
Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children 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DRAFT GUIDANCE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)**

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Revision 1

Pediatric Drug Development: Regulatory Considerations — Complying With the Pediatric Research Equity Act and Qualifying for Pediatric Exclusivity Under the Best Pharmaceuticals for Children Act Guidance for Industry

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1 **Pediatric Drug Development: Regulatory Considerations —**
2 **Complying With the Pediatric Research Equity Act and**
3 **Qualifying for Pediatric Exclusivity Under the**
4 **Best Pharmaceuticals for Children Act**
5 **Guidance for Industry¹**
6
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8

9
10 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
11 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
12 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
13 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
14 for this guidance as listed on the title page.
15

16
17
18
19 **I. INTRODUCTION**
20

21 This guidance is intended to assist industry developing drug products² to comply with the
22 pediatric study requirements under the Pediatric Research Equity Act (PREA),³ and to describe
23 the process for qualifying for pediatric exclusivity and the protections that pediatric exclusivity
24 offers under the Best Pharmaceuticals for Children Act (BPCA).⁴ In 2010, the Biologics Price
25 Competition and Innovation Act of 2009 extended provisions of the BPCA to biological
26 products.⁵
27

¹ This guidance has been prepared by the Division of Pediatrics and Maternal Health 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 For the purposes of this guidance, unless otherwise specified, references to *drugs* or *drug products* include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service (PHS) Act (42 U.S.C. 262) that are regulated as drugs.

³ Public Law 108-155 (2003), codified at section 505B of the FD&C Act (21 U.S.C. 355c). Although section 505B has been amended since the passage of PREA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, PREA. We adopt that convention in this guidance.

⁴ Public Law 107-109 (2002), codified at section 505A of the FD&C Act (21 U.S.C. 355a). Although section 505A has been amended since the passage of the BPCA, by convention, that section of the FD&C Act is often referred to by the acronym for the Act that created it, the BPCA. We adopt that convention in this guidance.

⁵ See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

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28 Note that section 505B(b) of the Federal Food, Drug, and Cosmetic (FD&C) Act on already-
29 marketed drugs and section 409I of the Public Health Service (PHS) Act are only briefly
30 addressed in this guidance. Future guidance may address these issues in greater detail.
31 Furthermore, this guidance only briefly addresses the Food and Drug Administration
32 Reauthorization Act of 2017's (FDARA's) amendments to section 505B of the FD&C Act
33 relating to requirements that sponsors of certain adult oncology drugs with molecular targets that
34 are determined to be substantially relevant to the growth or progression of a pediatric cancer
35 submit reports on ***molecularly targeted pediatric cancer investigations***.^{6,7}

36
37 The scientific aspects of a pediatric program (e.g., considerations regarding data in pediatric
38 subjects, timing of pediatric studies) are addressed in the draft guidance for industry *Pediatric
39 Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for
40 Children Act: Scientific Considerations* (May 2023).⁸

41
42 This guidance, along with the draft guidance for industry *Pediatric Drug Development Under the
43 Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific
44 Considerations*,⁹ revises and replaces the draft guidance for industry *How to Comply With the
45 Pediatric Research Equity Act*.¹⁰ In addition to addressing the PREA topics covered in the
46 earlier draft guidance (i.e., the pediatric ***assessment***, pediatric plan, ***waivers*** and ***deferrals***,
47 compliance issues, and pediatric exclusivity provisions), this guidance addresses statutory
48 changes relating to adverse event reporting, ***pediatric study plans (PSPs)***, deferral extensions,
49 and noncompliance.

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

56
57

⁶ Certain terms used in this guidance, which appear in bold italics at first mention, are defined for purposes of this guidance in the Glossary.

⁷ For additional information on FDA's implementation of these amendments to section 505B of the FD&C Act, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act* (May 2021). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

⁸ 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>.

⁹ When final, this guidance will represent the FDA's current thinking on this topic.

¹⁰ This guidance also addresses certain topics previously addressed in the guidance for industry *Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act*. That guidance was withdrawn August 7, 2013 (78 FR 48175).

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58 **II. OVERVIEW OF REGULATORY STRATEGY FOR PEDIATRIC DRUG** 59 **DEVELOPMENT**

60 61 **A. General Approach**

62
63 For purposes of pediatric drug development, FDA generally considers the pediatric population to
64 include those patients from birth to younger than 17 years (i.e., birth through 16 years of age),
65 and to include the subpopulation age groups of neonates, infants, children, and adolescents.¹¹
66 Consistent with International Council for Harmonisation (ICH) guidelines,¹² FDA considers
67 these subpopulation age groups to be divided as follows:

- 68
- 69 • Neonates: birth through 27 days (corrected gestational age)
- 70 • Infants: 28 days to 23 months
- 71 • Children: 2 years to 11 years
- 72 • Adolescents: 12 years to younger than 17 years
- 73

74 The BPCA defines *pediatric studies* to mean at least one clinical investigation in “pediatric age
75 groups (including neonates in appropriate cases) in which a drug is anticipated to be used, and, at
76 the discretion of the Secretary, may include preclinical studies.”¹³ For purposes of satisfying the
77 requirements of PREA, assessments of safety and effectiveness must be performed in all relevant
78 pediatric age groups, unless the assessments are waived or deferred.¹⁴

79
80 The BPCA and PREA are designed to work together to encourage the development of data to
81 inform the safe and effective use of drugs in pediatric populations. Under PREA, pediatric
82 assessments are *required* for drug products with a new active ingredient, new indication, new
83 dosage form, new dosing regimen, or new route of administration unless the drug is for an
84 indication for which orphan designation has been granted.¹⁵ Also under PREA, molecularly
85 targeted pediatric cancer investigations are *required* for original new drug applications (NDAs)
86 or biologics license applications (BLAs) submitted on or after August 18, 2020, for a new active
87 ingredient, if the drug that is the subject of the application is intended for the treatment of an

¹¹ See 21 CFR 201.57(c)(9)(iv)(A) (“the terms *pediatric population(s)* and *pediatric patient(s)* are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents”). FDA interprets “birth to 16 years” in 21 CFR 201.57(c)(9)(iv)(A) to mean from birth to younger than 17 years old. See, for example, the guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling* (March 2019).

¹² For additional information, see the ICH guidances for industry *E11 Clinical Investigation of Medicinal Products in the Pediatric Population* (December 2000) and *E11(R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population* (April 2018).

¹³ See section 505A(a) of the FD&C Act (21 U.S.C. 355a(a)).

¹⁴ See sections 505B(a)(2)(A), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(2)(A), 21 U.S.C. 355c(a)(4), and 21 U.S.C. 355c(a)(5)).

¹⁵ See sections 505B(a)(1)(A) and 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)(A) and 21 U.S.C. 355c(k)(1)).

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88 adult cancer, and directed at a molecular target that FDA determines to be substantially relevant
89 to the growth or progression of a pediatric cancer.¹⁶ Studies conducted under the BPCA, on the
90 other hand, are *optional* because sponsors have the option of declining to undertake them in
91 response to a **written request** (WR). Nevertheless, it is critical that sponsors consider both laws
92 when planning their pediatric clinical development programs.
93

94 PREA requires that any application falling within the requirements of section 505B(a)(1) of the
95 FD&C Act for a new active ingredient, new indication, new dosage form, new dosing regimen,
96 or new route of administration must either include pediatric assessments or reports on the
97 molecularly targeted pediatric cancer investigation (as appropriate);¹⁷ or a request for waiver
98 and/or deferral of the pediatric assessments or reports on the molecularly targeted pediatric
99 cancer investigation.¹⁸ There are certain exceptions; for example, PREA requirements generally
100 do not apply to a drug for an indication for which orphan designation has been granted (see
101 section II.B.4., Orphan Products).¹⁹
102

103 The FD&C Act requires sponsors to submit an initial pediatric study plan (iPSP) during the
104 investigational phase of development, which helps to ensure that sponsors thoroughly consider a
105 pediatric clinical development program earlier in their overall clinical development program.²⁰
106 See sections III., Pediatric Research Equity Act, and V., Elements Common to PREA and the
107 BPCA, for additional information about PREA.
108

109 While addressing PREA, sponsors should also consider whether to seek a WR under the BPCA.
110 It is important to note that sponsors may qualify for pediatric exclusivity under the BPCA for
111 completed PREA studies when those studies are described in a WR,²¹ and the WR is issued by
112 FDA before the sponsor submits any reports about the studies described in the WR.²² If FDA
113 determines that “information relating to the use of a new drug in the pediatric population may
114 produce health benefits in that population” and issues a WR, a sponsor may qualify for 6 months
115 of exclusivity under the BPCA for conducting studies that are required under PREA.²³ However,
116 as discussed in Section IV. A. 2., Written Request Studies, FDA does not expect to issue WRs
117 solely for studies or planned studies that are required under PREA.

¹⁶ Section 505B(a)(1)(B) of the FD&C Act (21 U.S.C. 355c(a)(1)(B)).

¹⁷ For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

¹⁸ See sections 505B(a)(1), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(1), 21 U.S.C. 355c(a)(4), and 21 U.S.C. 355c(a)(5)).

¹⁹ See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(k)(1)). Under section 505B(k)(2) of the FD&C Act, this orphan exemption does not apply to products that trigger PREA under section 505B(a)(1)(B) of the FD&C Act.

²⁰ See section 505B(e) of the FD&C Act (21 U.S.C. 355c(e)).

²¹ See section 505A(h) of the FD&C Act (21 U.S.C. 355a(h)).

²² See section 505A(b)(1) of the FD&C Act (21 U.S.C. 355a(b)(1)).

²³ See section 505A(b)(1) of the FD&C Act (21 U.S.C. 355a(b)(1)).

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118
119 In addition, sponsors should consider other indications for development in the pediatric
120 population based on the current understanding of the effect of the drug (e.g., mechanism of
121 action), and include them as appropriate when seeking a WR. FDA reviews adult safety and
122 effectiveness data and, in some instances, information from postmarketing safety reports,
123 information regarding unapproved uses, and the scientific literature to identify a potential health
124 benefit in pediatric populations when contemplating a WR. This knowledge not only informs
125 FDA’s decision to issue a WR for a given indication, but also whether to include a request to
126 study additional indications in children beyond those already approved in adults. See sections
127 IV., Best Pharmaceuticals for Children Act, and V., Elements Common to PREA and the BPCA,
128 for more information about the BPCA.

B. Developing Drugs for Pediatric Use

131
132 During clinical development programs, a sponsor should consider whether the eventual
133 marketing application will trigger the requirements of PREA. FDA encourages sponsors to
134 interact with FDA early, including, when applicable, to discuss studies to meet PREA and other
135 requirements. See section III., Pediatric Research Equity Act, for information about the
136 requirements of PREA.

137
138 FDA has identified a number of scenarios and considerations that may affect a sponsor’s
139 approach to developing a drug product for use in pediatric patients. Some common ones are
140 described below.

1. Drugs for Life-Threatening or Severely Debilitating Conditions and Unmet Medical Needs

141
142
143
144
145 Early consultation and discussions are particularly important for drugs intended for life-
146 threatening or severely debilitating conditions.²⁴ For these drugs, FDA encourages sponsors to
147 discuss the pediatric plan at pre-investigational new drug application (pre-IND) and end-of-phase
148 1 meetings.²⁵ In some cases, pediatric studies of drugs for life-threatening or severely
149 debilitating conditions that lack adequate therapies might begin earlier than usual in the drug
150 development process. The need for new therapies might justify early trials despite the relative
151 lack of safety and effectiveness information in humans. Pediatric studies might be considered
152 appropriate when prospects of direct benefit to the enrolled children are sufficient to justify the
153 risks.²⁶

154

²⁴ See the guidance for industry *Expedited Programs for Serious Conditions — Drugs and Biologics* (May 2014) for more information.

²⁵ See section 505B(e)(2)(C)(i)(I) of the FD&C Act (21 U.S.C. 355c(e)(2)(C)(i)(I)).

²⁶ See 21 CFR 50.52.

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155 2. *Drugs for Diseases or Conditions That Occur Primarily in Pediatric Populations*

156
157 Sponsors developing drug products for diseases or conditions that primarily or substantially
158 occur in the pediatric population should discuss their plans with FDA as early as possible (e.g.,
159 pre-IND meeting). They should consider submitting an iPSP earlier than is required under
160 PREA because the initial clinical studies will likely include pediatric subjects (see section
161 III.B.1., Pediatric Study Plans).

162 163 3. *Neonates*

164
165 The complex medical state of neonates makes it critical to evaluate drugs specifically for their
166 use. However, FDA is aware that studies in neonates present special challenges, including the
167 short time period to conduct studies during the neonatal period (e.g., birth through 27 days
168 corrected gestational age), the differences in neonatal physiology that may affect dose and
169 endpoint selection, as well as ethical issues that may be age-specific. Under PREA, studies in
170 neonates may be required. However, it is possible that partial waivers for this and other specific
171 age groups might be appropriate under certain circumstances.²⁷

172
173 FDA encourages specific activities regarding neonates. Under PREA, if a sponsor does not plan
174 to study an investigational drug in neonates, the rationale and supporting data explaining why the
175 drug is not appropriate for use in this population should be included in the iPSP.²⁸ Under the
176 BPCA, similar rationale and supporting data explaining why the investigational drug is not
177 appropriate for use in this population should be included in the ***proposed pediatric study request***
178 ***(PPSR)*** if a sponsor does not plan to study the drug in neonates. When FDA issues a WR that
179 does not include studies in neonates, the WR must state the rationale for not including
180 neonates.²⁹ See sections IV.A.1., Description of the Written Request, and IV.B., How to Obtain
181 a Written Request, as well as the draft guidance for industry *Pediatric Drug Development Under*
182 *the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific*
183 *Considerations*³⁰ for more information regarding clinical studies in neonates.

184 185 4. *Orphan Products*

186
187 PREA requirements generally do not apply “to any drug or biological product for an indication
188 for which orphan designation has been granted;” however, this *orphan exemption* does not apply
189 to drugs that trigger the PREA requirement for submission of reports on the molecularly targeted

²⁷ See section 505B(a)(5)(B) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)).

²⁸ See section 505B(e)(2)(B) of the FD&C Act (21 U.S.C. 355c(e)(2)(B)) and the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).

²⁹ See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

³⁰ When final, this guidance will represent FDA’s current thinking on this topic.

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190 pediatric cancer investigation.³¹ Thus, PREA does not require submission of pediatric
191 assessments for an application (or supplemental application) to market a drug for an indication
192 for which orphan designation has been granted.³² As FDA has interpreted PREA, if orphan
193 designation is granted after approval of a drug, and postmarketing studies were required under
194 PREA at the time of the drug’s approval, the granting of orphan designation does not alter the
195 already existing requirement for such studies.³³ The PREA orphan exemption is not revisited to
196 retroactively abrogate a PREA requirement that was properly imposed before orphan designation
197 was granted. Additionally, if marketing approval is sought for multiple indications for a drug
198 product, some of which have not been granted orphan designation, the sponsor must submit
199 pediatric assessments for all indications that do not have an orphan designation, unless the
200 assessments are waived or deferred.³⁴ If the orphan-designated indication(s) involve the
201 pediatric population, we encourage sponsors to conduct studies in the relevant age group(s)
202 whenever appropriate.

203
204 Despite this orphan exemption under PREA, a sponsor that submits an application to market a
205 drug for an indication for which orphan designation has been granted may be eligible to qualify
206 for pediatric exclusivity if FDA issues a WR to the sponsor in connection with the application
207 and the sponsor accepts. Sponsors should contact FDA about the feasibility and timing of a WR
208 and about submitting a PPSR, if appropriate. For more information, see sections III.C.2.,
209 Submission of Pediatric Assessments or Reports on the Molecularly Targeted Pediatric Cancer
210 Investigation, IV.F.2., Biological Products, and V.B.1., Pediatric Exclusivity Determinations, as
211 well as FDA’s Office of Orphan Products Development web page on developing drug products
212 for rare diseases and conditions,³⁵ and the guidance for industry *Clarification of Orphan*
213 *Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases* (July
214 2018).
215

³¹ See sections 505B(a)(1)(B), 505B(a)(3), and 505B(k) of the FD&C Act (21 U.S.C. 355c(a)(1)(B), 21 U.S.C. 355c(a)(3), and 21 U.S.C. 355c(k)). Note that, although section 505B(k) authorizes FDA to issue regulations that would alter the orphan exemption, as of the date of publication of this guidance, FDA has not issued any such regulations.

³² See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(k)(1)). For products meeting the criteria in section 505B(a)(1)(B) of the FD&C Act, the requirement to submit reports on the investigation described in section 505B(a)(3) of the FD&C Act applies even if the drug is for an adult indication for which orphan designation has been granted. See section 505B(k)(2) of the FD&C Act (21 U.S.C. 355c(k)(2)). See also the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

³³ Because the orphan exemption in section 505B(k)(1) of the FD&C Act can affect whether PREA applies to a particular application or supplement submitted to the Agency for review, FDA evaluates whether the orphan exemption is applicable at the time it evaluates whether PREA would otherwise be triggered for any application or supplement under section 505B(a)(1)(A).

³⁴ See sections 505B(a)(1)(A), 505B(a)(4), 505B(a)(5), and 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)(A), 21 U.S.C. 355c(a)(4), 21 U.S.C. 355c(a)(5), and 21 U.S.C. 355c(k)(1)).

³⁵ See the Medical Products for Rare Diseases and Conditions web page at <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm>.

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216 5. *Drug Development in Foreign Countries*

217
218 Many sponsors conduct their entire clinical programs in other countries and occasionally submit
219 a marketing application with little, if any, prior interaction with FDA. All sponsors who seek to
220 market their drugs in the United States are strongly encouraged to contact FDA as early as
221 possible to avoid any delay in providing any required pediatric information in their applications.
222 Sponsors should include an agreed iPSP in any NDA, BLA, or supplement that is required by
223 PREA to include pediatric assessments or reports on the molecularly targeted pediatric cancer
224 investigation. PREA requirements are described in more detail in section III., Pediatric Research
225 Equity Act.

227 6. *Drugs for Diseases or Conditions That Only Occur in Adults*

228
229 Sponsors focusing on clinical development programs for drugs for diseases and conditions that
230 only occur in adults must submit an iPSP, assuming the application triggers PREA.³⁶ A list of
231 diseases and conditions that rarely or never occur in pediatrics can be found on FDA's website.³⁷
232 Generally, applications for drugs for such diseases or conditions that rarely or never occur in
233 pediatrics will qualify for a waiver because the necessary studies would be impossible or highly
234 impracticable.³⁸ However, sponsors should consider all potential pediatric indications for their
235 drugs. FDA may consider issuance of a WR for other indications that may have health benefits
236 in the pediatric population.

237 238 239 **III. PEDIATRIC RESEARCH EQUITY ACT**

241 **A. Overview — Requirements of PREA**

242 243 *1. PREA Applicability*

244
245 With limited exception (for example, the orphan exemption described in section II.B.4., Orphan
246 Products), PREA applies to the following:

- 247
248 • Applications (or supplements to an application) submitted under section 505 of the
249 FD&C Act or section 351 of the PHS Act for a new active ingredient, new indication,
250 new dosage form, new dosing regimen, or new route of administration, and

251

³⁶ See section 505B(e)(1) of the FD&C Act (21 U.S.C. 355c(e)(1)); see also section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)).

³⁷ See Adult-Related Conditions That Qualify for a Waiver Because They Rarely or Never Occur in Pediatrics, available at <https://www.fda.gov/media/101440/download>.

³⁸ See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)). FDA anticipates that there will be additional considerations for applications described in section 505B(a)(1)(B) of the FD&C Act that require submission of reports on the molecularly targeted pediatric cancer investigation described in section 505B(a)(3) of the FD&C Act. For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

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- 252 • Original applications for a new active ingredient submitted under section 505 of the
253 FD&C Act or section 351 of the PHS Act on or after August 18, 2020, if the drug that is
254 the subject of the application is intended for the treatment of an adult cancer and is
255 directed at a molecular target that FDA determines to be substantially relevant to the
256 growth or progression of a pediatric cancer.³⁹
257

258 PREA also authorizes FDA to require holders of already approved applications to conduct
259 pediatric assessments under certain circumstances.⁴⁰
260

2. Scope of Requirements — Generic drugs

263 Abbreviated new drug applications (ANDAs) submitted under section 505(j) of the FD&C Act
264 most often are applications for drugs containing the *same* active ingredient(s), strength(s),
265 indication(s), dosage form(s), dosing regimen(s), and route(s) of administration as the listed
266 drugs they reference and are not subject to PREA. ANDA applicants may petition the Agency to
267 request a change from a listed drug per section 505(j)(2)(C) of the FD&C Act and 21 CFR
268 314.93, a process referred to as a suitability petition. The regulation at 314.93 limits the types of
269 changes that may be permitted to changes in strength, dosage form, route of administration, or of
270 a single active ingredient in a combination drug subject to the restrictions identified in
271 314.93(d)(1) through (3). ANDAs submitted pursuant to an approved suitability petition for
272 changes in dosage form, route of administration, or for a change in active ingredient in a
273 combination drug do trigger PREA, but they are only eligible for submission as ANDAs if the
274 pediatric assessment or molecularly targeted pediatric cancer investigation requirements are
275 waived.⁴¹ If a change proposed in a suitability petition triggers PREA and FDA does not waive
276 the requirement to submit pediatric assessments or reports on the molecularly targeted pediatric
277 cancer investigation, the suitability petition will be denied, and the proposed drug product will
278 not be eligible for submission as an ANDA.⁴²
279

B. Development of Drugs for Pediatric Use

1. Pediatric Study Plans

284 A sponsor planning to submit a marketing application or supplement that is subject to PREA is
285 required to submit an iPSP before submission of pediatric assessments or reports on the
286 molecularly targeted pediatric cancer investigation.⁴³ A sponsor should submit an iPSP to its
287 investigational new drug application (IND) for review by the appropriate review division as early

³⁹ See section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)).

⁴⁰ See section 505B(b) of the FD&C Act (21 U.S.C. 355c(b)).

⁴¹ See section 505(j)(2)(C) of the FD&C Act (21 U.S.C. 355(j)(2)(C)) and section 505B(a)(1) of the FD&C Act (21 U.S.C. 355c(a)(1)).

⁴² See, for example, 21 CFR 314.93.

⁴³ See section 505B(e)(1) of the FD&C Act (21 U.S.C. 355c(e)(1)).

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288 as practicable and must submit it no later than 60 calendar days after the date of the end-of-phase
289 2 meeting or such other time as agreed upon between FDA and the applicant.⁴⁴ More
290 information on the timing and contents of iPSPs, the process for reaching agreement with FDA
291 on iPSPs, and the process for amending an agreed iPSP can be found in the guidance for industry
292 *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and*
293 *Amended Initial Pediatric Study Plans* (July 2020). Sponsors are also encouraged to consider the
294 possibility of submitting a PPSR to obtain a WR during the PSP process. An iPSP and a PPSR
295 are different documents and have different considerations for submission; the former is a
296 requirement for compliance with PREA and the latter may be submitted at a sponsor’s discretion
297 to seek a WR under the BPCA. See sections IV.A., Written Requests, and IV.B., How to Obtain
298 a Written Request, for further discussion about PPSRs and WRs.

2. Developing a Pediatric Formulation

301
302 Under PREA, sponsors are required to conduct pediatric studies “using appropriate formulations
303 for each age group” for which the assessment or investigation is required.⁴⁵ However, FDA may
304 grant a partial waiver if a sponsor is unable to develop an age-appropriate formulation after
305 reasonable attempts to do so.⁴⁶ (See discussion of waivers in section III.D., Waivers and
306 Deferrals Under PREA.) Under PREA, sponsors must submit “a request for approval of a
307 pediatric formulation” used in their pediatric studies, and if a sponsor fails to submit such a
308 request, the drug may be considered misbranded.⁴⁷ Accordingly, sponsors should submit an
309 application or supplemental application for any formulation(s) not previously approved that were
310 used during pediatric studies and for which the sponsor has data to assess the safety and
311 effectiveness and to support dosing and administration. To avoid delays in initiation of pediatric
312 clinical studies, sponsors should begin the development of an age-appropriate formulation as
313 early as possible.

C. Pediatric Assessments and Molecularly Targeted Pediatric Cancer Investigations Under PREA

1. Definitions

319
320 Pediatric assessments must contain data, gathered using appropriate formulations for each age
321 group for which the assessment is required and that are adequate to:

- 322 • Assess the safety and effectiveness of the drug for the claimed indications in all relevant
323 pediatric subpopulations; and
324
325

⁴⁴ See section 505B(e)(2)(A)(ii) of the FD&C Act (21 U.S.C. 355c(e)(2)(A)(ii)).

⁴⁵ See section 505B(a)(2)(A) and 505B(a)(3)(A) of the FD&C Act (21 U.S.C. 355c(a)(2)(A) and 355c(a)(3)(A)).

⁴⁶ See section 505B(a)(5)(B)(iv) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(iv)).

⁴⁷ See section 505B(d) of the FD&C Act (21 U.S.C. 355c(d)).

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- 326 • Support dosing and administration for each pediatric subpopulation for which the drug is
327 safe and effective.⁴⁸

328
329 A molecularly targeted pediatric cancer investigation “shall be designed to yield clinically
330 meaningful pediatric study data, gathered using appropriate formulations for each age group for
331 which the study is required, regarding dosing, safety, and preliminary efficacy to inform
332 potential pediatric labeling.”⁴⁹

333
334 2. *Submission of Pediatric Assessments or Reports on the Molecularly Targeted*
335 *Pediatric Cancer Investigation*

336
337 Sponsors must submit pediatric assessments or reports on the molecularly targeted pediatric
338 cancer investigation with any application for which such assessments or reports are required by
339 PREA, unless FDA defers and/or waives the requirement.⁵⁰ (For pediatric assessments, if the
340 drug is for an indication for which orphan designation has been granted, the requirements of
341 PREA do not apply.)⁵¹ See section III.D., Waivers and Deferrals Under PREA, for discussion of
342 waivers and deferrals. In general, sponsors should include pediatric studies at the time of
343 submission of an application when there is sufficient knowledge to proceed and it is feasible to
344 complete studies in children in parallel with adult studies.

345
346 Information about the results of pediatric assessments under PREA must be included in product
347 labeling whether findings are positive, negative, or inconclusive.⁵² Labeling changes for
348 approved products must be submitted in accordance with applicable requirements in 21 CFR
349 601.12 and 21 CFR 314.70. For more information about labeling, see section V.D.,
350 Considerations for Labeling of Drug Products, and the guidance for industry *Pediatric*
351 *Information Incorporated Into Human Prescription Drug and Biological Product Labeling*
352 (March 2019).

353
354 For information about the specific types of data that may be needed to complete a pediatric
355 assessment, refer to the draft guidance for industry *Pediatric Drug Development Under the*
356 *Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific*
357 *Considerations*.⁵³

358

⁴⁸ See section 505B(a)(2)(A) of the FD&C Act (21 U.S.C. 355c(a)(2)(A)).

⁴⁹ Section 505B(a)(3)(A) of the FD&C Act (21 U.S.C. 355c(a)(3)(A)).

⁵⁰ See sections 505B(a)(1), 505B(a)(4), and 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(1), 21 U.S.C. 355c(a)(4), and 21 U.S.C. 355c(a)(5)).

⁵¹ See section 505B(k)(1) of the FD&C Act (21 U.S.C. 355c(k)(1)).

⁵² See section 505B(g)(2) of the FD&C Act (21 U.S.C. 355c(g)(2)).

⁵³ When final, this guidance will represent FDA’s current thinking on this topic.

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359 **D. Waivers and Deferrals Under PREA**

360

361 ***I. Waivers***

362

363 PREA authorizes FDA to waive the requirement to submit pediatric assessments or reports on
364 the molecularly targeted pediatric cancer investigation, based on established criteria, for some or
365 all pediatric age groups.⁵⁴ FDA can grant a full or partial waiver of the requirements on its own
366 initiative or at the request of an applicant.⁵⁵ Any applicant requesting a waiver should provide
367 written justification for the waiver and evidence to support the request.

368

369 a. Criteria for full waiver

370

371 FDA will, as appropriate, grant a full waiver of the requirement to submit pediatric assessments
372 or reports on the molecularly targeted pediatric cancer investigation if the applicant *certifies* and
373 FDA finds one or more of the following criteria:

374

375 • Necessary studies are impossible or highly impracticable (because, for example, the
376 number of patients is so small or the patients are geographically dispersed).⁵⁶ For further
377 information, see Section II.B.6., Drugs for Diseases or Conditions That Only Occur in
378 Adults.

379

380 • There is evidence strongly suggesting that the drug would be ineffective or unsafe in all
381 pediatric age groups.⁵⁷

382

383 • The drug (1) does not represent a meaningful therapeutic benefit over existing therapies
384 for pediatric patients; and (2) is not likely to be used in a substantial number of pediatric
385 patients.⁵⁸

386

387 — Importantly, we note that *both* criteria must be met for this waiver justification to
388 apply. A drug is considered to represent a meaningful therapeutic benefit over
389 existing therapies if FDA determines that (1) “if approved, the drug or biological
390 product could represent an improvement in the treatment, diagnosis, or prevention of
391 a disease, compared with marketed products adequately labeled for that use in the
392 relevant pediatric population;” or (2) “the drug or biological product is in a class of
393 products or for an indication for which there is a need for additional options.”⁵⁹ FDA
394 anticipates that improvement over marketed drugs might be demonstrated by

⁵⁴ See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)).

⁵⁵ See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)).

⁵⁶ See section 505B(a)(5)(A)(i) of the FD&C Act (21 U.S.C. 355c(a)(5)(A)(i)).

⁵⁷ See section 505B(a)(5)(A)(ii) of the FD&C Act (21 U.S.C. 355c(a)(5)(A)(ii)).

⁵⁸ See section 505B(a)(5)(A)(iii) of the FD&C Act (21 U.S.C. 355c(a)(5)(A)(iii)).

⁵⁹ See section 505B(c) of the FD&C Act (21 U.S.C. 355c(c)).

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395 showing, for example (1) evidence of increased effectiveness in treatment,
396 prevention, or diagnosis of disease; (2) an improved safety profile; (3) enhancement
397 of compliance (e.g., by virtue of less frequent dosing or mode of delivery); or (4)
398 safety and effectiveness in a new subpopulation for which marketed drugs are not
399 currently labeled.

400
401 b. Criteria for partial waiver

402
403 FDA will, as appropriate, grant a partial waiver of the requirement to submit pediatric
404 assessments or reports on the molecularly targeted pediatric cancer investigation with respect to
405 a specific pediatric age group, if the applicant certifies and FDA finds one or more of the
406 following criteria:

- 407
408 • Necessary studies are impossible or highly impracticable (because, for example, the
409 number of patients in that age group is so small or patients in that age group are
410 geographically dispersed);⁶⁰
- 411
412 • There is evidence strongly suggesting that the drug would be ineffective or unsafe in that
413 age group;⁶¹
- 414
415 • The drug (1) does not represent a meaningful therapeutic benefit over existing therapies
416 for pediatric patients in that age group; and (2) is not likely to be used in a substantial
417 number of pediatric patients in that age group;⁶²
- 418
419 • The applicant can demonstrate that reasonable attempts to produce a pediatric
420 formulation necessary for that age group have failed.⁶³

421
422 We note that if a partial waiver is granted on the basis that it is not possible to develop a pediatric
423 formulation, the waiver will cover only the pediatric age groups requiring that formulation.⁶⁴

424
425 FDA believes that a partial waiver granted based on the inability to develop a pediatric
426 formulation generally should apply to situations in which the applicant can demonstrate that
427 unusually difficult technological problems prevented it from developing a pediatric formulation.
428 In certain cases, FDA may seek appropriate external expert opinion (e.g., from an advisory
429 committee) to help assess whether to grant such a waiver.

430

⁶⁰ See section 505B(a)(5)(B)(i) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(i)).

⁶¹ See section 505B(a)(5)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(ii)).

⁶² See section 505B(a)(5)(B)(iii) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(iii)).

⁶³ See section 505B(a)(5)(B)(iv) of the FD&C Act (21 U.S.C. 355c(a)(5)(B)(iv)).

⁶⁴ See section 505B(a)(5)(C) of the FD&C Act (21 U.S.C. 355c(a)(5)(C)).

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431 If the sponsor seeks a partial waiver on the grounds that it is not possible to develop a pediatric
432 formulation, the sponsor must submit documentation detailing why a pediatric formulation
433 cannot be developed.⁶⁵ This should include a detailed description of the sponsor’s efforts to
434 develop a pediatric formulation.⁶⁶ If FDA grants such a waiver, the sponsor’s submission will be
435 made publicly available.⁶⁷

c. Information for requesting a waiver

438
439 To request a waiver, sponsors should provide the following:

- 440 • The drug name, applicant name, and indication.
- 441
- 442 • The age group(s) included in the waiver request.
- 443
- 444 • The statutory reason(s) for requesting a waiver, including reference to the applicable
445 statutory authority.⁶⁸
- 446
- 447 • Evidence that the request meets the statutory reason(s) for waiver.⁶⁹ All relevant
448 scientific/clinical justifications for the waiver request should be included.
- 449

d. Waiver decision

450
451
452
453 FDA grants a waiver at the time of approval of an application that triggers PREA if it determines
454 that the application satisfies the statutory requirements for a waiver. FDA generally includes a
455 preliminary evaluation of the sponsor’s plan to request a waiver in FDA’s comments on the iPSP
456 (see section III.B.1., Pediatric Study Plans). This evaluation reflects FDA’s best judgment at that
457 time.

2. *Deferrals*

458
459
460
461 PREA authorizes FDA to defer the requirement to submit pediatric assessments or reports on the
462 molecularly targeted pediatric cancer investigation, based on established criteria.⁷⁰ A deferral
463 acknowledges that pediatric assessments or reports on the molecularly targeted pediatric cancer
464 investigation are required, but permits the applicant to submit the assessments or reports after the

⁶⁵ See section 505B(a)(5)(C) of the FD&C Act (21 U.S.C. 355c(a)(5)(C)).

⁶⁶ A partial waiver on this basis hinges on whether “the applicant can demonstrate” the failure of reasonable attempts to produce a pediatric formulation (section 505B(a)(5)(B)(iv) (21 U.S.C. 355c(a)(5)(B)(iv)).

⁶⁷ See section 505B(a)(5)(C) of the FD&C Act (21 U.S.C. 355c(a)(5)(C)).

⁶⁸ See sections 505B(a)(5) and 505B(e)(2)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(5) and 21 U.S.C. 355c(e)(2)(B)(ii)).

⁶⁹ See, for example, section 505B(e)(2)(B)(ii) of the FD&C Act (21 U.S.C. 355c(e)(2)(B)(ii)).

⁷⁰ See section 505B(a)(4) of the FD&C Act (21 U.S.C. 355c(a)(4)).

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465 approval of an NDA, BLA, or supplement. FDA may, on its own initiative or at the request of
466 an applicant, defer the submission of some or all of the pediatric assessments or reports on the
467 molecularly targeted pediatric cancer investigation until a specified date after approval of the
468 drug.⁷¹

a. Timeline

470
471
472 Sponsors can discuss a plan for a deferral and the status of a deferred study with FDA as follows:
473

- 474 • **Premarketing** — It is important to include in the iPSP any plans for a deferral request. In
475 certain cases it may be appropriate to initiate early discussion of a plan for deferral, for
476 example, as part of a pre-IND meeting or during phase 1 of clinical development.
477
- 478 • **Application review** — FDA grants the deferral, as appropriate, upon approval of the
479 application or supplement.
480
- 481 • **Postmarketing** — The applicant must submit an annual review of the status of a deferred
482 pediatric study (PREA postmarketing requirement) to FDA until it has submitted the final
483 study report.⁷² The final due date of a deferred pediatric study may be extended under
484 certain circumstances (see section III.D.2.e., Deferral extensions).
485

b. Criteria for deferral

486
487
488 FDA may defer the timing of submission of some or all required assessments or reports on the
489 molecularly targeted pediatric cancer investigation if the applicant submits certain required
490 information to FDA, as discussed below, and FDA finds one or more of the following:⁷³
491

- 492 • The drug is ready for approval for use in adults before pediatric studies are complete;
493
- 494 • Pediatric studies should be delayed until additional safety or effectiveness data have been
495 collected; or
496
- 497 • There is another appropriate reason for deferral
498

499 An “appropriate reason” for deferral may include, for example, that development of a pediatric
500 formulation is not complete.
501

⁷¹ See section 505B(a)(4) of the FD&C Act (21 U.S.C. 355c(a)(3)).

⁷² See section 505B(a)(4)(C) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)).

⁷³ See section 505B(a)(4)(A)(i) of the FD&C Act (21 U.S.C. 355c(a)(4)(A)(i)).

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c. Information for requesting a deferral

To request a deferral, an applicant must provide the following:⁷⁴

- A certification of the grounds for deferral;
- A pediatric study plan as described in section 505B(e) of the FD&C Act (see section III.B.1., Pediatric Study Plans);
- Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time; and
- A timeline for completion of such studies.

d. Deferral review and decision

The decision to defer and the deferral date are determined on a case-by-case basis. FDA may, as appropriate, consider the following in determining whether and how long to defer submission of a pediatric assessment:

- The need for the drug in pediatric patients;
- Availability of sufficient safety data to initiate pediatric clinical studies;
- The nature and extent of pediatric data needed to support pediatric labeling;
- The existence of clearly documented difficulties in enrolling subjects; and/or
- Evidence of technical problems in developing pediatric formulations.

For additional information on the circumstances in which a deferral may be appropriate for a molecularly targeted pediatric cancer investigation, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

The iPSP, agreed iPSP, and any subsequent amendments should include the key elements of any planned deferred studies. FDA does not intend to make recommendations on planned deferral requests that are submitted in the absence of an iPSP, except under rare circumstances (e.g., urgent public health need).

FDA grants a deferral, as appropriate, in the approval letter for an NDA, BLA, or supplement.

e. Deferral extensions

The FD&C Act provides a mechanism for FDA to grant an extension of the timeline for a deferral granted by FDA.⁷⁵ Examples of reasons assessments or investigations may be delayed

⁷⁴ See section 505B(a)(4)(A)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(A)(ii)).

⁷⁵ See section 505B(a)(4)(B) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)).

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544 include, but are not limited to, unexpected difficulties with enrollment, unexpected delays in
545 reaching agreement with FDA on protocols for the pediatric clinical studies, or an unanticipated
546 need for additional safety or effectiveness data before proceeding with studies in children.
547 During consideration of the deferral extension request, in general, FDA considers whether the
548 applicant could have prevented or foreseen the delay. FDA also generally considers the
549 likelihood that studies can be completed given the circumstances.

550

551 To request a deferral extension, an applicant must submit a new timeline for the completion of
552 pediatric studies along with any significant updates to the following information from the
553 original deferral request:⁷⁶

554

555 • A certification of the grounds for deferral;

556

557 • PSP; and

558

559 • Evidence that the studies are being conducted or will be conducted with due diligence
560 and at the earliest possible time.

561

562 Applicants should submit information to support the need for an extension of the timeline for
563 deferred studies. For example, if an applicant needs additional time to complete the deferred
564 pediatric studies because of difficulty recruiting subjects, the applicant should provide
565 information outlining the reasons for the difficulties, evidence supporting the reasons outlined
566 (including information on the incidence of the condition and global geographic distribution, if
567 applicable), and information outlining its efforts to increase enrollment such as the number of
568 clinical sites contacted and the number of subjects screened and enrolled.

569

570 An applicant must submit a request for deferral extension, along with the required information, at
571 least 90 days before the date that the studies are due.⁷⁷ FDA will respond to such request within
572 45 days of receipt of the request.⁷⁸ If FDA grants the deferral extension, the specified date will
573 be the new due date for submission of the deferred assessments or deferred reports on the
574 molecularly targeted pediatric cancer investigation.⁷⁹

575

576 3. *Annual Review*

577

578 Pediatric assessments deferred under PREA are required postmarketing studies subject to annual
579 status reporting requirements under PREA and FDA regulations.⁸⁰

⁷⁶ See section 505B(a)(4)(B)(i)(II) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(i)(II)).

⁷⁷ See section 505B(a)(4)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(ii)).

⁷⁸ See section 505B(a)(4)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(ii)).

⁷⁹ See section 505B(a)(4)(B)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(B)(ii)).

⁸⁰ See section 505B(a)(4)(C) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)); 21 CFR 314.81(b)(2)(vii), and 21 CFR 601.70.

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An applicant’s annual status report under PREA must contain the following:⁸¹

- Information detailing the progress made in conducting pediatric studies
- If no progress has been made in conducting such studies, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time
- The projected completion date for pediatric studies
- The reason(s) that a deferral or deferral extension continues to be necessary

E. Compliance With PREA

If an applicant submits an application or supplement subject to PREA and fails to comply with applicable PREA requirements, FDA may, as appropriate, refuse to file the application or issue a complete response letter after reviewing the application.⁸² If an applicant fails to fulfill required deferred pediatric studies under PREA that were established in the approval letter, FDA will issue to the applicant a noncompliance letter that informs it of such failure.⁸³ The applicant must respond to this letter in writing within 45 days and may request a deferral extension as part of that response.⁸⁴

FDA will post the noncompliance letter and the applicant’s response on the FDA public website after redacting any information protected by applicable law.⁸⁵ If FDA grants a deferral extension before the initial study due date, FDA does not intend to issue a noncompliance letter unless and until the newly established due date has passed.

After FDA issues a noncompliance letter, it may take additional steps to ensure compliance if needed. The drug may be considered misbranded solely because of the applicant’s failure to comply with PREA and subject to relevant enforcement action.⁸⁶ For an approved drug, the failure to submit pediatric assessments or reports on the molecularly targeted pediatric cancer investigation, or a request for waiver or deferral of those studies, will not be the basis for

⁸¹ See section 505B(a)(4)(C)(i) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)(i)).

⁸² See 21 CFR 314.101(d), 21 CFR 314.110, and 21 CFR 601.3.

⁸³ See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

⁸⁴ See section 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)).

⁸⁵ See 505B(d)(1) of the FD&C Act (21 U.S.C. 355c(d)(1)). See also the Noncompliance Letters Under 505B(d)(1) of the FD&C Act web page at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm343203.htm>.

⁸⁶ See section 505B(d)(2) of the FD&C Act (21 U.S.C. 355c(d)(2)).

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612 withdrawing approval of a drug or revoking a license for a biological product.⁸⁷ However, if
613 FDA finds a drug to be misbranded, the drug could be subject to an injunction or seizure
614 proceedings.⁸⁸

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616

IV. BEST PHARMACEUTICALS FOR CHILDREN ACT

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A. Written Requests

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1. Description of the Written Request

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622

623 A WR is a document issued by FDA requesting submission of a study or studies intended to
624 provide meaningful health benefits in the pediatric population. The WR specifies the elements
625 of the study or studies that the sponsor or application holder must complete to qualify for
626 pediatric exclusivity.⁸⁹ FDA can issue a WR at the request of an interested party or on its own
627 initiative. Completion of studies described in a WR is voluntary.⁹⁰ FDA does not limit issuance
628 of a WR to a specific drug product, and the WR can result in only one 6-month period of
629 pediatric exclusivity for that sponsor, as described in section IV.F., Attaching the Period of
630 Pediatric Exclusivity After a Determination That a Drug Qualifies for Pediatric Exclusivity.
631 FDA's authority to issue a WR extends to use of an active moiety for indications that may
632 produce health benefits in the pediatric population, regardless of whether the indications have
633 been previously approved in adults.⁹¹

634

635 Generally, a WR seeks all applicable information necessary to establish safety and effectiveness
636 of a drug for use in all relevant pediatric populations, including study information (e.g., type,
637 timing, endpoints), drug-specific safety concerns to be monitored, statistical analysis plan, and
638 timeline for completing the studies.

639

640 FDA can use a PPSR to develop a WR or use alternative information (see section IV.B., How to
641 Obtain a Written Request). As a greater understanding of the indication or of the mechanism of
642 action of a particular drug or drug class develops, WRs, including elements within a study or
643 studies necessary to qualify for pediatric exclusivity, may evolve.

644

⁸⁷ See section 505B(d)(2) of the FD&C Act (21 U.S.C. 355c(d)(2)).

⁸⁸ See sections 302 and 304 of the FD&C Act (21 U.S.C. 332 and 21 U.S.C. 334).

⁸⁹ See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

⁹⁰ Section 505A of the FD&C Act does not require the sponsor or application holder to conduct pediatric studies; instead, it creates an exclusivity incentive to encourage such studies. However, the sponsor or application holder may be required to conduct pediatric studies of certain new and marketed drugs under section 505B of the FD&C Act.

⁹¹ See sections 505A(a), 505A(b)(1), 505A(c)(1), and 505A(d)(1)(B) of the FD&C Act (21 U.S.C. 355a(a), 21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), and 21 U.S.C. 355a(d)(1)(B)).

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645 In addition, the BPCA requires that, in issuing a WR, FDA take into account adequate
646 representation of children of ethnic and racial minorities.⁹² If a WR does not request studies in
647 neonates, the request will include a statement describing the rationale for not requesting such
648 studies.⁹³

649
650 A sponsor will not be eligible for pediatric exclusivity based on requirements or requests to
651 conduct postmarketing studies (e.g., studies required under PREA) or other communications
652 about pediatric studies unless it is in receipt of a WR.⁹⁴

653 654 2. *Written Request Studies*

655
656 In general, FDA decides what studies to include in a WR by determining what information is
657 needed to use the drug appropriately in the pediatric population. When making this
658 determination, in general, FDA obtains the following from the sponsor:

- 659
660 • Information on any other indications for this product that may have health benefits in
661 children. For example, the sponsor should provide information on any indications for
662 which there are ongoing clinical studies in adults and/or children or for which the sponsor
663 has opened an IND.
- 664
665 • Information that exists in the literature on the drug or on pharmacologically related drugs.

666
667 In some instances, FDA may ask a sponsor to submit information to an IND before issuing a
668 WR. Similarly, in some cases, a sponsor may wish to submit pediatric study data to its IND in
669 support of an amendment to its WR. Pediatric studies previously submitted to an IND can be
670 used as the basis of a PPSR or can be submitted to an NDA or BLA to qualify for pediatric
671 exclusivity in response to a WR; however, FDA does not consider pediatric studies a sponsor
672 submits to an NDA or BLA (either in an original application, amendment, or supplement) before
673 FDA issues a WR as being responsive to that WR.

674
675 In certain situations, FDA may determine that a WR for additional pediatric studies will **not** be
676 issued. Such situations may include the following:

- 677
678 • Sufficient pediatric information has already been submitted to the NDA or BLA, even if
679 the pediatric information is not yet included in the labeling;
- 680
681 • Study of the drug for the specified indication(s) in the pediatric population would not
682 offer a health benefit in that population;

683

⁹² See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

⁹³ See section 505A(d)(1)(A) of the FD&C Act (21 U.S.C. 355a(d)(1)(A)).

⁹⁴ See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

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- It is not possible to conduct a study or studies of the drug for the specified indications in the pediatric population in a manner that would provide useful information (e.g., the study population is too small to yield interpretable results); and/or
 - Outstanding safety concerns from studies or significant theoretical concerns need to be clarified with additional studies to support conducting studies in the pediatric population.

691 Historically, FDA has at times issued WRs solely for studies required under PREA, even if there
692 were no other indications that may produce health benefits in the pediatric population. However,
693 over time, data on pediatric labeling changes pursuant to BPCA and/or PREA have been
694 collected. Between 2002 and 2019, there were 768 products with pediatric labeling changes
695 under BPCA and/or PREA. Sixty-three percent of these labeling changes were based on studies
696 conducted under PREA/Pediatric Rule alone; 21 percent were based on studies conducted under
697 BPCA alone; 16 percent were based on studies conducted under both the BPCA and PREA.
698 These data suggest that studies required under PREA are successfully completed, and that PREA
699 requirements have resulted in an increase in pediatric labeling, even without the added incentive
700 of the BPCA.

701

702 The BPCA provides FDA with discretion to determine whether to issue, and the appropriate
703 scope of, WRs based on the information that “may produce health benefits” in the pediatric
704 population.⁹⁵ In light of the data on pediatric labeling changes pursuant to the BPCA and/or
705 PREA, FDA believes WRs should be reserved for those sponsors who conduct additional
706 pediatric studies — beyond what is required under PREA — that may produce health benefits in
707 children. Thus, upon finalization of this guidance, FDA does not expect to issue WRs solely for
708 studies or planned studies that are required under PREA. In general, FDA expects that a WR
709 that includes studies or planned studies required under PREA will also include additional
710 indications or populations. If there are no additional studies for indications or populations that
711 may produce health benefits in the pediatric population beyond the studies or planned studies
712 required under PREA, then FDA does not expect to issue a WR for that drug. For example, if a
713 sponsor has an iPSP that includes a plan for deferred studies of a drug for pediatric juvenile
714 idiopathic arthritis (pJIA), FDA does not expect to issue a WR solely for studies of pJIA in the
715 same pediatric population. However, if FDA determines that this drug may produce health
716 benefits in pediatric systemic juvenile idiopathic arthritis (sJIA), and there are no studies or
717 planned studies required under PREA for this indication, then it may be appropriate for FDA to
718 issue a WR for pediatric studies for *both* pJIA and sJIA.

719

720 In general, when considering issuance of a WR, FDA evaluates the need for studies for all
721 pediatric subpopulations and for all indications for which the drug is being used or could be used
722 in the pediatric population. In general, FDA considers the indications already approved for
723 adults, indications pending for adults, and unapproved uses including uses that might be specific
724 to the pediatric population. A single WR may address multiple indications and uses that are both
725 approved and unapproved.⁹⁶

⁹⁵ See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

⁹⁶ See section 505A(d)(1)(B) of the FD&C Act (21 U.S.C. 355a(d)(1)(B)).

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726
727 FDA can issue a WR that includes nonclinical studies.⁹⁷ Section 505A(a) of the FD&C Act
728 defines the term *pediatric studies* to mean “at least one clinical investigation (that, at the
729 Secretary’s discretion, may include pharmacokinetic studies) in pediatric age groups (including
730 neonates in appropriate cases) in which a drug is anticipated to be used, and, at the discretion of
731 the Secretary, may include preclinical studies.” FDA may need certain toxicology studies in
732 immature animals to evaluate the safety of drugs for use in pediatric populations.⁹⁸ Accordingly,
733 FDA may request that a sponsor or holder of an approved application conduct nonclinical studies
734 before completing pediatric studies in humans. FDA may need to review such studies before it
735 can determine whether information relating to use of the drug could produce health benefits in
736 the pediatric population; thus, FDA may need these studies to determine if it will issue a WR.

737
738 In response to a WR, sponsors may, as appropriate, submit studies conducted by a third party.
739 However, the sponsor should submit reports of studies that it has not conducted only if (1) the
740 data from the studies appear to provide useful pediatric information that *fairly responds* to the
741 WR issued by FDA; **and** (2) the sponsor obtains a right of reference to submit the reports of
742 studies along with the underlying data.

743
744 A sponsor can use data it collects before or after FDA issues a WR to respond to the WR.
745 Although FDA can request literature reviews as part of a larger WR, reviews of published
746 literature alone are not pediatric studies that will qualify a drug for pediatric exclusivity.⁹⁹

747
748 Although a sponsor may, as appropriate, use studies it conducts to meet PREA requirements to
749 qualify also for pediatric exclusivity,¹⁰⁰ as mentioned, FDA does not consider pediatric studies a
750 sponsor submits to an NDA or BLA (either in an original application, amendment, or
751 supplement) before FDA issues a WR as being responsive to that WR. To qualify for pediatric
752 exclusivity, sponsors and holders of an approved application should obtain a WR or an
753 amendment to an existing WR before submitting the pediatric studies to an application.

754 755 3. *Amended Written Requests*

756
757 Each WR states that the WR may be amended. A sponsor may request an amendment to the
758 WR, or FDA may issue an amendment on its own initiative. However, FDA does not anticipate
759 amending WRs in the absence of scientific, medical, or regulatory justification.

760

⁹⁷ See section 505A(a) of the FD&C Act (21 U.S.C. 355a(a)).

⁹⁸ We support the principles of the 3Rs (reduce/refine/replace) for animal use in testing when feasible. The FDA encourages sponsors to consult with review divisions when considering a nonanimal testing method believed to be suitable, adequate, validated, and feasible. The FDA will consider if the alternative method could be assessed for equivalency to an animal test method.

⁹⁹ See sections 505A(a), 505A(b), and 505A(c) of the FD&C Act (21 U.S.C. 355a(a), 21 U.S.C. 355a(b), and 21 U.S.C. 355a(c)).

¹⁰⁰ As noted earlier in this section, going forward, FDA does not expect to issue WRs solely for studies or planned studies that are required under PREA.

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761 Sponsors can request a change in the studies' due date in the WR by submitting a proposed
762 amendment to the WR. If a sponsor believes it will be unable to meet the time frames in a WR,
763 it should contact FDA to request such a change as soon as possible. If FDA agrees to the
764 change, it intends to notify the sponsor in writing regarding the extension time. Any request for
765 an extension of time should take into consideration that completed reports of all studies should
766 be submitted for filing at least 15 months before the expiration of the patent or exclusivity to
767 which the pediatric exclusivity would attach. Sponsors should be aware that if they choose to
768 submit within less than 15 months, FDA may not be able to complete the review and make a
769 determination in time to meet the 9-month deadline.¹⁰¹

770
771 FDA intends to issue all amendments to a WR in writing. Sponsors should also request any
772 amendments to a WR in writing. Discussion of a proposed amendment at a meeting with FDA
773 does not constitute a request to amend a WR nor does it constitute FDA's amendment of the WR.
774 In addition, if a sponsor has submitted a protocol that is inconsistent with the WR, and FDA has
775 not commented on the protocol, the sponsor should not assume FDA agrees that the protocol is
776 consistent with the WR. Even a minor change to a study, such as a change in the number of
777 subjects, the age groups enrolled, or the elimination of certain testing requirements, may warrant
778 a change in the protocol and a revision of the WR if it relates to a specified term of the WR.

779
780 Sponsors can submit preliminary data to an IND in support of a request for amendment.
781 Sponsors that believe that their studies may not fairly respond to the WR as issued but
782 nonetheless provide valuable pediatric information should (1) seek to obtain an amended WR
783 *before* submitting any pediatric study reports to their NDAs or BLAs; and (2) submit proposed
784 amendments to their WRs early enough to ensure enough time for FDA to issue an amended WR
785 and to ensure the sponsor has enough time to submit its studies at least 15 months before the
786 expiration of any patent or exclusivity to which pediatric exclusivity would attach.

787
788 Sponsors should not submit the requested study reports to their NDAs or BLAs until *after* they
789 have received FDA's response to requested amendments in writing. Reports of studies that do
790 not fairly respond to the existing WR will *not* qualify for pediatric exclusivity (see sections
791 IV.C., How to Submit Study Reports in Response to a Written Request, IV.D., Qualifying for
792 Pediatric Exclusivity, and IV.E., Determining Eligibility For Pediatric Exclusivity).¹⁰²

B. How to Obtain a Written Request

794
795
796 Historically, WRs have generally been issued after a drug is approved for use in adults.
797 However, there may be situations in which it is appropriate to issue a WR before such an action.
798 See sections II., Overview of Regulatory Strategy for Pediatric Drug Development, and III.B.1.,
799 Pediatric Study Plans, and previous subsections of this section for additional considerations
800 relating to timing of a WR. Additionally, the appropriate timing of the submission of a specific

¹⁰¹ See sections 505A(b)(2), 505A(c)(2), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b)(2), 21 U.S.C. 355a(c)(2), and 21 U.S.C. 355a(d)(4)).

¹⁰² See sections 505A(b)(1), 505A(c)(1), 505A(d)(4), and 505A(h) of the FD&C Act (21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), 21 U.S.C. 355a(d)(4), and 21 U.S.C. 355a(h)).

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801 PPSR can be discussed with the relevant review division(s). FDA may issue a WR either in
802 response to a PPSR **or** on its own initiative (see sections IV.A., Written Requests).

803

804 *I. Submitting a PPSR*

805

806 If a sponsor has exclusivity or patent protection for a drug or exclusivity for a biological product,
807 or anticipates that it will have such exclusivity or patent protection, the sponsor can submit a
808 PPSR to the appropriate review division (such a proposal can help to expedite FDA's issuance of
809 a WR). Sponsors should mark PPSRs with the header PROPOSED PEDIATRIC STUDY
810 REQUEST and submit it to the appropriate IND. Sponsors that seek to qualify for pediatric
811 exclusivity to attach to existing patents and/or exclusivities should plan to submit their PPSRs
812 with sufficient time to:

813

814 • Permit FDA to review the PPSR, confer with the party submitting the PPSR as necessary,
815 and issue the WR (including review by the FDA's internal pediatric review committee
816 (the PeRC) as required before issuance¹⁰³);

817

818 • Allow time for the sponsor, after the WR is issued, to initiate the studies, complete the
819 studies, and submit the reports for filing; **and**

820

821 • Provide FDA 180 days to review the studies and make an exclusivity determination, with
822 a remaining, nonoverlapping 9 months before expiration of the patent or exclusivity
823 period.¹⁰⁴

824

825 The PPSR should describe the studies the sponsor or application holder proposes to conduct to
826 qualify for pediatric exclusivity. The PPSR should include (1) a background section, (2)
827 nonclinical studies, (3) drug information, (4) clinical studies, (5) known drug safety concerns and
828 monitoring, (6) statistical information, including power of studies and statistical assessments, and
829 (7) time frame for submitting reports of the study or studies.

830

831 It is important to note that a PPSR is not a substitute for an iPSP (section III.B.1., Pediatric Study
832 Plans). Although these submissions may have some similarities, each one is submitted under a
833 different statutory scheme and serves a distinct purpose. See sections II., Overview of
834 Regulatory Strategy for Pediatric Drug Development, III., Pediatric Research Equity Act, and
835 V.C., PREA and Pediatric Exclusivity, for additional information.

836

837 FDA intends to consider PPSRs that include requests to study multiple pediatric age groups in
838 the same study, as appropriate. FDA recognizes that studies defined by age may be
839 inappropriate when it is reasonable to define subgroups using methods other than age, such as
840 development stage. If the sponsor submits data as part of a PPSR to indicate that a drug should

¹⁰³ See section 505A(f) of the FD&C Act (21 U.S.C. 355a(f)).

¹⁰⁴ See sections 505A(b)(2), 505A(c)(2), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b)(2), 21 U.S.C. 355a(c)(2), and 21 U.S.C. 355a(d)(4)).

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841 be studied in pediatric groups identified by characteristics other than age, in general, FDA
842 intends to consider that data when developing the WR.

843
844 FDA has 120 days after a sponsor submits a PPSR to review and act on the submission.¹⁰⁵ Our
845 response to the PPSR is either a WR or a PPSR inadequate letter, in which we inform the
846 sponsor of the reasons we will not issue a WR at this time. In general, FDA also makes
847 suggestions as to what the sponsor should include in a resubmitted PPSR that might support our
848 issuance of a WR.

849
850 **2. *Issuance and Acceptance of a WR***

851
852 The sponsor or application holder must respond to FDA within 180 days after receiving the WR
853 indicating whether it will conduct the studies and, if so, indicate when it will initiate the
854 studies.¹⁰⁶

855
856 The procedure for qualifying for exclusivity and the protections that exclusivity will confer are
857 described in more detail in sections IV.E., Determining Eligibility For Pediatric Exclusivity, and
858 IV.F., Attaching the Period of Pediatric Exclusivity After a Determination That a Drug Qualifies
859 for Pediatric Exclusivity.

860
861 If a sponsor declines a WR that is issued by FDA, the sponsor must provide the reasons it
862 declined the request.¹⁰⁷ If the sponsor declines the WR because it is not possible to develop an
863 appropriate pediatric formulation, the sponsor must submit to FDA the reasons such pediatric
864 formulation cannot be developed.¹⁰⁸ If a sponsor declines a WR, the sponsor is not eligible to
865 qualify for pediatric exclusivity for the studies under that WR.

866
867 **C. *How to Submit Study Reports in Response to a Written Request***

868
869 To qualify for pediatric exclusivity, sponsors or application holders must submit study reports in
870 accordance with FDA requirements for filing.¹⁰⁹ Studies submitted in an application or
871 supplement that does not meet requirements for filing of an NDA, BLA, or supplement (i.e.,
872 FDA refuses to file the application or supplement) are not considered submitted to FDA.

873
874 In general, sponsors should also submit study reports in accordance with the guidance for
875 industry *Guideline for the Format and Content of the Clinical and Statistical Sections of an*
876 *Application* (July 1988) and the ICH guidance for industry *E3 Structure and Content of Clinical*
877 *Study Reports* (July 1996).

¹⁰⁵ See section 505A(d)(3) of the FD&C Act (21 U.S.C. 355a(d)(3)).

¹⁰⁶ See section 505A(d)(2)(A)(i) of the FD&C Act (21 U.S.C. 355a(d)(2)(A)(i)).

¹⁰⁷ See section 505A(d)(2)(A)(i) of the FD&C Act (21 U.S.C. 355a(d)(2)(A)(i)).

¹⁰⁸ See section 505A(d)(2)(A)(ii) of the FD&C Act (21 U.S.C. 355a(d)(2)(A)(ii)).

¹⁰⁹ See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)). For additional information on filing requirements and refusal to file, see, for example, 21 CFR 314.50, 21 CFR 314.101, and 21 CFR 601.2.

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878
879 To help ensure that pediatric study reports are evaluated for eligibility for pediatric exclusivity in
880 a timely manner, sponsors should include the following with the application or supplement:

- 881
- 882 • A header that states SUBMISSION OF PEDIATRIC STUDY REPORTS —
883 PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED;
 - 884
 - 885 • A copy of the WR and any amendments;
 - 886
 - 887 • A summary of the pediatric studies conducted in response to the WR;
 - 888
 - 889 • An annotated WR indicating how and where in the submitted study reports each term of
890 the WR has been addressed; and
 - 891
 - 892 • Proposed labeling that includes information regarding the results of the study or studies.
 - 893

894 If there is information that is adequate to support the evaluation of dosing, safety, and efficacy in
895 a subpopulation of the population included in the WR, FDA encourages the sponsor to submit an
896 NDA, BLA, or supplement to incorporate that information into labeling for the drug before the
897 determination of exclusivity. If making multiple submissions in response to a single WR, the
898 sponsor should, in the final submission, reference prior submissions (including relevant
899 submission dates) and mark only the last submission as described above.

900 901 **D. Qualifying for Pediatric Exclusivity**

902
903 We note at the outset that a commitment to complete a study at some future date is not sufficient
904 to qualify a drug for pediatric exclusivity.¹¹⁰ Rather, to qualify for an initial period of pediatric
905 exclusivity, a sponsor must submit study reports that fairly respond to an issued WR, were
906 conducted in accordance with commonly accepted scientific principles and protocols, and have
907 been reported in accordance with filing requirements.¹¹¹ It is not necessary for the uses studied
908 under the WR to be approved.¹¹²

909 910 *1. For a Drug Product That Is the Subject of a New Drug Application or Biologics* 911 *License Application*

912
913 A drug product qualifies for pediatric exclusivity when all of the following have occurred:¹¹³

¹¹⁰ See sections 505A(b) and 505A(c) of the FD&C Act (21 U.S.C. 355a(b) and 21 U.S.C. 355A(c)).

¹¹¹ See sections 505A(b), 505A(c), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b), 21 U.S.C. 355a(c), and 21 U.S.C. 355a(d)(4)).

¹¹² Approval is required for a sponsor to qualify for a second 6-month period of pediatric exclusivity under section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)). See section IV.F.1.b., A second 6-month period of pediatric exclusivity, for further discussion of that process.

¹¹³ See sections 505A(b), 505A(c), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b), 21 U.S.C. 355a(c), and 21 U.S.C. 355a(d)(4)).

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- 931
- FDA issued a WR for pediatric studies, and the sponsor or holder of an approved application agreed to the request.
 - The sponsor or the holder of an approved application has submitted reports of the requested studies. Such reports should be submitted to the NDA or BLA **after** FDA issues the WR.
 - The studies were completed using appropriate formulations for each age group and within the requested time frame.
 - FDA has determined the studies fairly respond to the WR, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with filing requirements.
 - FDA makes an exclusivity determination at least 9 months before the expiration date of the patent and/or exclusivity protection to which the pediatric exclusivity will attach.¹¹⁴

2. Nonprescription Drugs

932

933

934 Nonprescription drugs marketed under an approved application may be eligible for pediatric

935 exclusivity, and the recommendations in this guidance apply to those nonprescription drugs.

936

937 Nonprescription drugs that are marketed pursuant to a monograph developed under the over-the-

938 counter drug review are not eligible for exclusivity under section 505A of the FD&C Act.

939

E. Determining Eligibility For Pediatric Exclusivity

940

941

942 For a drug to be considered eligible for pediatric exclusivity, FDA recommends that the sponsor

943 submit a complete report of all studies to FDA at least 15 months before the expiration of any

944 existing patent or exclusivity it wishes to protect (i.e., the 9-month time period¹¹⁵ plus the 180-

945 day exclusivity determination review period¹¹⁶). If sponsors choose to submit within less than

946 15 months, FDA may not be able to complete its review of such studies and make a

947 determination about the drug's eligibility for pediatric exclusivity in time to meet the 9-month

948 deadline.

949

950 In making an eligibility determination, FDA will evaluate whether the studies fairly respond to

951 the WR, were conducted in accordance with commonly accepted scientific principles and

¹¹⁴ See section 505A(b)(2) and 505A(c)(2) of the FD&C Act (21 U.S.C. 355a(b)(2) and 21 U.S.C. 355a(c)(2)) and section 351(m)(4) of the PHS Act (42 U.S.C. 262(m)(4)).

¹¹⁵ See section 505A(b)(2) and 505A(c)(2) of the FD&C Act; 21 U.S.C. 355a(b)(2) and 21 U.S.C. 355a(c)(2).

¹¹⁶ See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)).

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952 protocols, and have been reported in accordance with filing requirements.¹¹⁷ FDA’s pediatric
953 exclusivity boards (Boards), which are comprised of representatives from the Center for Drug
954 Evaluation and Research or the Center for Biologics Evaluation and Research, including
955 representatives with pediatric expertise, make this determination. In general, the Boards
956 consider the following when assessing, as required by statute, whether the studies *fairly respond*
957 to a WR:

- 958
- 959 • The purpose of the pediatric exclusivity provision as described in the statute, with
960 reference to the legislative history. The statute makes clear that its purpose is to generate
961 meaningful clinical information on the use of drug products in children that will result in
962 a health benefit to pediatric populations.¹¹⁸
- 963
- 964 • Whether the sponsor met the terms of a WR.
- 965
- 966 • The information sought in the WR and the objectives stated in the WR.
- 967

968 In general, the Boards ask whether the studies were designed and carried out by the sponsor in a
969 way likely to meet those objectives specified in the WR and underlying the exclusivity provision
970 as a whole. When a sponsor meets the terms of a WR, the resulting studies fairly respond to that
971 WR because studies that are carried out in accordance with the trial’s plans and objectives, as
972 expressed in the WR, generally satisfy the statutory goal of obtaining meaningful pediatric use
973 information. Sometimes, a sponsor fails to produce meaningful pediatric information despite
974 conducting the studies in the manner requested. Under such circumstances, FDA nevertheless
975 considers the sponsor to have fairly responded to the WR. FDA understands that the failure to
976 generate meaningful information in such cases is at least partially attributable to study design,
977 and FDA and the sponsor generally design studies described in a WR jointly.

978

979 Where the sponsor has not met the terms of the WR, FDA evaluates whether the information
980 generated by the studies is nevertheless sufficient to meet the objectives of the WR in light of the
981 information sought in the WR. If FDA determines that the objectives of the WR were met, then
982 FDA concludes that the sponsor has fairly responded, even if it did not meet the terms of the
983 WR. FDA considers studies that do not meet the terms of the written request to have fairly
984 responded if, considering the data provided by the sponsor as a whole (i.e., by considering all
985 relevant data, and not just data generated by those studies), the sponsor meets the objectives of
986 the WR by generating clinically meaningful information of the general type (quality and
987 quantity) the WR contemplates.

988

¹¹⁷ See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)).

¹¹⁸ See, for example, section 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)) requiring FDA to determine “that information relating to the use of a new drug in the pediatric population may produce health benefits,” section 505A(f)(2) of the FD&C Act (21 U.S.C. 355a(f)(2)) requiring review by the PeRC before FDA issues a WR, section 505A(f)(3) of the FD&C Act, providing that the same committee may review the reports of studies conducted in response to a WR before FDA makes a determination regarding pediatric exclusivity, section 505A(f)(6)(E) of the FD&C Act (21 U.S.C. 355a(f)(6)(E)) requiring FDA to publicly report, among other things, labeling changes made as a result of studies conducted in response to a WR, and section 505A(k)(2) of the FD&C Act (21 U.S.C. 355a(k)(2)) requiring sponsors to distribute the same to physicians and other health care providers.

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989 For example, if a specific number of subjects is requested or a specific study duration or
990 endpoint is specified to ensure that the study will generate adequate data to provide a health
991 benefit, failure to comply with these elements of the WR may result in a denial of exclusivity.
992 Denial is likely if, in the absence of compliance with the terms of the WR, the studies are not
993 expected to be interpretable or will not provide information that otherwise yields a health benefit
994 to the pediatric populations addressed in the WR.

995
996 Where a WR is capable of more than one interpretation, the Boards generally consider a fair
997 response to be one that interprets the WR in a manner likely to generate information that will
998 provide a health benefit (including meaningful pediatric labeling) in the relevant populations that
999 the WR asked the sponsor to study. If the studies submitted fairly respond to the WR, the Boards
1000 will recommend that the drug is eligible for pediatric exclusivity (assuming the other statutory
1001 requirements for pediatric exclusivity are met).¹¹⁹ If, on the other hand, the sponsor responds to
1002 the WR in such a way that the possibility of a health benefit (including meaningful pediatric
1003 labeling in relevant age groups) from the studies conducted is not likely, the Boards are likely to
1004 conclude that the submission does not fairly respond to the WR.

1005
1006 Generally, FDA expects to notify sponsors or holders of an approved application within the 180-
1007 day period after the study reports are submitted whether the study reports fairly responded to the
1008 WR and the drug qualifies for pediatric exclusivity.¹²⁰

F. Attaching the Period of Pediatric Exclusivity After a Determination That a Drug Qualifies for Pediatric Exclusivity

I. Drug Products¹²¹

a. An initial 6-month period of pediatric exclusivity

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1016
1017 Pediatric exclusivity will attach to all unexpired exclusivities and patents¹²² listed in the
1018 *Approved Drug Products With Therapeutic Equivalence Evaluations* publication (the Orange

¹¹⁹ See sections 505A(b)(1), 505A(c)(1), and 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), and 21 U.S.C. 355a(d)(4)).

¹²⁰ See section 505A(d)(4) of the FD&C Act (21 U.S.C. 355a(d)(4)).

¹²¹ For the purposes of this section IV.F.1., references to *drugs* or *drug products* do not include biological products licensed under section 351 of the PHS Act (42 U.S.C. 262). Although the considerations in this section are generally relevant to such biological products, pediatric exclusivity for biological products differs in certain ways from pediatric exclusivity for other drug products. For more information see section IV.F.2., Biological Products, below.

¹²² Pediatric exclusivity that has attached to the end of the patent term will block for an additional 6 months after the patent expires approval of an ANDA or 505(b)(2) application if (1) the ANDA or 505(b)(2) sponsor did not seek approval until the end of the patent term; or (2) the ANDA or 505(b)(2) sponsor's patent challenge has been unsuccessful. See, for example, sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)). In addition, if an ANDA or 505(b)(2) sponsor files a paragraph IV certification challenging a listed patent, and the patent litigation is ongoing when the patent expires, the pediatric exclusivity will attach at the

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1019 Book)¹²³ for any drug product containing the drug the sponsor studies and for which it holds the
1020 approved NDA.¹²⁴ For studies a sponsor conducts on a previously unapproved drug, pediatric
1021 exclusivity will attach to any exclusivities or patents that will be listed in the Orange Book upon
1022 approval of that drug and to certain later listed patents or exclusivities.¹²⁵ For studies a sponsor
1023 conducts on a previously approved drug, pediatric exclusivity will attach to protections listed for
1024 the previously approved drug *at the time the drug qualifies for pediatric exclusivity* and to certain
1025 later listed patents and exclusivities,¹²⁶ as described further in section IV.F.1.c., Later-filed
1026 applications containing the same drug. Pediatric exclusivity for combination drugs may raise
1027 additional considerations that are not addressed in this guidance.

1028
1029 b. A second 6-month period of pediatric exclusivity

1030
1031 Each WR may result in only one 6-month period of pediatric exclusivity.¹²⁷ However, after a
1032 drug has qualified for an initial period of pediatric exclusivity, a sponsor submitting a
1033 supplement to an application can submit additional pediatric studies meeting the relevant
1034 statutory requirements in response to a second WR.¹²⁸ The second 6-month period of pediatric
1035 exclusivity will attach only to any new 3-year exclusivity period for which the supplemental
1036 application qualifies.¹²⁹ In addition, several other considerations regarding a second period of
1037 pediatric exclusivity are presented as follows:¹³⁰

- 1038
1039 • A second WR can result in a 6-month period of exclusivity only if the response to the
1040 WR results in an approved *supplemental application* for a new use.
1041
1042 • A new use is a use not included in the approved labeling of an approved drug.¹³¹ For
1043 example, expansion of the labeling to include a new pediatric population constitutes a
1044 new use.
1045

end of the patent term to block approval of that ANDA or 505(b)(2) application for an additional 6 months after the patent expires (*Ranbaxy Labs. v. FDA*).

¹²³ The Orange Book is available at <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm>.

¹²⁴ See section 505A(c) of the FD&C Act (21 U.S.C. 355a(c)).

¹²⁵ See section 505A(b) of the FD&C Act (21 U.S.C. 355a(b)).

¹²⁶ See section 505A(c) of the FD&C Act (21 U.S.C. 355a(c)).

¹²⁷ See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

¹²⁸ See section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)).

¹²⁹ See section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)).

¹³⁰ See section 505A(g) of the FD&C Act (21 U.S.C. 355a(g)).

¹³¹ See 21 CFR 99.3(g).

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- The supplement for a new use submitted in response to the second WR must qualify for 3-year exclusivity¹³² or no 6-month period of pediatric exclusivity will attach.
 - The second 6-month period of pediatric exclusivity attaches *only* to the 3-year exclusivity applied to the supplement for a new use containing the studies submitted in response to the second WR and not to any other exclusivity or patent protections applicable to the drug.
 - No more than two 6-month periods of exclusivity under the BPCA are possible for any specific drug product.

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c. Later-filed applications containing the same drug

In situations where a sponsor submits an application or supplement containing an active moiety for which the sponsor previously qualified for pediatric exclusivity, pediatric exclusivity does not attach to new (not previously listed) patents or exclusivity covering the later filed applications or supplements unless the subsequent drug product could not be labeled without the data that qualified the previously approved drug product for the prior pediatric exclusivity.¹³³

FDA notes that if pediatric exclusivity for which a drug product previously qualified has attached to a listed patent or exclusivity protecting the previously approved application that also protects the new application or new supplement held by the same sponsor, the pediatric exclusivity also attaches to that patent in conjunction with the new application or supplement.¹³⁴ For example, if a sponsor qualifies for a 6-month pediatric exclusivity that attaches to a 5-year exclusivity, that exclusivity attaches to each of the sponsor's NDAs protected by that 5-year exclusivity, regardless of when the new application or supplement is filed or what it contains. The following examples are provided:

- **Example 1** — Drug 1 (D1) qualifies for pediatric exclusivity. The sponsor or holder of an approved application for D1 later files a different application for a drug product containing D1 or a supplement to an existing application for a drug product containing D1. FDA does not need any of the data the sponsor or holder of an approved application submitted for pediatric exclusivity to approve the new application or new supplement. The pediatric exclusivity does not attach to any exclusivities or patents that apply solely to the new application or the new supplement.
- **Example 2** — D1 qualifies for pediatric exclusivity. The sponsor or holder of the approved application for D1 later files a different application for a drug product containing D1 or a supplement to an existing application for a drug product containing D1. The drug product could not be labeled with the data submitted in the later-filed applications or supplements without the data the sponsor or holder of an approved

¹³² See sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act (21 U.S.C. 355(c)(3)(E)(iv) and 21 U.S.C. (j)(5)(F)(iv)).

¹³³ See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

¹³⁴ See sections 505A(b)(1) and 505A(c)(1) of the FD&C Act (21 U.S.C. 355a(b)(1) and 21 U.S.C. 355a(c)(1)).

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1087 application previously submitted for pediatric exclusivity. The pediatric exclusivity
1088 attaches to any exclusivities or patents that apply to the new application or the new
1089 supplement. In addition, if the pediatric exclusivity attaches to a patent or exclusivity
1090 that also protects the new application or new supplement, the pediatric exclusivity applies
1091 to the new application or supplement to the same extent it applies to the previously
1092 approved application.

1093 1094 2. *Biological Products*

1095
1096 Pediatric exclusivity for biological products differs in some ways from provisions applicable to
1097 other drug products. First, as described below, pediatric exclusivity only attaches to reference
1098 product and orphan drug exclusivity periods. Second, unlike other drug products, pediatric
1099 exclusivity does not attach to patents for biological products.¹³⁵

1100
1101 Under section 351(k)(7)(A) of the PHS Act, approval of an application for a biosimilar or
1102 interchangeable biological product submitted under section 351(k) of the PHS Act may not be
1103 made effective until 12 years after the date on which the reference product was first licensed
1104 under section 351(a) of the PHS Act. Moreover, under section 351(k)(7)(B) of the PHS Act, an
1105 application for a biosimilar or interchangeable biological product submitted under section 351(k)
1106 of the PHS Act may not be submitted for review until 4 years after the date on which the
1107 reference product was first licensed under section 351(a) of the PHS Act. An additional 6-month
1108 period of pediatric exclusivity will attach to the 12- and 4-year periods if the sponsor meets the
1109 requirements for pediatric exclusivity pursuant to section 505A of the FD&C Act.¹³⁶
1110 Furthermore, an additional 6-month period of pediatric exclusivity will also attach to the 7 years
1111 of orphan drug exclusivity for a biological product designated under section 526 of the FD&C
1112 Act for a rare disease or condition.¹³⁷

1113 1114 1115 **V. ELEMENTS COMMON TO PREA AND THE BPCA**

1116 1117 **A. The Pediatric Review Committee**

1118
1119 Section 505C of the FD&C Act directed FDA to establish the PeRC that must review all WRs
1120 and all requests for deferrals, deferral extensions, and waivers.¹³⁸ The PeRC also provides
1121 consultation on pediatric assessments and on iPSPs, agreed iPSPs, and any significant
1122 amendments to such plans.¹³⁹

¹³⁵ See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

¹³⁶ See section 351(m) of the PHS Act (42 U.S.C. 262(m)).

¹³⁷ See section 527(a) of the FD&C Act and section 351(m) of the PHS Act (21 U.S.C. 360cc(a); 42 U.S.C. 262(m)).

¹³⁸ See sections 505C, 505A(f), and 505B(f) of the FD&C Act (21 U.S.C. 355d, 21 U.S.C. 355a(f), and 21 U.S.C. 355c(f)).

¹³⁹ See section 505B(f) of the FD&C Act (21 U.S.C. 355c(f)).

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1124 As a general matter, the PeRC also reviews significant amendments to WRs and PPSR
1125 inadequate letters to ensure consistency.

1126

1127 Members of the PeRC include FDA employees with expertise in pediatrics (including
1128 representation from the Office of Pediatric Therapeutics (OPT)), neonatology, biopharmacology
1129 (i.e., pharmacology/toxicology), statistics, chemistry, legal issues, pediatric ethics, the
1130 appropriate expertise pertaining to the pediatric drug under review, and other individuals as
1131 needed.¹⁴⁰ In addition to the responsibilities above, the PeRC also provides consultation on
1132 tracking information regarding pediatric assessments and labeling changes.¹⁴¹ As a general
1133 matter, members of the relevant drug review division provide background information to the
1134 PeRC and are present during the discussion of an application.

1135

B. Publishing Information About Pediatric Studies

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1. Pediatric Exclusivity Determinations

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1140 FDA posts on its website a list of exclusivity determinations on approved drugs that have
1141 qualified for pediatric exclusivity.¹⁴² FDA also publishes pediatric exclusivity information for
1142 drugs in the Patent and Exclusivity Information section of the Orange Book and its supplements
1143 in the same manner as FDA publishes information regarding 5-year exclusivity, 3-year
1144 exclusivity, patent listings, and orphan drug exclusivity.¹⁴³

1145

2. Medical, Statistical, and Clinical Pharmacology Reviews

1146

1147

1148 Sections 505A(k) and 505B(h) of the FD&C Act require that FDA publish the medical,
1149 statistical, and clinical pharmacology reviews of pediatric studies conducted under the BPCA
1150 and of pediatric assessments under PREA. For studies submitted in response to a WR, FDA
1151 must do so within 210 days after the submission.¹⁴⁴ For most pediatric assessments submitted
1152 under PREA, FDA must do so within 330 days after the submission.¹⁴⁵ FDA makes such

¹⁴⁰ See section 505C of the FD&C Act (21 U.S.C. 355d).

¹⁴¹ See sections 505A(f)(6) and 505B(f)(6) of the FD&C Act (21 U.S.C. 355a(f)(6) and 21 U.S.C. 355c(f)(6)).

¹⁴² See the FDA's Pediatric Exclusivity Granted web page at <https://www.fda.gov/drugs/development-resources/pediatric-exclusivity-granted>.

¹⁴³ See the Orange Book available at <https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

¹⁴⁴ See section 505A(k)(1) of the FD&C Act (21 U.S.C. 355a(k)(1)). For drug products for which exclusivity determinations were made before September 27, 2007, we have posted summaries of medical and clinical pharmacology reviews of studies conducted under section 505A of the FD&C Act, consistent with applicable BPCA requirements at that time.

¹⁴⁵ See section 505B(h)(1) of the FD&C Act (21 U.S.C. 355c(h)(1)). This provision of the law first went into effect on September 27, 2007.

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1153 information publicly available consistent with section 301(j) of the FD&C Act, the Freedom of
1154 Information Act, and the Trade Secrets Act.¹⁴⁶

1155
1156 Before disclosure, the medical, statistical, and clinical pharmacology reviews are redacted, as
1157 appropriate, for trade secret information and for confidential commercial information.¹⁴⁷

1158
1159 As FDA interprets section 505A(k) of the FD&C Act, the 210-day BPCA disclosure requirement
1160 is triggered when a sponsor or holder of an approved application submits an application or a
1161 supplement in response to a WR that FDA determines meets filing requirements (see section
1162 IV.C., How to Submit Study Reports in Response to a Written Request). FDA interprets the
1163 disclosure requirement to apply to such applications and supplements submitted in response to a
1164 WR under the BPCA, regardless of whether (1) the application process is completed or it is later
1165 withdrawn; (2) the drug qualifies for pediatric exclusivity; or (3) the application or supplement is
1166 approved or the sponsor receives a complete response letter. In addition, FDA interprets the
1167 disclosure requirement to apply to partial responses to a WR under the BPCA that meet the filing
1168 requirements. (See section IV.C., How to Submit Study Reports in Response to a Written
1169 Request, for a discussion of partial responses.)

1170
1171 *3. Other Pediatric Information*

1172
1173 FDA maintains a web page¹⁴⁸ containing extensive information about pediatric studies
1174 conducted under sections 505A and 505B of the FD&C Act. The web page includes, among
1175 other things, statistics and other information regarding the relevant studies, drugs, labeling
1176 changes, and reports. Statistics we post include the number of waivers, deferrals, and deferral
1177 extensions granted; the number of pediatric formulations developed; and the number of
1178 formulations not developed (including the reason they were not developed).¹⁴⁹ The web page
1179 also identifies drugs approved for use in a pediatric population for which a pediatric formulation

¹⁴⁶ See 5 U.S.C. 552 and 18 U.S.C. 1905.

¹⁴⁷ 21 CFR 314.430 is FDA's regulation regarding the public disclosure of information in a drug application or abbreviated application. 21 CFR 601.51 is FDA's regulation regarding the public disclosure of information in a biological product file. Under 21 CFR 314.430(b), we will not publicly disclose the existence of an application or abbreviated application before an approval or tentative approval letter is sent, unless the existence of the application or abbreviated application has been previously publicly disclosed or acknowledged. Under 21 CFR 601.51(b), we will not disclose the existence of a biological product file before the application has been approved if the existence of the file has not been previously publicly disclosed or acknowledged. Under 21 CFR 314.430(d)(1) and 601.51(d)(1), if the existence of the application or biological product file has been publicly disclosed or acknowledged, as a general matter, no data or information contained in the application, abbreviated application, or biological product file is available for public disclosure before we send an approval letter or before a license is issued. We note that 21 CFR 314.430 and 601.51 were promulgated before the passage of PREA and the BPCA and do not specifically discuss the disclosure of medical, statistical, and clinical pharmacology reviews of pediatric studies conducted under the BPCA and of pediatric assessments under PREA. As a general matter, FDA discloses such reviews only to the extent the drug product studied has already been approved. Additionally, the protected status of particular information in the reviews is determined on a case-by-case basis.

¹⁴⁸ See the Pediatric Reports, Statistics, Reviews, and Databases web page at <https://www.fda.gov/science-research/pediatrics/reports-statistics-reviews-and-databases>.

¹⁴⁹ See section 505B(f)(6) of the FD&C Act (21 U.S.C. 355c(f)(6)).

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1180 was developed and that qualified for pediatric exclusivity, but the formulation was not marketed
1181 within 1 year of the exclusivity determination.¹⁵⁰ FDA also maintains a web page containing
1182 information about section 409I of the PHS Act.¹⁵¹

1183
1184 A list of approved drugs for which WRs have been issued is published on the FDA website.¹⁵²
1185 In addition, WRs, including any amendment(s) if not otherwise incorporated into one document,
1186 are posted on the FDA website within 30 days of the determination that the requirements for
1187 exclusivity have been met.¹⁵³

1188
1189 Information from a required annual review following the granting of a deferral will be posted
1190 publicly within 90 days of submission.¹⁵⁴ The posting will include the information submitted
1191 through the annual review, the name of the applicant, the date on which the drug was approved,
1192 and the date of each deferral or deferral extension.¹⁵⁵

1193
1194 Finally, FDA posts guidances, relevant regulations, relevant presentations from conferences,
1195 press releases, and reports, among other information. Transcripts from Pediatric Advisory
1196 Committee meetings, beginning September 2004, are posted as well, as are transcripts from past
1197 meetings of the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory
1198 Committee, held between April 1999 and June 2004.¹⁵⁶ FDA intends to update these sites
1199 regularly.

1200

C. PREA and Pediatric Exclusivity

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1203 To qualify for pediatric exclusivity, the pediatric studies conducted to satisfy the requirements of
1204 PREA must be the subject of a WR and satisfy all other requirements for pediatric exclusivity

¹⁵⁰ See section 505A(e)(2) of the FD&C Act (21 U.S.C. 355a(e)(2)).

¹⁵¹ See the Off-Patent Studies Under BPCA web page at <https://www.fda.gov/drugs/development-resources/patent-studies-under-bpca>.

¹⁵² See the Written Requests Issued web page at <https://www.fda.gov/drugs/development-resources/written-requests-issued>. On occasion, information obtained by FDA subsequent to issuance of a WR causes FDA to rescind the WR. This list is not updated to indicate when a WR has been rescinded.

¹⁵³ See section 505A(e)(1) of the FD&C Act (21 U.S.C. 355a(e)(1)). See also the FDA's Pediatric Exclusivity Granted web page at <https://www.fda.gov/drugs/development-resources/pediatric-exclusivity-granted>.

¹⁵⁴ See section 505B(a)(4)(C)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)(ii)). See also FDA's Postmarket Requirements and Commitments web page at <https://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>.

¹⁵⁵ See section 505B(a)(4)(C)(ii) of the FD&C Act (21 U.S.C. 355c(a)(4)(C)(ii)).

¹⁵⁶ See <https://www.fda.gov/advisory-committees/pediatric-advisory-committee/past-meeting-materials-pediatric-advisory-committee>.

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1205 under the BPCA.¹⁵⁷ As discussed in section IV.A.2., Written Request Studies, FDA does not
1206 expect to issue WRs solely for studies or planned studies that are required under PREA.

1207
1208 For already marketed drugs, FDA may require pediatric assessments under PREA if it finds, for
1209 example, that the drug is used for a substantial number of pediatric patients for the labeled
1210 indications and adequate pediatric labeling could confer a benefit on pediatric patients.¹⁵⁸ In
1211 some cases, FDA may first issue a WR under section 505A of the FD&C Act before requiring
1212 studies under section 505B(b). In those cases, if the sponsor declines the WR for the labeled
1213 indication(s), FDA may still require those studies under PREA.¹⁵⁹

1214
1215 It is important to note the distinction between the scope of the studies FDA requests under the
1216 BPCA and those required under PREA. The scope of studies described in a WR may be broader
1217 than those required under PREA. FDA’s authority to issue a WR extends to the use of an active
1218 moiety for indications that may produce health benefits in the pediatric population, regardless of
1219 whether it has previously approved the indications in adults.¹⁶⁰ Under PREA, pediatric
1220 assessments are required only for those indications the sponsor has included in the pending
1221 application.¹⁶¹ To learn more about eligibility for pediatric exclusivity, see section IV., Best
1222 Pharmaceuticals for Children Act, or contact the relevant review division.

1223

D. Considerations for Labeling of Drug Products

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1. Labeling Study Results

1225

1226 Study results submitted in response to PREA or a WR must be described in labeling regardless of
1227 whether these findings support safety and/or effectiveness, do not support safety and/or

1228

1229

¹⁵⁷ See sections 505A(b)(1), 505A(c)(1), 505A(d) and 505A(h) of the FD&C Act (21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), 21 U.S.C. 355a(d), and 21 U.S.C. 355a(h)).

¹⁵⁸ See section 505B(b)(1) of the FD&C Act (21 U.S.C. 355c(b)(1)).

¹⁵⁹ See section 505B(b) of the FD&C Act (21 U.S.C. 355c(b)). This section states that the Secretary may require a sponsor or holder of an approved application to submit pediatric assessments as described under section 505B(a)(2) of the FD&C Act if the Secretary finds that “(A) (i) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and (ii) adequate pediatric labeling could confer a benefit on pediatric patients; (B) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for 1 or more of the claimed indications; or (C) the absence of adequate pediatric labeling could pose a risk to pediatric patients.”

¹⁶⁰ See sections 505A(a), 505A(b)(1), 505A(c)(1), and 505A(d)(1)(B) of the FD&C Act (21 U.S.C. 355a(a); 21 U.S.C. 355a(b)(1), 21 U.S.C. 355a(c)(1), and 21 U.S.C. 355a(d)(1)(B)).

¹⁶¹ See sections 505B(a)(1)(A) and 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(1)(A) and 21 U.S.C. 355c(a)(2)). Note, however, that molecularly targeted pediatric cancer investigations are based on molecular mechanism of action rather than clinical indication. See sections 505B(a)(1)(B) and 505B(a)(3) of the FD&C Act (21 U.S.C. 355c(a)(1)(B) and 21 U.S.C. 355c(a)(3)). For additional information, see the guidance for industry *FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act*.

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1230 effectiveness, or are inconclusive.¹⁶² If a full or partial waiver is granted because there is
1231 evidence that a drug would be unsafe or ineffective in pediatric populations, applicants must
1232 include this information in labeling.¹⁶³

1233

1234 Applicants must distribute information to health care providers describing any labeling changes
1235 that are approved as a result of these studies as required by FDA.¹⁶⁴

1236

1237 2. *Dispute Resolution*

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1239 The BPCA and PREA provide for a dispute resolution process when FDA and the applicant fail
1240 to agree on appropriate labeling changes.¹⁶⁵ If the applicant does not agree within the specified
1241 time period after FDA's request to make labeling changes, FDA must refer the matter to the
1242 Pediatric Advisory Committee (PAC).¹⁶⁶ The PAC then has 90 days after receiving the referral
1243 to review the pediatric study reports and make a recommendation to FDA.¹⁶⁷ FDA will consider
1244 the recommendation, and, if appropriate, within 30 days after receiving the recommendation,
1245 make a request to the applicant to make the labeling changes FDA determines to be
1246 appropriate.¹⁶⁸ If the applicant fails to agree to make the labeling changes within 30 days after
1247 receiving such a request, the drug may be deemed misbranded.¹⁶⁹

1248

1249 3. *Priority Review of Applications and Labeling Supplements*

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1251 Any application or supplement to an application that proposes a labeling change as a result of
1252 pediatric studies a sponsor conducts under section 505A of the FD&C Act will be considered a
1253 priority application or supplement.¹⁷⁰ This priority status applies even if the studies submitted

¹⁶² See sections 505A(j) and 505B(g)(2) of the FD&C Act (21 U.S.C. 355a(j) and 21 U.S.C. 355c(g)(2)). See also the guidance for industry *Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling*.

¹⁶³ See section 505B(a)(5)(D) of the FD&C Act (21 U.S.C. 355c(a)(5)(D)).

¹⁶⁴ See sections 505A(k)(2) and 505B(h)(2) of the FD&C Act (21 U.S.C. 355a(k)(2) and 355c(h)(2)).

¹⁶⁵ See sections 505A(i)(2) and 505B(g)(1) of the FD&C Act (21 U.S.C. 355a(i)(2) and 355c(g)(1)).

¹⁶⁶ See sections 505A(i)(2)(A) and 505B(g)(1)(A) of the FD&C Act (21 U.S.C. 355a(i)(2)(A) and 355c(g)(1)(A)).

¹⁶⁷ See sections 505A(i)(2)(B) and 505B(g)(1)(B) of the FD&C Act (21 U.S.C. 355a(i)(2)(B) and 355c(g)(1)(B)).

¹⁶⁸ See sections 505A(i)(2)(C) and 505B(g)(1)(C) of the FD&C Act (21 U.S.C. 355a(i)(2)(C) and 355c(g)(1)(C)).

¹⁶⁹ See sections 505A(i)(2)(D) and 505B(g)(1)(D) of the FD&C Act (21 U.S.C. 355a(i)(2)(D) and 355c(g)(1)(D)).

¹⁷⁰ See section 505A(i)(1) of the FD&C Act (21 U.S.C. 355a(i)(1)). This priority review provision applies only to applications and supplements containing studies conducted under section 505A of the FD&C Act; it does not apply to an application or supplement solely because it contains pediatric information. Note that NDAs and BLAs may be otherwise eligible for priority review. For information on Prescription Drug User Fee Act VI performance goals and procedures, see <https://www.fda.gov/industry/fda-user-fee-programs/prescription-drug-user-fee-amendments>.

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1254 did not respond completely to the WR or did not otherwise qualify for pediatric exclusivity.¹⁷¹
1255 Applications that include a pediatric assessment submitted with the sole intention of responding
1256 to PREA requirements do not necessarily receive priority review.

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1258 For more information about priority review, see FDA’s Prescription Drug User Fee Act
1259 reauthorization performance goals and procedures document.¹⁷²

E. Adverse Event Reporting for Drug Products Subject to the BPCA and PREA

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1263 At the same time that a sponsor submits reports of studies responding to a WR, the sponsor must
1264 also provide FDA with all available postmarketing adverse event reports regarding the studied
1265 drug.¹⁷³ The format of the postmarketing adverse event report should follow the model for a
1266 periodic safety update report described in the ICH guidance for industry *E2C(R2) Periodic*
1267 *Benefit-Risk Evaluation Report (PBRER)* (July 2016). In addition, the sponsor may contact the
1268 review division for further information.

1269
1270 Eighteen months after the date of a labeling change made to reflect studies conducted under
1271 PREA or the BPCA, the applicable center refers to OPT a report of all adverse events received
1272 by FDA for the drug product.¹⁷⁴ As a general matter, OPT presents a report and analysis to the
1273 PAC, and the PAC reviews this analysis and recommends whether additional monitoring (other
1274 than the usual surveillance) is necessary. When the PAC considers additional monitoring
1275 necessary after the 18-month period, the center generally continues to refer adverse event reports
1276 to OPT.

VI. ADDITIONAL INFORMATION

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1278
1279 The Division of Pediatrics and Maternal Health can provide general information about
1280 complying with PREA and the BPCA. Additional pediatric information and contact information
1281 is available on the Pediatric Product Development web page.¹⁷⁵
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¹⁷¹ See section 505A(i)(1) of the FD&C Act (21 U.S.C. 355a(i)(1)).

¹⁷² See PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 Through 2017 at <https://www.fda.gov/media/81306/download>.

¹⁷³ See section 505A(d)(2)(B) of the FD&C Act (21 U.S.C. 355a(d)(2)(B)).

¹⁷⁴ See sections 505A(l) and 505B(i) of the FD&C Act (21 U.S.C. 355a(l) and 355c(i)).

¹⁷⁵ Available at <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>.

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GLOSSARY

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Assessment — Contains data, gathered using appropriate formulations for each age group for which the assessment is required, that are adequate to assess the safety and effectiveness as well as support the dosing and administration of a drug product for each relevant pediatric age group (see section 505B(a)(2) of the FD&C Act (21 U.S.C. 355c(a)(2))).

Certify/Certification — In general, a certification is a statement from the applicant that the data provided to support a deferral¹ and/or waiver² request are accurate and complete.

Deferral — Defers submission of some or all of the required assessments or reports on the molecularly targeted pediatric cancer investigation until a specified date (see section 505B(a)(4) of the FD&C Act (21 U.S.C. 355c(a)(4))).

Pediatric Study Plan (PSP) — An outline of planned pediatric studies, along with any deferral and/or waiver requests, that is submitted by a sponsor for an application subject to PREA before the submission of assessments or reports on the molecularly targeted pediatric cancer investigation (see section 505B(e) of FD&C Act (21 U.S.C. 355c(e))). For more information, see the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans* (July 2020).³

Proposed Pediatric Study Request (PPSR) — In general, a PPSR is a submission describing what pediatric studies a sponsor or application holder believes will yield information about the use of a drug that may produce health benefits in the pediatric population.

Molecularly Targeted Pediatric Cancer Investigation — An investigation of a drug described in section 505B(a)(1)(B) of the FD&C Act that must be designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling (see section 505B(a)(3) of the FD&C Act (21 U.S.C. 355c(a)(3))).

Waiver — Waives the requirement to submit assessments or reports on the molecularly targeted pediatric cancer investigation for the entire pediatric population or specific age group(s) (see section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5))).

Written Request (WR) — In general, a WR is a document from FDA, signed by the applicable office director(s), requesting submission of a certain study or studies to determine whether the use of a drug could provide a meaningful health benefit in the pediatric population that is issued under section 505A of the FD&C Act (21 U.S.C. 355a) or section 351(m) of the PHS Act (42 U.S.C. 262(m)).

¹ See section 505B(a)(4)(A)(ii)(I) of the FD&C Act (21 U.S.C. 355c(a)(4)(A)(ii)(I)).

² See section 505B(a)(5) of the FD&C Act (21 U.S.C. 355c(a)(5)).

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.