characteristics, FDA considers the following when
284 determining the sufficiency of the ARIA system in a particular case:

285

- 286 • Is it possible to identify exposure to the drug within the available data?
- 287
- 288 • Is a validated or sufficiently defined health outcome of interest identifiable within the
289 available data?
- 290
- 291 • Are sufficient data available in the ARIA system on important confounders, and to what
292 extent might these confounders influence the outcome of the study?
- 293
- 294 • Is the population (i.e., cohort) of interest identifiable within the available data?
- 295
- 296 • Can an appropriate reference population be identified within the available data to make
297 risk-based comparisons?
- 298
- 299 • Is there sufficient statistical power to assess the questions of interest?
- 300
- 301 • Is there sufficient patient follow-up time (i.e., duration of observation time after medical
302 product exposure) in the ARIA system to inform the question of interest?
- 303

304

304 b. ARIA analytic capabilities needed to assess or identify a serious risk

305

306 FDA considers the following with respect to the analysis tools when determining the sufficiency
307 of the ARIA system for the purposes under section 505(o)(3)(B):

308

- 309 • Are the analysis tools currently available through the ARIA system adequate for
310 assessing the serious risk?

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312 3. *Other Considerations About the Sufficiency of ARIA*

313
314 Another important consideration is whether electronic health care data systems available to FDA
315 have the capacity to manage the FDA's need for multiple, concurrent, and relatively rapid ARIA
316 queries. The number of proposed analyses may exceed ARIA's capacity. If this will occur,
317 FDA may consider requiring a postmarketing study.

318
319 If, after the original determination of sufficiency, FDA determines the ARIA system's analytic
320 methods and/or Sentinel's data are insufficient to meet the purposes in section 505(o)(3)(B) of
321 the FD&C Act, FDA may require a postmarketing study or clinical trial.

322 4. *FDA Conduct of ARIA-Based Analyses of Similar Safety Concerns to Those* 323 *Evaluated Under a PMR*

324
325
326 Even after requiring that an applicant conduct a postmarketing study or clinical trial for a
327 particular purpose, FDA may also perform ARIA analyses as part of its pharmacovigilance
328 activities for a drug to further evaluate the drug's safety. That is, even if the FDA considers the
329 ARIA system insufficient to adequately address a specific serious risk (based upon the
330 considerations above) and a PMR is issued, the ARIA system may still play a role in
331 understanding a broader or related aspect of the issue.

332
333 For example, evaluation of a specific safety concern may need to be assessed within both the
334 intended general population and a subpopulation. FDA may require an applicant to conduct a
335 postmarketing study or clinical trial to assess a serious risk in a specific subpopulation that
336 cannot be identified in ARIA and FDA may perform its own assessment of the same safety
337 concern in the general population using the ARIA system. In this example, FDA would issue a
338 PMR focusing on the specific subpopulation but would not issue a PMR for the related
339 assessment of the safety concern in the general population. The combination of the information
340 obtained from the postmarketing study or clinical trial performed by the applicant with the
341 information FDA obtains from its own assessment within ARIA would provide a more
342 comprehensive understanding of the serious risk at issue.

343 5. *FDA Conduct of Sentinel-Based Studies When a PMR Has Not Been Required*

344
345
346 FDA may use analyses to study the safety of a drug using the Sentinel system when a PMR is not
347 required. These studies may be useful to gather additional safety information or clarify
348 observations that were made at the time of approval. FDA studies using Sentinel may also help
349 identify and/or assess safety outcomes when drugs are used more broadly than was studied
350 during drug development.

351 6. *Applicant Conduct of Analyses Using Other Electronic Health Care Systems*

352
353
354 An FDA determination, with regard to a particular drug, that the ARIA system is insufficient to
355 meet the purposes under section 505(o)(3)(B) of the FD&C Act does not necessarily represent
356 the following conclusions:

357

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- 358 • That analyses using any type of administrative claims or electronic health care database
359 will be insufficient to evaluate the serious risk.
360
- 361 – The characteristics of, and the data contained within, electronic health care databases
362 differ, as do available analytic methods.
363
- 364 – FDA may determine that an applicant could conduct a postmarketing study utilizing
365 data from other electronic health care systems and require a PMR.
366
- 367 • That the administrative claims and health care databases that comprise the ARIA system
368 are insufficient as an information source. Safety evaluations that use non-ARIA analytic
369 methods to analyze those databases may be appropriate. In those cases, FDA may
370 determine that an applicant could conduct a postmarketing study using these other
371 databases and require a PMR.
372

373 In summary, to obtain more information about a known serious risk, a signal of a serious risk, or
374 an unexpected serious risk associated with the use of a drug, FDA can require applicants to
375 conduct (1) a postmarketing study or studies after the Agency has determined that neither
376 adverse event report data nor the ARIA system will be sufficient for such purpose, or (2) a
377 postmarketing clinical trial or trials after it has determined that a postmarketing study or studies
378 will not be sufficient for such purpose.
379

C. Examples of Postmarketing Requirements Under Section 505(o) of the FD&C Act

383 This section describes examples of postmarketing studies and clinical trials that FDA will
384 generally consider requiring under section 505(o)(3) of the FD&C Act.
385

386 Examples of postmarketing *studies* include the following:
387

- 388 • Safety studies in animals investigating specific end-organ toxicities
389

390 These studies include, but are not limited to, carcinogenicity and reproductive toxicity
391 studies. Although in most instances applicants complete these studies before marketing
392 approval, the studies could be conducted postapproval for certain drugs—for example,
393 drugs intended to treat serious and life-threatening diseases.²⁷ If conducted postapproval,
394 these studies would be required under 505(o) of the FD&C Act. Examples include
395 studies designed to do the following:
396

- 397 – Assess carcinogenic potential in appropriate species (e.g., mice and rats)
398
- 399 – Assess the potential for reproductive toxicology in appropriate species (e.g., monkeys
400 or rabbits)
401

²⁷ See the ICH guidance for industry *S1A The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals* (March 1996).

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- 402 • In vitro laboratory safety studies designed to do the following:
403
404 – Assess certain receptor affinities for any circulating or major metabolites, including
405 conjugates, to evaluate the potential for off-target binding and resulting serious risk
406
407 – Determine whether resistance to a drug has developed in those organisms specific to
408 the labeled indication, resulting in increased serious risk
409
410 – Define the mechanism of drug resistance for certain organisms
411
412 – Assess the risk of cross contamination between drugs that could result from sharing
413 drug-contacting equipment and parts
414
415 – Validate the accuracy, precision, sensitivity, specificity, and robustness of an
416 immunogenicity assay for a drug to assess an immunologic safety concern
417
- 418 • Observational pharmacoepidemiologic studies
419
- 420 Such studies are generally designed to assess a serious risk associated with a drug
421 exposure or quantify risk or evaluate factors that affect this risk (e.g., drug dose, timing of
422 exposure, patient characteristics). Data sources for observational studies could include
423 administrative health care claims data, electronic medical records, registries,
424 prospectively collected observational data, or other sources of observational information.
425
- 426 Applicants should consider the following when designing pharmacoepidemiologic
427 studies.²⁸
428
- 429 – To facilitate interpretation of the findings, the studies should always have protocols
430 (including a statistical analysis plan), should include control groups, and should test
431 prespecified hypotheses. A control group may be omitted when there is a
432 scientifically valid reason.
433
- 434 – For a solely descriptive study, instead of one with a prespecified hypothesis, the
435 protocol may include clearly stated objectives for describing the safety issue,
436 including a defined upper bound for detectable risk, if applicable.
437
- 438 Registries²⁹ are a type of prospective pharmacoepidemiologic study. Applicants should
439 consider the following points in the use of registry studies:
440

²⁸ See also the guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data*. (May 2013).

²⁹ Registries established with the primary purpose of enrolling patients to mitigate a serious risk associated with a drug would be required as part of a REMS under section 505-1(f)(3)(F). When part of a REMS, they are an element necessary for the safe use of the drug and are not designed as a study with completion dates. These types of registries would not be required as PMRs and are not described further in this guidance.

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441 – FDA may approve a drug with a requirement for a registry that would collect data for
442 a study required as a PMR (under section 505(o)(3) of the FD&C Act). When a
443 pharmacoepidemiologic study using registry data meets the statutory criteria for a
444 PMR described in section III., Implementation of Postmarketing Study and Clinical
445 Trial Requirements Under Section 505(o)(3) of the FD&C Act, FDA intends to
446 require the registry and the study as a PMR.

447
448 – A sponsor can voluntarily create a registry to serve as a repository for clinical data,
449 such as an outcomes registry, that is not part of a PMR issued under section 505(o)(3)
450 of the FD&C Act. However, if FDA becomes aware of new safety information in the
451 postapproval setting, FDA could require the sponsor to conduct a PMR study, which
452 may utilize the registry data.

453
454 Other examples of required observational pharmacoepidemiologic studies include, but are
455 not necessarily limited to, studies designed to do the following:

456
457 – Provide estimates of absolute risk (e.g., incidence rates) for a serious adverse event or
458 toxicity or provide estimates of relative risk

459
460 – Obtain long-term clinical outcome data, including information about potentially rare
461 serious adverse events, in patients exposed to the drug compared to patients not
462 exposed to the drug

463
464 – Identify risk factors (e.g., patient characteristics, duration of drug use) associated with
465 the occurrence of adverse events among patients exposed to specified drugs

466
467 – Compare pregnancy incidence, pregnancy outcomes, and/or child outcomes for
468 patients exposed to the drug compared to patients not exposed to the drug

469
470 • Meta-analyses

471
472 Meta-analyses³⁰ are studies that can be designed to evaluate a safety endpoint by
473 statistical analysis of data from completed studies or clinical trials. A meta-analysis
474 should use a prospectively designed study protocol and analysis plan with a
475 comprehensive selection of relevant studies or clinical trials and appropriate statistical
476 methodology. An example of a required meta-analysis is one designed to:

477
478 – Evaluate the occurrence of all-cause mortality, cardiovascular death, and cancer
479 incidence and identify potential predictive factors in patients treated with the drug
480 compared to control therapies in all completed randomized clinical trials that include
481 the drug

482

³⁰ See the draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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483 Postmarketing *clinical trials* required under section 505(o)(3) of the FD&C Act to assess or
484 identify a serious risk typically have a safety endpoint evaluated with prespecified assessments
485 and are adequately powered to analyze the serious risk identified by FDA. In some cases, when
486 a serious risk relates to failure of expected pharmacological action, including reduced
487 effectiveness, the trial might be designed with an efficacy endpoint, for example, to further
488 assess whether a potential failure of expected pharmacological action, including reduced
489 effectiveness, may result in a serious adverse drug experience.

490

491 Examples of clinical trials designed with safety endpoints include trials intended to:

492

493 – Evaluate, in a controlled clinical trial, the occurrence of asthma exacerbations
494 associated with potential serious adverse effects of the irritative component of an
495 inhalation treatment for asthma

496

497 – Determine the incidence of myocardial infarction in patients treated with the
498 approved drug in a follow-on clinical trial after approval, using the original
499 randomized population

500

501 – Evaluate differences in safety outcomes between patients who are randomized after a
502 defined period of treatment to either placebo or continued treatment (randomized
503 withdrawal trial)

504

505 – Evaluate the potential for QT interval prolongation in a thorough QT clinical trial

506

507 – Measure growth and neurocognitive function in pediatric patients treated chronically
508 with the drug³¹

509

510 – Evaluate safety in a particular racial or ethnic group or vulnerable population such as
511 the immunocompromised³¹

512

513 – Evaluate the safety of the drug in pregnant women³¹

514

515 – Evaluate drug toxicity in patients with hepatic or renal impairment³¹

516

517 – Evaluate long-term safety of cell and gene therapy products depending on the type of
518 vector used and the inherent risk of integration

519

520 – Evaluate the safety of a drug in patients with HIV-1 coinfecting with hepatitis C or B³¹

521

522 Examples of clinical trials intended to further assess or identify a serious risk related to failure of
523 expected pharmacological action, including reduced effectiveness, could be designed to do the
524 following:

525

³¹ Patients are treated with the drug at a dose and schedule specified in the clinical trial protocol.

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- 526 – Determine whether extending the treatment duration of an antiviral drug, which is
527 indicated to treat a serious viral infection, mitigates the risk for relapse after
528 completing the course of treatment
- 529
- 530 – Evaluate a newly identified potential drug-drug interaction that may reduce the
531 systemic exposure of a drug approved to reduce the risk of cardiovascular events
532
- 533 – Evaluate a newly identified antidrug antibody response to a biological drug product
534 approved to treat a serious disease, when information suggests that the antibody may
535 reduce the drug’s effectiveness either by altering its pharmacokinetics or by binding
536 to domains of the drug critical to its functional activity
537
- 538 – Evaluate a new signal that a subgroup of patients (e.g., defined by age, sex, race,
539 biomarker) with a life-threatening cancer may not respond to a drug that had been
540 approved based on a clinically meaningful effect in the overall population with the
541 cancer, such that certain patients may be exposed to toxicity with less prospect for
542 benefit
543

544 The following describe examples of evaluations designed for the purposes under section
545 505(o)(3) of the FD&C Act that could be required as either a postmarketing study or clinical
546 trial, depending on the type of information and/or data necessary to assess the risk being
547 addressed by the PMR:
548

- 549 • PMRs designed to evaluate the pharmacokinetics of the drug in the labeled population or
550 in a subpopulation at potential risk for high drug exposures that could lead to toxicity.
551 These could include studies or clinical trials designed to do the following:
552
- 553 – Determine the optimal dose for maintenance therapy in patients with chronic renal
554 disease, a population at risk for drug accumulation
555
- 556 – Study the pharmacokinetic profile in a rodent model of hepatic dysfunction to
557 evaluate the potential for toxicity in patients with liver impairment
558
- 559 • PMRs designed to evaluate drug interactions or bioavailability when scientific data
560 indicate the potential for a serious safety risk. These could include studies or clinical
561 trials to do the following:
562
- 563 – Assess in vitro whether drugs are p-glycoprotein substrates and therefore could lead
564 to increased drug concentrations and toxicity
565
- 566 – Assess potential interactions of an approved drug with a frequently concomitantly
567 prescribed medication
568
- 569 – Evaluate whether multiple doses of an approved drug alter the metabolism of a
570 sensitive cytochrome P450 2C9 substrate
571

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572 – Evaluate bioavailability of an oral drug in the presence of food

573

D. Examples of Postmarketing Commitments

574

575
576 In general, the following types of studies or clinical trials can be considered for agreed-upon
577 PMCs:

578

579 • Drug and biologic product quality studies, including manufacturing, stability, and
580 immunogenicity studies that do not have a primary safety endpoint, such as studies
581 designed to do the following:

582

583 – Develop an optical rotation test, collect data on commercial batches, and use the data
584 to update drug substance specification standards

585

586 – Evaluate immune response to concomitant vaccination or vaccinations that are a part
587 of routine U.S. immunization practice

588

589 • Pharmacoepidemiologic studies designed to examine the natural history of a disease or to
590 estimate background rates for adverse events in a population not treated with the drug
591 that is the subject of the marketing application

592

593 • Studies and clinical trials conducted with vaccines, such as surveillance and observational
594 pharmacoepidemiologic studies when data do not suggest a serious risk or signals of
595 serious risk related to the use of the vaccine and when available data do not indicate the
596 potential for serious risk, such as the following:

597

598 – A surveillance study of cases of the infectious disease targeted by the approved
599 vaccine occurring in vaccinated populations using product-specific surveys and
600 calculating product-specific rates of infectious disease within the monitored
601 population

602

603 – A clinical trial conducted with vaccines in which the objective is a further
604 characterization of the safety profile and the primary endpoint is not related to a
605 serious risk identified by FDA under section 505(o) of the FD&C Act

606

607

IV. BENEFIT-RISK ASSESSMENT

608

609
610 The intent of a PMR is to achieve a better understanding and more fully characterize a serious
611 risk, if one exists. FDA will review the data and/or information obtained under a PMR and
612 assess its effect on the benefit-risk profile of the drug in the context of the serious risk being
613 evaluated. This may result, for example, in labeling changes under section 505(o)(4) of the
614 FD&C Act.

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617 **V. PROCEDURES**

618

619 The following general PMR and PMC procedures apply to PMRs issued under section 505(o)(3)
620 of the FD&C Act.

621

622 For new marketing applications, FDA plans to inform the applicant of the planned target date for
623 communication of feedback from the review division regarding PMRs and PMCs in the filing
624 communication letter.³²

625

626 In both the pre- and postapproval settings, FDA plans to communicate a list of potential PMRs
627 and PMCs, clearly delineated as to which are required and which may be agreed upon, to the
628 applicant along with a brief rationale for why FDA thinks these studies and clinical trials are
629 appropriate. The list should also include a request for a proposed timetable for completion.

630

631 The applicant will have the opportunity to discuss the design and conduct of the PMRs and
632 PMCs, as well as the overall goal, with the FDA review team. The applicant should provide
633 prompt feedback and engage in discussion as needed with the FDA review team to facilitate
634 completion of clearly written and well-designed PMRs and PMCs. The applicant should also
635 provide a timetable for completion of the study or clinical trial for the PMRs and a schedule for
636 milestone submissions and final reports for PMCs. For PMRs and PMCs, the first milestone is
637 generally the “final protocol submission” date. FDA considers the term *final* to mean that the
638 applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and
639 the protocol has been revised as needed to meet the goal of the study or clinical trial. Thus, the
640 date for this milestone should be selected to allow for the discussion period needed to create a
641 well-designed study or clinical trial. As described in section II.B., Applicants Are Required to
642 Report on the Status of Studies and Clinical Trials, public status of PMRs and PMCs is based on
643 the original schedule, so appropriate and realistic dates should be proposed.

644

645 The FDA review team intends to (1) review the potential study or clinical trial designs to make
646 sure they will serve the purposes of the study or clinical trial and (2) assess whether the proposed
647 timetable will be realistic and will provide for timely completion of the study or clinical trial.

648

649 Section 505(o)(3) of the FD&C Act gives FDA the authority to require PMRs without prior
650 agreement from the applicant. For PMCs, the applicant should submit a written agreement to
651 conduct the PMCs. FDA intends to include the PMRs and PMCs and their milestones and dates
652 in the action letter issued at the completion of the application review. In the postapproval setting,
653 FDA intends to include the new PMRs and PMCs and their milestones and dates in the letter
654 establishing the PMRs and PMCs.

655

656

³² See CDER Manual of Policies and Procedures (MAPP) 6010.8 Rev. 1 *NDA*s and *BLA*s: *Communications to Applicants of Planned Review Timelines*. For this and other MAPPs, see the CDER MAPPs web page at: <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cder-manual-policies-procedures-mapp>.

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657 **VI. DISPUTE RESOLUTION**

658
659 The applicant may appeal a requirement to conduct a postmarketing study or clinical trial using
660 the usual dispute resolution procedures (see the guidance for industry and review staff *Formal*
661 *Dispute Resolution: Appeals Above the Division Level* (November 2017))³³ (see section
662 505(o)(3)(F) of the FD&C Act).

663

664

665 **VII. ENFORCEMENT OF REQUIREMENTS FOR POSTMARKETING STUDIES** 666 **AND CLINICAL TRIALS**

667

668 FDA has authority to enforce the section 505(o)(3)(E)(ii) requirements for postmarketing studies
669 and clinical trials.³⁴ An applicant's failure to comply with the timetable, periodic report
670 submissions, and other requirements of section 505(o)(3)(E)(ii) of the FD&C Act will be
671 considered a violation unless the applicant demonstrates good cause for the noncompliance.
672 Section 505(o)(3)(E)(ii) of the FD&C Act provides that FDA shall determine what constitutes
673 good cause. In addition, under section 505(p)(2) of the FD&C Act, failure to conduct a
674 postmarketing study or clinical trial required under section 506B of the FD&C Act and subparts
675 H and E (21 CFR 314.510 and 601.41) may result in enforcement action.

676

677 Enforcement action could include one or more of the following:

678

- 679 • Charges under section 505 of the FD&C Act. A responsible person³⁵ may not introduce
680 or deliver into interstate commerce the drug involved if the person is in violation of
681 section 505(o) (postmarketing study and clinical trial requirements) (see section
682 505(o)(1) of the FD&C Act) or 505(p)(2) (certain postmarketing studies).
- 683 • Misbranding charges. A drug is misbranded under section 502(z) of the FD&C Act (21
684 U.S.C. 332(z)) if the applicant for that drug violates postmarketing study or clinical trial
685 requirements, including those outlined in section II.B., Applicants Are Required to
686 Report on the Status of Studies and Clinical Trials.
- 687 • Civil monetary penalties. Under section 303(f)(4)(A) of the FD&C Act (21 U.S.C.
688 333(f)(4)(A)), an applicant that violates postmarketing study or clinical trial requirements
689 may be subject to civil monetary penalties of up to \$250,000 per violation, but no more
690 than \$1 million for all violations adjudicated in a single proceeding. These penalties
691 increase if the violation continues more than 30 days after FDA notifies the applicant of
692 the violation. The penalties double for the following 30-day period and continue to
693
694

³³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

³⁴ FDA has the authority to review records upon inspection of postmarketing studies and clinical trials, including underlying data and source documents (see section 505(k) of the FD&C Act).

³⁵ Defined at section 505(o)(2)(A) of the FD&C Act.

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695 double for subsequent 30-day periods, up to \$1 million per period and \$10 million for all
696 violations adjudicated in a single proceeding. In determining the amount of a civil
697 penalty, FDA will consider the applicant's efforts to correct the violation (see section
698 303(f)(4)(B) of the FD&C Act).
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GLOSSARY¹

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Adverse drug experience is any adverse event associated with the use of a drug in humans, whether or not considered drug related, including:

- (A) an adverse event occurring in the course of the use of the drug in professional practice;
- (B) an adverse event occurring from an overdose of the drug, whether accidental or intentional;
- (C) an adverse event occurring from abuse of the drug;
- (D) an adverse event occurring from withdrawal of the drug; and
- (E) any failure of expected pharmacological action of the drug, which may include reduced effectiveness under the conditions of use prescribed in the labeling of such drug, but which may not include reduced effectiveness that is in accordance with such labeling.

Clinical trials are any prospective investigations in which the applicant or investigator determines the method of assigning the drug or drugs or other interventions to one or more human subjects. Clinical trials are one type of clinical investigation, as defined at 21 CFR 312.3(b).

New safety information with respect to a drug, means information derived from a clinical trial, an adverse event report, a postapproval study (including a study under section 505(o)(3) of the FD&C Act), or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system under section 505(k) of the FD&C Act; or other scientific data deemed appropriate by FDA about—

- (A) a serious risk or unexpected serious risk associated with use of the drug that FDA has become aware of (that may be based on a new analysis of existing information) since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug; or
- (B) the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy.

¹ The definitions in this glossary are presented for purposes of this guidance only. The definitions of the following terms are adapted from section 505-1(b) of the FD&C Act (21 U.S.C. 355-1(b)): adverse drug experience, new safety information, serious adverse drug experience, serious risk, signal of a serious risk and unexpected serious risk. FDA considers these definitions to include safety information related to a class effect, not apparently limited to a single member of the class for structural, mechanistic, or other reasons.

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738 ***Serious adverse drug experience*** is an adverse drug experience that—

739

740 (A) results in—

741

(i) death;

742

(ii) an adverse drug experience that places the patient at immediate risk of death from the
743 adverse drug experience as it occurred (not including an adverse drug experience that
744 might have caused death had it occurred in a more severe form);

745

(iii) inpatient hospitalization or prolongation of existing hospitalization;

746

(iv) a persistent or significant incapacity or substantial disruption of the ability to conduct
747 normal life functions; or

748

(v) a congenital anomaly or birth defect; or

749

(B) based on appropriate medical judgment, may jeopardize the patient and may require a
751 medical or surgical intervention to prevent an outcome described under subparagraph (A).

752

753 ***Serious risk*** means a risk of a serious adverse drug experience.

754

755 ***Signal of a serious risk*** means information related to a serious adverse drug experience
756 associated with use of a drug and derived from —

757

(A) a clinical trial;

758

(B) adverse event reports;

759

(C) a postapproval study, including a study under section 505(o)(3) of the FD&C Act;

760

(D) peer-reviewed biomedical literature;

761

(E) data derived from the postmarket risk identification and analysis system under section
767 505(k)(4) of the FD&C Act;

768

(F) other scientific data deemed appropriate by the Secretary.

769

770
771 ***Studies*** are all other (not clinical trial) investigations, such as investigations with humans that are
772 not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies,
773 and laboratory experiments.

774

775 ***Unexpected serious risk*** means a serious adverse drug experience that is not listed in the labeling
776 of a drug or that may be symptomatically and pathophysiologically related to an adverse drug
777 experience identified in the labeling, but differs because of greater severity, specificity, or
778 prevalence.

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APPENDIX A: PMR AND PMC AUTHORITIES

Postmarketing Requirement (PMR) Authorities	Postmarketing Commitment (PMC) Authorities
<p>Pediatric Research under section 505B of the Federal Food, Drug, and Cosmetic Act (the FD&C Act):¹</p> <ul style="list-style-type: none">• 21 CFR 314.55(b) (drugs)• 21 CFR 601.27(b) (biologics)	<p>Agreed -upon postmarketing studies and clinical trials:</p> <ul style="list-style-type: none">• 21 CFR 312.85
<p>Accelerated approval regulations:²</p> <ul style="list-style-type: none">• 21 CFR 314.510, Subpart H (drugs)• 21 CFR 601.41, Subpart E (biologics)	
<p>Animal Rule:³</p> <ul style="list-style-type: none">• 21 CFR 314.610(b)(1), Subpart I (drugs)• 21CFR 601.91(b)(1), Subpart H (biologics)	
<p>Food and Drug Administration Amendments Act of 2007 (FDAAA), section 901.</p> <ul style="list-style-type: none">• Section 505(o)(3) of the FD&C Act	

783

¹ See the draft guidance for industry *How to Comply with the Pediatric Research Equity Act* (September 2005). When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

² See the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* (May 2014).

³ See the guidance for industry *Product Development Under the Animal Rule* (October 2015).