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# **FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry**

## ***DRAFT GUIDANCE***

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For questions regarding this draft document, contact (OCE/CDER) Gregory Reaman at 301-796-0785 or [Gregory.Reaman@fda.hhs.gov](mailto:Gregory.Reaman@fda.hhs.gov), or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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

**December 2019  
Procedural**

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# **FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry**

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*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

**FDARA Implementation Guidance for Pediatric Studies of Molecularly Targeted Oncology Drugs: Amendments to Sec. 505B of the FD&C Act Guidance for Industry<sup>1</sup>**

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

**I. INTRODUCTION**

The purpose of this guidance is to provide the pharmaceutical industry, clinical investigators, and institutional review boards (IRBs) with information to facilitate pediatric studies of molecularly targeted (also referred to as “targeted” in this guidance) oncology drugs.<sup>2</sup> This guidance addresses early planning for pediatric evaluation of certain molecularly targeted oncology drugs for which original New Drug Applications (NDAs) and Biologics License Applications (BLAs) are expected to be submitted to the FDA on or after August 18, 2020 in accordance with section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (also referred to as the Pediatric Research Equity Act, or PREA) as amended by the FDA Reauthorization Act of 2017 (FDARA).<sup>3</sup>

This guidance addresses the implementation of amendments made by FDARA section 504 to section 505B of the FD&C Act regarding molecularly targeted oncology drugs. This guidance does not contain a complete discussion of general requirements for development of drugs for pediatric use under PREA or section 505A of the FD&C Act (also referred to as the Best Pharmaceuticals for Children Act or BPCA).

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

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<sup>1</sup> This guidance has been prepared by the Oncology Center of Excellence in cooperation with the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> For purposes of this guidance, references to drugs and drug products include drugs approved under section 505 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355) and biological products licensed under section 351 of the Public Health Service Act (42 U.S.C. 262).

<sup>3</sup> Public Law 115-52, 131 Stat. 1005 (August 18, 2017).

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### 39 **II. BACKGROUND**

40  
41 Section 504 of FDARA amended section 505B of the FD&C Act to require—for original  
42 applications submitted on or after August 18, 2020—pediatric investigations of certain targeted  
43 cancer drugs with new active ingredients, based on molecular mechanism of action rather than  
44 clinical indication. Specifically, if an original NDA or BLA is for a new active ingredient, and  
45 the drug that is the subject of the application is intended for treatment of an adult cancer and  
46 directed at a molecular target FDA determines to be substantially relevant to the growth or  
47 progression of a pediatric cancer, reports on the molecularly targeted pediatric cancer  
48 investigation required under section 505B(a)(3) of the FD&C Act must be submitted with the  
49 marketing application, unless the required investigations are waived or deferred.<sup>4</sup> FDARA thus  
50 created a mechanism to require evaluation of certain novel drugs that may have the potential to  
51 address an unmet medical need in the pediatric population (i.e., children ages 0-2 years, 2-11  
52 years and adolescents ages 12-<17 years).<sup>5</sup> Timely investigation in pediatric patients of the  
53 antitumor activity of potentially effective targeted drugs under development in adults, and of  
54 those drugs' toxicities relative to the unique growth and developmental considerations of  
55 pediatric patients, is intended to accelerate early pediatric evaluation of these products and  
56 ultimately facilitate development of appropriate new therapies for pediatric patients.  
57

58 Advances in the understanding of the molecular etiology and genetic epidemiology of human  
59 cancer have transformed the paradigm of cancer drug development; molecularly targeted drugs  
60 have advanced the concept of precision medicine in oncology. However, the extension of this  
61 scientific development to pediatric cancers has been both delayed and limited due in part to the  
62 fact that the requirements for pediatric assessments of new cancer drugs have historically been  
63 based on indication (i.e., requirements for assessment of the safety and effectiveness of a drug  
64 for intended or approved indications in relevant pediatric subpopulations). Often, the types of  
65 cancers in pediatric patients and adults differ in etiology, biology, organ of origin, and natural  
66 history, which could result in pediatric trials not being required under the pre-FDARA iteration  
67 of PREA (e.g., if the requirements were waived because the drug in question was being  
68 developed for a cancer that rarely or never occurs in children, thereby making the necessary  
69 studies impossible or highly impracticable). In addition, new drugs developed for rare cancers  
70 which do occur in both adults and pediatric patients are generally exempt from PREA  
71 assessment requirements under section 505B(a)(1)(A) because they are for indications for  
72 which orphan designation has been granted (see section 505B(k)(1) of the FD&C Act).  
73

74 However, malignancies occurring in children and adolescents can harbor the same molecular  
75 abnormalities as those found in adult cancers, and therefore, many new targeted oncology drugs  
76 may prove effective in the treatment of pediatric patients with cancer, even if the adult cancer  
77 indication does not occur in the pediatric population. Large scale pediatric cancer genome  
78 sequencing efforts, such as the National Cancer Institute's Therapeutically Applicable Research

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<sup>4</sup> Sections 505B(a)(1)(B) and 505B(a)(3)(C) of the FD&C Act.

<sup>5</sup> The amendments to 505B of the FD&C Act made by FDARA section 504 are sometimes referred to as The Research Acceleration for Cure and Equity (RACE) for Children Act.

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79 to Generate Effect Treatments (TARGET) program<sup>6</sup>, the Pediatric Cancer Genome Project<sup>7</sup>,  
80 and the International Cancer Genome Consortium’s PedBrain Tumor<sup>8</sup> and ICGC-MMML-seq<sup>9</sup>  
81 projects provide evidence that the genetic and epigenetic repertoires of driver gene aberrations  
82 may differ between adult and pediatric cancers. A growing body of evidence suggests that  
83 genetic and other molecular biological vulnerabilities of certain adult cancers also exist in  
84 pediatric cancers.<sup>10,11</sup> Up to 50% of pediatric cancers have been reported to harbor a potentially  
85 druggable event, i.e. a molecular abnormality which can be potentially addressed by a targeted  
86 drug already approved for use in adults.<sup>12</sup>

87  
88 Section 505B of the FD&C Act, as amended by FDARA, requires that any **original** NDA or  
89 BLA submitted on or after August 18, 2020, for a new active ingredient, must contain reports of  
90 molecularly targeted pediatric cancer investigations described in section 505B(a)(3) of the  
91 FD&C Act, unless a deferral or waiver of that requirement is granted, if the drug that is the  
92 subject of the application is:

- 93 (1) intended for the treatment of an adult cancer, and  
94 (2) directed at a molecular target that the Secretary determines to be substantially relevant  
95 to the growth or progression of a pediatric cancer.<sup>13</sup>

96  
97 This requirement for pediatric investigations applies even if the adult cancer indication does not  
98 occur in the pediatric population, and, per section 505B(k)(2) of the FD&C Act, even if the drug  
99 is for an adult indication for which orphan designation has been granted.

100  
101 The statute directs FDA, in consultation with the National Cancer Institute (NCI), members of  
102 the internal committee established under section 505C of the FD&C Act, and the Pediatric  
103 Oncology Subcommittee of the Oncologic Drugs Advisory Committee, to establish, publish,  
104 and regularly update a list of molecular targets considered, on the basis of data the Agency  
105 determines to be adequate, to be substantially relevant to the growth or progression of a  
106 pediatric cancer, and that may trigger the requirements for pediatric investigations under PREA  
107 (see sections 505B(m)(1)(A) and 505B(m)(2) of the FD&C Act). Molecular targets that are  
108 considered “not substantially relevant” to the growth or progression of pediatric cancers and  
109 that would warrant a waiver of pediatric study requirements under PREA constitute a second  
110 list (see section 505B(m)(1)(B) of the FD&C Act) (see section III.C for more information

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<sup>6</sup> For additional information, see <https://ocg.cancer.gov/programs/target> (accessed October 8, 2019).

<sup>7</sup> For additional information, see <https://www.stjude.org/research/pediatric-cancer-genome-project.html> (accessed October 8, 2019).

<sup>8</sup> For additional information, see <http://www.pedbraintumor.org/icgc/index.php/ct-menu-item-7> (accessed October 8, 2019).

<sup>9</sup> For additional information, see <https://icgc.org/icgc/cgp/64/345/53049> (accessed October 8, 2019).

<sup>10</sup> Gröbner SN, Worst BC, Weischenfeldt J, et.al., 2018, The Landscape of Genomic Alterations Across Childhood Cancers, *Nature*, 555:321-327.

<sup>11</sup> Ma X, Liu Y, Liu Y, et. al., 2018, Pan-Cancer Genome and Transcriptome Analyses of 1,699 Paediatric Leukaemias and Solid Tumours, *Nature*, 555:371-376.

<sup>12</sup> See footnotes 10 and 11.

<sup>13</sup> Section 505B(a)(1)(B) of the FD&C Act.

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111 regarding the lists). FDA sometimes refers to these as “The Relevant Molecular Target List”  
112 and “The Non-Relevant Molecular Target Leading to Waiver List,” respectively. The statute  
113 neither stipulates that a molecular target to which a specific drug is directed must appear on  
114 The Relevant Molecular Target List to require a clinical evaluation of the drug in the pediatric  
115 population nor specifies that the presence of a target on the relevant target list in itself  
116 constitutes a requirement for a clinical study. The lists are a guide to sponsors as they consider  
117 development plans for new targeted drugs and early pediatric assessments in light of the  
118 amended PREA provisions.

119  
120

### **121 III. REGULATORY CONSIDERATIONS<sup>14</sup>**

122  
123

#### **A. Molecular Target**

124  
125

126 For purposes of section 505B of the FD&C Act, the Agency interprets a “molecular target” in  
127 cancer drug development as a molecule in human cells (normal or cancer cells) that is  
128 intrinsically associated with a particular malignant disease process such as etiology, progression,  
129 and/or drug resistance. For a molecule to be considered a molecular target for purposes of  
130 section 505B, there should be evidence that addressing the molecule with a drug produces a  
131 predictable therapeutic effect resulting in alteration of the disease process.

132  
133

#### **B. Factors Considered in the Determination of Relevance**

134  
135

136 FDA intends to consider the totality of evidence when determining whether a molecular target is  
137 substantially relevant to the growth or progression of pediatric cancer. A specific or minimum  
138 evidence standard for determining target relevance is not feasible because of the different classes  
139 and characteristics of molecular targets, variability in available evidence base among targets, and  
140 continued emerging science. FDA is responsible for determining whether a molecular target is  
141 substantially relevant for purposes of section 505B of the FD&C Act. Molecular targets that lack  
142 sufficient evidence for FDA to determine whether they are “substantially relevant” or “not  
143 substantially relevant” will not be included in a target list, however, the lists will be updated  
144 regularly to reflect additional determinations regarding the relevance of molecular targets.

145  
146

147 One or more of the following may, as appropriate, inform FDA’s determination that a molecular  
148 target is substantially relevant for purposes of section 505B:

- 149 • The target has been identified in a cancer which occurs in pediatric patients. For  
150 targets within a cancer cell lineage, the target is intrinsically or differentially  
expressed in the cancer of interest compared to normal site-specific tissues.
- The biological function of the target is relevant to the etiology, growth, and survival  
of a cancer that occurs in pediatric patients. For a gene abnormality, modulation of

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<sup>14</sup> While this guidance focuses on requirements under PREA, FDA also intends to take into account certain of the considerations described in this section of the guidance (e.g., considerations relating to whether a molecular target is substantially relevant to the growth or progression of a pediatric cancer and those relating to innovative study designs for rare cancers), as appropriate, to streamline and improve the Written Request process under section 505A of the FD&C Act, including amendments to Written Requests.

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- 151 the affected gene product or a critical downstream pathway or correction/deletion of  
152 the affected gene defect adversely affects cancer cells.
- 153 • Non-clinical in vitro or in vivo evidence supports relevance of the target in one or  
154 more cancers in pediatric patients.
    - 155 ○ In vitro activity: Target modulation shows in vitro selectivity for cancer cell lines  
156 containing/expressing the molecular target compared to the sensitivity of cell lines  
157 not containing/expressing the target
    - 158 ○ In vivo activity: Target modulation shows in vivo activity manifested as tumor  
159 stabilization or regression in models of pediatric cancers with the molecular target  
160 of interest or relevant adult cancer models
    - 161 ○ In vitro or in vivo activity of drugs in combination: When single agents do not  
162 result in target modulation, support for substantial relevance may be found in  
163 evidence for additive or synergistic activity when an agent which effects target  
164 modulation is used as part of a biologically rational combination in appropriate  
165 model systems.
  - 166 • Clinical activity in adults with specific cancers, for which direct evidence  
167 demonstrates that target modulation by investigational drugs is known to affect tumor  
168 growth
  - 169 • Biomarkers expressed by tumor cells of cancers that occur in pediatric patients and  
170 that may predict response to target modulation may contribute to the concept of  
171 substantial relevance and also be useful in selection of the appropriate pediatric study  
172 population.

173  
174 Data from a non-clinical evaluation of a drug that interferes with a known molecular target in a  
175 pediatric-specific model system can contribute evidence for determining the target's relevance to  
176 a cancer which occurs in pediatric patients. Therefore, every effort should be made to initiate  
177 pediatric non-clinical investigations early in the development timeline.

178  
179 FDA may determine available evidence demonstrates that a molecular target is not substantially  
180 relevant to the growth or progression of pediatric cancer based on, for example, the absence of a  
181 biologic rationale for a specific target's function as an oncogenic driver, or a lineage associated  
182 target that is not a component of a pediatric cancer cell, or pre-clinical data that demonstrates no  
183 tumor cell growth effect by inhibition of the target.

184  
185 The lists may be updated based on information from, for example, semi-annual public workshops  
186 or meetings, including meetings of the Pediatric Subcommittee of the Oncologic Drugs Advisory  
187 Committee. In addition, the Federal Register Notice [Docket No. FDA-2018-N-3633] published  
188 on October 17, 2018 announced the opening of a docket to allow public comment with respect to  
189 possible additions to or deletions from the existing lists.

### **C. Target Lists**

#### *1. The Relevant Molecular Target List*

190  
191  
192  
193  
194  
195 The list includes molecular targets for which adequate data exist to determine their substantial  
196 relevance to the growth or progression of one or more pediatric cancers. Categories include, for



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197 example:

198

199

- Targets Related to Specific Gene Abnormalities

200

- Targets Associated with Cell Lineage Determinants

201

- Targets on Normal Immune Cells and Cellular Components of the Tumor

202

Microenvironment

203

- Other Targets Associated with Specific Pathways or Functional Mechanisms of Normal and/or Malignant Cells.

204

205

206

### *2. The Non-Relevant Molecular Target Leading to Waiver List*

207

208 The list includes molecular targets of new cancer drugs in development for which pediatric  
209 cancer study requirements under PREA will be automatically waived. This includes targets for  
210 which there is adequate data to determine that the targets are not substantially relevant to the  
211 growth or progression of one or more pediatric cancers. FDA anticipates that it will agree with  
212 sponsors' plans (as outlined in their iPSPs) to request full waivers for pediatric evaluation of  
213 oncology drugs with a molecular target that is on the Non-Relevant Molecular Target Leading to  
214 Waiver List.

215

216 These lists are available at the following link: [Molecular Target Lists](#).

217

### **D. Content of the Initial Pediatric Study Plan (iPSP) and Description of Recommended Studies**

218

219

220

221 Section 505B(e) of the FD&C Act requires applicants subject to PREA to submit an initial  
222 pediatric study plan prior to the submission of an NDA or BLA.<sup>15</sup> Prior to the enactment of  
223 FDARA, which added section 505B(a)(1)(B) and 505B(a)(3) to the FD&C Act, the pediatric  
224 study plans for oncology drugs were generally proposals to request waivers for pediatric  
225 assessments because the adult cancer indications for which a drug was developed often did not  
226 occur or occurred only rarely in pediatric patients, making pediatric studies impossible or  
227 highly impracticable.<sup>16</sup> An extensive list of cancer diagnoses occurring almost exclusively in  
228 adults thus is included in a list of adult-related conditions that qualify for a waiver because they  
229 rarely or never occur in pediatrics.<sup>17</sup> The provisions for PREA mandated studies for oncology  
230 drugs under section 505B(a)(1)(B), however, require that certain oncology drugs for adult  
231 cancer indications be studied based not on clinical indication, but rather on the molecular  
232 mechanism of action of the investigational drug. Therefore, original applications for a new  
233 active ingredient that are submitted on or after August 18, 2020, and for which the drug that is  
234 the subject of the application is intended for the treatment of an adult cancer and is directed at a  
235 molecular target determined to be substantially relevant to the growth or progression of a

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<sup>15</sup> See sections 505B(a)(1)(A), 505B(a)(1)(B), and 505B(e)(1) of the FD&C Act.

<sup>16</sup> See section 505B(a)(5) of the FD&C Act.

<sup>17</sup> See the list of "Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics" at <https://www.fda.gov/media/101440/download>.

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236 pediatric cancer must include reports of molecularly targeted pediatric cancer investigations  
237 (which were described in an iPSP under section 505B(e) of the FD&C Act), unless a deferral or  
238 waiver is granted.<sup>18</sup> Sponsors are advised of the opportunity to seek early interaction with  
239 FDA to address their pediatric development. Questions can be addressed to the Pediatric  
240 Oncology Program in the FDA’s Oncology Center of Excellence.

241

### *1. iPSP content*

242

243 Details of the required iPSP contents and format can be found in section 505B(e)(2)(B) of the  
244 FD&C Act. Additionally, FDA has issued a draft guidance for industry, *Pediatric Study Plans:  
245 Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial  
246 Pediatric Study Plans* (the Draft iPSP Guidance). Once finalized, the Draft iPSP guidance will  
247 describe, among other things, FDA’s recommendations regarding iPSP content. An iPSP for a  
248 molecularly targeted oncology drug should include the following elements:  
249

250

- 251 • Description of the cancer(s) in the pediatric population for which the drug warrants  
252 early evaluation
- 253 • Overview of the drug product
- 254 • Overview of planned extrapolation of effectiveness to the pediatric population
- 255 • Planned request for drug-specific waivers and partial waivers with justification
- 256 • Planned request for deferrals of pediatric studies
- 257 • Tabular summary of proposed non-clinical and clinical studies
- 258 • Age-appropriate formulation including details of existing/planned excipients
- 259 • Non-clinical proof-of-concept studies; planned and completed
- 260 • Data to support clinical studies in pediatric patients
- 261 • Planned pediatric clinical study(ies)
- 262 • Timeline of pediatric development plan
- 263 • Agreements for pediatric studies with other regulatory agencies

264

### *2. Description of recommended studies to be included*

265

266 Studies to be described in the iPSP under section 505B(e) of the FD&C Act should evaluate  
267 dosing whether based on PK or PK-based modeling, safety, and preliminary efficacy. Trials  
268 should typically be non-hypothesis testing, single-arm studies using standard response  
269 assessments such as overall response rate and duration of response at a minimum.  
270

271

272 Objectives of the studies described in the iPSP under section 505B(e) of the FD&C Act should  
273 include the following:

274

- 275 • Evaluating tolerability and identifying dose limiting toxicities in pediatric patients.
- 276 • Evaluation of PK across various age groups as appropriate.
- 277 • Definition of the pediatric Recommended Phase 2 Dose(s) (RP2D).

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<sup>18</sup> See section 505B(a)(1)(B) of the FD&C Act.

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- 278           • Assessment of activity (defined as overall response rate (ORR)) across the entire  
279 study population, in biomarker enriched population(s), in pre-specified disease  
280 cohorts, or in adaptive design settings, successively opened disease cohorts as  
281 evidence of activity warrants.

282  
283 Sample size may vary but should support the study objectives. Factors to consider should  
284 include the frequency of the molecular target expected across pediatric cancers in general and/or  
285 within a specified histology or sub-type, the number of dose levels to be evaluated to identify a  
286 recommended pediatric dose, and statistical considerations including estimated response rate that  
287 would support further development.

288  
289 More definite evaluation of a product, if warranted based upon the initial pediatric evaluation  
290 described in the iPSP, may be the subject of a Proposed Pediatric Study request (PPSR).  
291 Following review of the PPSR and discussions with the sponsor, FDA may issue a Written  
292 Request, if appropriate.<sup>19</sup>

293  
294 Early in the development of the iPSP, sponsors are encouraged to collaborate and seek advice  
295 from recognized subject matter experts, including those involved in clinical trial networks and  
296 academic investigators, to develop an appropriate non-clinical rationale for the iPSP and to  
297 facilitate scientifically rigorous study designs in clinically relevant diagnoses or subgroups of  
298 patients with the same diagnosis, or groups defined by biomarker detection of the target of  
299 interest irrespective of specific diagnosis. If evaluation of the investigational drug is expected  
300 to be performed in a biomarker-enriched or restricted population, early discussion with FDA’s  
301 Center for Devices and Radiological Health (CDRH) is encouraged regarding Investigational  
302 Device Exemptions and the use of companion or complementary diagnostics.

303  
304           3.     *Early advice on pediatric development meetings for oncology projects subject to*  
305                 *the amended provisions of section 505B of the FD&C Act*  
306

307 Sponsors planning to submit applications on or after August 18, 2020, or sponsors who are  
308 uncertain of their submission date, may request a meeting<sup>20</sup> with the Oncology Center of  
309 Excellence Pediatric Oncology Program and members of the Oncology Subcommittee of the  
310 Pediatric Review Committee (PeRC) through the appropriate review division or office, to assist  
311 with development of the iPSP. These meetings are intended to provide an opportunity to discuss  
312 the Agency’s current thinking about the relevance of a specific target and the expectations for  
313 early assessment in the pediatric population unless justification for a waiver or deferral can be  
314 provided. The cover letter for these meeting requests should clearly state “REQUEST FOR  
315 FDARA iPSP MEETING.” Please contact the review division or office for any questions  
316 regarding these meetings.<sup>21</sup>

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<sup>19</sup> For additional information regarding Written Requests, see section 505A of the FD&C Act; 21 U.S.C. 355a.

<sup>20</sup> See section 505B(e)(2)(C)(i)(I) of the FD&C Act, added by section 503 of FDARA, which describes early meetings on pediatric study plans for drugs intended to treat a serious or life-threatening disease or condition.

<sup>21</sup> Sponsors should consult FDA’s guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*, when finalized, to help ensure open lines of dialogue before and during their drug development process. When final, this guidance will represent the FDA’s current thinking on this topic.

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### 317 **E. Additional Consideration for Rare Cancers**

318  
319 Given the challenges of stand-alone trials of investigational drugs in pediatric patients with a rare  
320 cancer associated with a specific molecular target, FDA encourages innovation in study design  
321 and encourages sponsors to request feedback from FDA about any planned clinical trials for such  
322 investigational drugs. In situations where a conventionally designed pediatric trial may be  
323 inefficient and extremely difficult to conduct given the scarcity of affected pediatric patients, the  
324 following scenarios may provide options to maintain the objective of early pediatric assessment  
325 of drugs directed at substantially relevant targets and satisfy requirements of section 505B of the  
326 FD&C Act:

#### 327 328 1. *Pediatric cohorts in existing adult trials*

329  
330 When a target being investigated in an adult clinical trial also occurs in a specific pediatric  
331 tumor(s), sponsors may consider including a pediatric cohort during the expansion phase of a  
332 clinical trial. Including a pediatric cohort in an existing adult trial allows for the inclusion of a  
333 specific pediatric population earlier in development of a targeted drug without having to open an  
334 entirely new pediatric trial. This allows sponsors to use already existing clinical sites and  
335 resources of the ongoing clinical trial, thus minimizing the resources and infrastructure required  
336 to study the targeted drug in the pediatric population.<sup>22, 23</sup>

#### 337 338 2. *Embedded pediatric trials*

339  
340 Embedding pediatric trials within an existing trial in adults may be particularly useful for the  
341 evaluation of drugs with a molecular target that is rare in the pediatric population. Embedding a  
342 pediatric trial within an adult trial could leverage resources of pre-existing global studies at  
343 multiple sites, improving enrollment. The embedded study could also take advantage of existing  
344 infrastructure arrangements (e.g., adding a sub-investigator rather than initiating a new study,  
345 having consistent personnel) within study sites for adult patients.

#### 346 347 3. *Adolescent patients*

348  
349 When the molecular target of the drug is relevant to cancers in both adult and adolescent  
350 patients, sponsors may consider including adolescent patients by lowering the age requirement  
351 for enrollment. Systemic exposure and clearance of drugs are generally similar in adolescent and  
352 adult patients after taking into account the effect of body size on pharmacokinetics. Inclusion of  
353 adolescents in adult trials would allow those patients access to investigational drugs with

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<sup>22</sup> See draft guidance for industry *Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics* (August 2018). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>23</sup> See draft guidance for industry *Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients* (March 2019). When final, this guidance will represent the FDA's current thinking on this topic.

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354 potential for benefit and generate clinical trial data in this population that could be included in  
355 prescribing information for safe and effective use at the time of approval.<sup>24</sup>

356  
357 In some instances, efficacy in adolescent patients may be extrapolated from adult data; however,  
358 adequate approaches to evaluate safety in this population are required.<sup>25</sup>

### 359 360 4. *Tissue/histology agnostic development*

361  
362 Tissue agnostic studies may facilitate the development of targeted therapies in multiple pediatric  
363 cancers with shared genetic aberrations (e.g., MSI-H/dMMR tumors, NTRK-fusion positive  
364 tumors) or may incorporate pediatric cohorts in adult studies which share genetic aberrations  
365 with pediatric cancers.

### 366 367 5. *Master protocols*

368  
369 Master protocols, including basket and umbrella trials, may be appropriate mechanisms to assure  
370 efficiency in light of the limited number of available patients for study and to minimize the  
371 number of pediatric patients who may be exposed to ineffective therapies. Such master protocols  
372 may require pre-competitive discussions, negotiations, and planning by multiple sponsors.<sup>26</sup>  
373 FDA encourages sponsors and investigators to consider this approach given the large number of  
374 similar- and same-in-class products to avoid unnecessary competition and duplication.

## 375 376 **F. Considerations for Planned Waivers and Deferrals**

377  
378 There may be circumstances, including those listed below, when a waiver or deferral of pediatric  
379 studies may be appropriate for a molecularly targeted pediatric cancer investigation.<sup>27</sup>

### 380 381 1. *Deferrals*

- 382
- 383 • Deferral of a pediatric study may be appropriate until sufficient evidence of clinical  
384 activity is observed in response to the known inhibition of a defined molecular  
385 target(s) or pathway.
  - 386 • Deferral of a pediatric study may be appropriate when there is uncertainty regarding  
387 the single agent activity of a drug until such time that one or more biologically  
388 rational combinations demonstrates a clinical effect.
  - 389 • Deferral of a pediatric study may be appropriate until such time that an appropriate  
390 pediatric formulation for investigational purposes is available, provided there has  
391 been due diligence in formulation development.

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<sup>24</sup> See the guidance for industry *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials* (March 2019).

<sup>25</sup> See sections 505B(a)(2)(B) and 505B(a)(3)(B) of the FD&C Act.

<sup>26</sup> See draft guidance for industry *Master Protocols: Efficient Clinical Trial Design Strategies to Expedited Development of Oncology Drugs and Biologics* (September 2018). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>27</sup> See sections 505B(a)(3)(C), 505B(a)(4) and 505B(a)(5) of the FD&C Act.

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### **2. *Waivers***

- A full or partial waiver (as appropriate) may be appropriate if known (e.g., from studies conducted in adult humans or animals) or strongly suspected (e.g., based on target biology) serious toxicity of a drug precludes its use in all or one or more pediatric age groups.
- Age group-specific waivers may be appropriate if there are known (e.g., from studies conducted in adult humans or animals) or strongly suspected (e.g., based on target biology) severe developmental toxicities which may present an unreasonable risk to pediatric patients of a particular maturational stage.
- Age group-specific waivers may be appropriate when a sponsor is not able to develop an appropriate pediatric formulation for an age group.
- A waiver may be appropriate for the third or later generation/same in class product (with identical mechanism of action) when ongoing competing studies in the pediatric population are being conducted and when there is no convincing evidence that the new drug provides a superior pharmacologic, toxicity, or activity profile to the same in class product(s) already studied or under investigation, potentially resulting in a very small number of patients available to participate in a new investigation.

## **IV. GLOBAL IMPLICATIONS AND INTERNATIONAL COLLABORATION**

FDA recognizes the global scope of drug development and strongly encourages all stakeholders to support internationally coordinated and collaborative approaches to development of drugs to treat cancers in pediatric patients. Due to the rarity of pediatric cancers, which are frequently being subdivided into even rarer subpopulations based on underlying molecular features, international collaboration is increasingly important for facilitating the development of new treatments. Furthermore, the number of investigational drugs of potential interest far exceeds the number of pediatric patients available to enroll in clinical trials. Therefore, global coordination is increasingly important for prioritizing drugs of interest in general and for specific cancers in pediatric patients, especially for drugs of the same class, for early pediatric evaluation. This will aid in preventing duplication of studies and competition for scarce patients and limit unnecessary exposure of pediatric patients to investigational drugs.

The following opportunities exist to facilitate coordinated, global approaches to pediatric development:

### **A. Pediatric Cluster Teleconferences**

- Informal at least monthly teleconferences between the FDA and the European Medicines Agency (EMA), together with representatives from Health Canada, the Japanese Pharmaceutical and Medical Devices Agency, and the Australian Therapeutic Goods Administration coordinated by FDA’s Office of Pediatric Therapeutics.
- Provide opportunities for high-level scientific discussion of issues relating to development of specific drug products. Relevant documents and information are

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438 shared between participating regulatory agencies under the terms of existing  
439 confidentiality agreements.

- 440 • Regulatory agencies may request that a particular topic be placed on the agenda for  
441 discussion. Sponsors are informed of specific comments resulting from the  
442 discussions and may receive details of the discussions after the teleconference.
- 443 • Sponsors also can submit a request to either the FDA or EMA that their drug product  
444 be considered for discussion.

445

### **B. Common Commentary Process**

446

- 448 • Established by FDA and the EMA to inform sponsors of the outcome of scientific  
449 exchanges related to select drug products or topics discussed at Pediatric Cluster  
450 teleconferences.
- 451 • Is intended to facilitate early sponsor interactions with the relevant agencies and  
452 neither alter nor replace routine review procedures.
- 453 • Applies to drug products for which a pediatric development plan has been submitted  
454 to both FDA and the EMA and is under review, preferably early in the regulatory  
455 process.
- 456 • FDA has assumed primary responsibility for drafting a document that summarizes the  
457 discussion and generally includes recommendations. After review and clearance by  
458 both agencies, the Common Commentary document is shared with the sponsor. This  
459 document is nonbinding, and it does not provide final regulatory decisions.

460

### **C. Formal Parallel Scientific Advice (PSA)**

461

- 463 • Provides formal mechanism for provision of concurrent exchange of advice from  
464 EMA assessors and FDA reviewers with sponsors on scientific issues to optimize  
465 drug development.
- 466 • Information regarding the PSA procedure, including how to apply, is available.<sup>28</sup>

467

468 Additionally, FDA encourages participation in international multi-stakeholder meetings  
469 including the Pediatric Strategy Forums organized by the ACCELERATE Platform<sup>29</sup> which  
470 bring sponsors, investigators, patient advocates, and regulators together to discuss development  
471 strategies for specific pediatric cancers in the context of the number of investigational drugs  
472 available for assessment and the highly variable unmet medical needs of distinct pediatric  
473 populations with specific childhood cancers. We recommend stakeholders, including sponsors,  
474 investigators, and patient advocates consider coordinating early multi-stakeholder input to  
475 inform decision-making related to the initial pediatric clinical evaluation of appropriate

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<sup>28</sup> GENERAL PRINCIPLES EMA-FDA PARALLEL SCIENTIFIC ADVICE (HUMAN MEDICINAL PRODUCTS)

<https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/OfficeofInternationalPrograms/UCM557100.pdf>.

<sup>29</sup> For additional information, see <https://www.accelerate-platform.eu/paediatric-strategy-forum/> (accessed October 8, 2019).

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476 investigational drugs to both avoid unnecessary duplication and provide a framework for a  
477 longer-term development strategy of promising new drugs.