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# Development of Non-Opioid Analgesics for Acute Pain 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## *DRAFT GUIDANCE*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)**

**February 2022  
Clinical/Medical**

# Development of Non-Opioid Analgesics for Acute Pain

## Guidance for Industry

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1                   **Development of Non-Opioid Analgesics for Acute Pain**  
2                   **Guidance for Industry<sup>1</sup>**  
3  
4

5  
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
10 for this guidance as listed on the title page.  
11

12  
13  
14 **I. INTRODUCTION**  
15

16 This guidance is written in response to the statutory requirements of section 3001(b) of the  
17 Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT)  
18 for Patients and Communities Act, which directs the Food and Drug Administration (FDA) to  
19 issue or update existing guidance to help address challenges to developing nonaddictive medical  
20 products to manage pain. In keeping with the mandate of section 3001(b), and considering the  
21 severity of the ongoing opioid crisis, this guidance is also intended to assist sponsors in the  
22 development of alternatives to opioids for the management of acute pain. Accordingly, this  
23 guidance addresses FDA’s current thinking about three specific topics: development of non-  
24 opioid analgesic products for acute pain, labeling claims, and expedited programs as they pertain  
25 to this purpose.  
26

27 This guidance does not address the management of chronic pain, which will be the focus of a  
28 future guidance. This guidance also does not address the development of opioid products.  
29

30 The contents of this document do not have the force and effect of law and are not meant to bind  
31 the public in any way, unless specifically incorporated into a contract. This document is  
32 intended only to provide clarity to the public regarding existing requirements under the law.  
33 FDA guidance documents, including this guidance, should be viewed only as recommendations,  
34 unless specific regulatory or statutory requirements are cited. The use of the word *should* in  
35 Agency guidances means that something is suggested or recommended, but not required.  
36  
37

38 **II. BACKGROUND**  
39

40 FDA is committed to using its authorities to take measures targeted to combat the opioid crisis.  
41 In 2017, FDA announced its intention to focus on four priorities, two of which directly relate to  
42 this guidance: (1) fostering the development of novel analgesic drugs and (2) decreasing opioid

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<sup>1</sup> This guidance has been prepared by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine in the Center for Drug Evaluation and Research at the Food and Drug Administration.

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43 analgesic exposure and preventing new addiction.<sup>2</sup> To address these two priorities, and  
44 consistent with our mandate under SUPPORT Act section 3001(b) to issue guidance in this area,  
45 FDA is publishing this guidance.

46  
47 For context, it is important to set forth FDA’s general understanding of pain and specific  
48 definition of acute pain. For the purposes of this guidance, *acute pain* is defined as pain, lasting  
49 up to 30 days, typically in response to some form of tissue injury, such as trauma or surgery.<sup>3</sup>  
50

51 This understanding informs the development of this guidance, which describes FDA’s current  
52 thinking about three aspects of non-opioid analgesic drug development:  
53

- 54 • The drug development program appropriate for a non-opioid analgesic to support an  
55 indication for the management of acute pain (“acute pain indication”)  
56
- 57 • The availability of claims in labeling of non-opioid analgesic products for acute pain  
58 regarding elimination or reduction of opioid use and the data needed to support those  
59 claims  
60
- 61 • The use of expedited programs to support the development program for non-opioid  
62 analgesics to manage acute pain  
63

### **III. DEVELOPMENT OF NON-OPIOID ANALGESICS**

#### **A. Non-Opioid Analgesic Product Development for Acute Pain**

##### *I. General Considerations*

71 Indications for analgesics intended to manage acute pain can be general or specific. A general  
72 acute pain indication would reflect the expectation that the product will be effective for most  
73 types of acute pain.<sup>4</sup> The number of adequate and well-controlled clinical trials needed to  
74 support a general acute pain indication depends on the mechanism of action of the drug, the  
75 populations studied, and the degree to which the available information would support the  
76 efficacy across the acute pain settings in which the product would be used. Products with well-  
77 established analgesic mechanisms of action may be able to obtain a general acute pain indication  
78 when supported by at least two clinical trials, each in a different pain population. For example, a  
79 novel nonsteroidal anti-inflammatory drug with two successful clinical trials in postoperative

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<sup>2</sup> See the Opioid Policy Steering Committee web page, available at <https://www.fda.gov/about-fda/office-medical-products-and-tobacco/opioid-policy-steering-committee>.

<sup>3</sup> This definition of *acute pain* is consistent with the International Association for the Study of Pain’s definition, which is as follows: “Acute Pain is generally accepted as being of recent onset and limited short duration. It usually has a temporal (follows immediately after surgery/trauma) and causal (has a known cause) relationship to injury or disease. The intensity of acute pain is greatest at the onset of injury, but with healing pain intensity reduces.”

<sup>4</sup> Because of interindividual differences, a product indicated for general acute pain, and expected to be appropriate to manage many kinds of acute pain, does not mean the product is expected to be effective for every patient.

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80 pain, one following bunionectomy and one following herniorrhaphy, may be suitable for a  
81 general acute pain indication. In contrast, products with novel mechanisms of action are likely to  
82 require clinical trials in more than two different pain populations to support a general acute pain  
83 indication. As it is generally not feasible to study all possible populations that fall within a  
84 general acute pain indication, it may be necessary to include language in labeling describing the  
85 limitations of the indication.

86  
87 A specific acute pain indication reflects results from studies in a specific pain population (e.g.,  
88 postsurgical analgesia following hernia repair). Some products may be suitable only for specific  
89 populations (e.g., topical analgesic for underlying soft tissue injury). A specific pain-type  
90 indication generally requires evidence from at least two adequate and well-controlled clinical  
91 trials.

92  
93 Some sponsors may initially choose to demonstrate effectiveness of a particular drug in a  
94 specific pain-type population and then subsequently pursue additional specific indications, or a  
95 general indication, with additional trials in other acute pain settings to support broader use. In  
96 both of these scenarios, additional patient populations and types of pain can be studied and study  
97 results submitted as efficacy supplements to broaden the indication. In many cases, for both  
98 additional specific indications or to expand the indication from a specific pain indication to a  
99 general indication, one additional adequate and well-controlled efficacy trial may be sufficient.

100

### 101 2. *Trial Design*

102

103 Clinical trials to support a finding of efficacy for a non-opioid analgesic should be randomized,  
104 double-blind, superiority trials. The trials should include repeat-dose design as appropriate.  
105 Treatment duration should be based on the pain model used to support the proposed indication  
106 sought but should be no fewer than 24 hours for products that are not limited to a single dose.  
107 The primary endpoint should be based on the change in pain intensity over a suitable time period  
108 based on the pain model used in the trial and the product's expected duration of pain relief;  
109 however, the time period assessed does not have to be for the full duration of the pain. After  
110 evaluation of the primary endpoint, we recommend continued evaluation of both safety and  
111 efficacy, for evidence of sustained effect, which may be relevant to acute pain lasting up to 30  
112 days.

113

114 For acute pain, it is common to use an analysis such as the Sum of Pain Intensity Difference  
115 (SPID) over a prespecified time period that reflects the expected duration of treatment effect of  
116 the product. Demonstrating superiority to a comparator is important in non-opioid analgesic  
117 trials because the primary endpoint, pain intensity, can be influenced by study design factors  
118 such as the use of rescue medication and placebo effect. As a result, a noninferiority trial  
119 showing no difference between analgesic treatments could mean that neither product worked in  
120 that study.<sup>5</sup> Suitable comparators for the superiority study could include placebo or another

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<sup>5</sup> See 21 CFR 314.126(b)(2)(iv) (providing "Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective.") For more information about noninferiority trials, see the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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121 analgesic if the new product is expected to be more effective than the comparator analgesic. In  
122 some cases, the test treatment and control (placebo or a different analgesic drug) may also be  
123 added to background therapy (an “add-on study”). The background therapy could be specified or  
124 caregiver selected.

125  
126 Protocols should prespecify allowed rescue medications. Depending on the pain condition being  
127 studied, rescue medications might include nonsteroidal anti-inflammatory drugs or, in clinical  
128 settings in which opioids are typically required for adequate pain relief, opioids may be  
129 considered. Protocols should also prespecify the frequency, amount, and threshold of pain at  
130 which allowable rescue medication(s) can be administered. This is particularly important in  
131 placebo-controlled trials where increased use of rescue medication in the control group may  
132 diminish the study drug’s treatment effect, leading to a conclusion of ineffectiveness. The  
133 statistical analysis plan should describe how discontinuations caused by inadequate pain control  
134 will be handled. The concept of rescue use, including the prospective plan in the effectiveness  
135 analysis to assess its use, as well as how the data support the overall indication, is important and  
136 is discussed further in section III. A. 3. below, under Secondary Efficacy Endpoints.

137  
138 3. *Outcome Measures to Obtain an Acute Pain Analgesic Indication*

139  
140 Primary Efficacy Endpoint

141  
142 In general, an assessment of pain intensity is the primary outcome measure to establish the  
143 efficacy of an analgesic intended to manage acute pain. Efficacy endpoints (e.g., change in pain  
144 intensity) in a non-opioid analgesic trial should reflect a direct rating of pain intensity by the  
145 subject for all settings in which the subject can communicate in a reliable manner. We  
146 recommend using a well-defined and reliable patient-reported outcome measure of the subject’s  
147 pain intensity.<sup>6</sup> The selected instrument should have the subject assess their pain at the time of  
148 the assessment (i.e., without using a recall period). Generally, a numerical rating scale is the  
149 appropriate measure.

150  
151 We recommend that sponsors take frequent pain intensity measurements at preselected time  
152 points during the trial to accurately measure the effect of a non-opioid analgesic and that effect  
153 over time (e.g., every hour for X number of hours, then every 4 hours for X number of hours).  
154 All pain intensity measurements, including at baseline, should be obtained before rescue drug  
155 administration. In general, the frequency of pain intensity assessment is greater with initial drug  
156 administration, early post-event (e.g., post-injury or surgery), when pain may be more intense.  
157 The primary efficacy analysis should compare the SPID between treatments at a prespecified  
158 time point that, at a minimum, includes the duration of drug effect, and may extend beyond this  
159 duration. For example, a non-opioid analgesic with an expected 4- to 6-hour duration of action  
160 might have the primary efficacy analysis performed at 24 hours post-dose (SPID<sub>24</sub>), but  
161 secondary efficacy analyses may also be performed at 6 and 12 hours post dose (SPID<sub>6</sub> and  
162 SPID<sub>12</sub>, respectively) to evaluate pain control during the recommended dosing interval.

163

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<sup>6</sup> For a thorough discussion of patient-reported outcome measures, see the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (December 2009).

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164 We discourage using a primary endpoint that is based on pain relief (i.e., decrease in pain) rather  
165 than pain intensity (i.e., how bad the pain is), as pain relief scales require subjects to report  
166 current pain relative to their prior pain experience and may be influenced by other factors such as  
167 concurrent adverse reactions, and may be limited by patients' ability to recall their prior  
168 experience of pain. Additionally, sponsors should generally avoid using composite scales that  
169 are composed of multiple domains (e.g., pain, function, sleep) as the primary outcome measure  
170 in a non-opioid analgesic trial. Such multiple domain scales may be difficult to interpret across a  
171 population, as the same change in overall score can be based on differing patterns of response to  
172 the individual domain scores. For example, an overall score may be higher at baseline, reflecting  
173 poor sleep (with functional consequences), with improvement in the score reflecting  
174 improvement in sleep, such as might be seen with a sedating drug that does not provide  
175 substantive pain control. Multi-item scales, where the items all relate to pain (e.g., pain at rest or  
176 with movement), may be useful depending on the type of pain being studied.

177

### 178 Secondary Efficacy Endpoints

179

180 Secondary outcome measures are important to fully characterize the efficacy of a non-opioid  
181 analgesic and should support the primary efficacy endpoint. These secondary outcome measures  
182 include measurement of time to onset of pain relief and time to rescue or request for next dose of  
183 the study drug. Other informative secondary outcome measures include assessment of use of  
184 rescue medications, physical function, and patient global impression of change of pain.

185

186 To measure time to onset of pain relief, FDA has accepted the “two stopwatch method.” In this  
187 method, patients are instructed to stop the first stopwatch when they first perceive any analgesic  
188 effect and instructed to stop the second stopwatch when they perceive a meaningful amount of  
189 analgesia, which may be translated into a description in labeling of median time to meaningful  
190 pain relief. FDA remains open to discussion and consideration of approaches beyond the “two  
191 stopwatch method” to assess the time to onset of pain relief, which is particularly important to  
192 establish if there is an expectation of rapid onset of action (e.g., intravenous formulation).

193

194 For all acute pain non-opioid analgesic studies, it is particularly important that sponsors record  
195 the following information:

196

- 197 • The type and amount of rescue medication used, including dose, frequency, and duration
- 198
- 199 • The time that the study drug or rescue medication was administered
- 200
- 201 • The pain intensity measurements before the rescue medication was used and throughout
- 202 the dosing interval (e.g., evaluating SPID over the course of expected duration of action)
- 203

204

205 Use of rescue medication can inform important properties of the drug and should be carefully  
206 considered in the design of the study so as not to jeopardize the validity of the study. A sooner-  
207 than-expected first use of rescue medication may suggest that the investigational drug has a  
208 delayed onset of pain relief. Time to second use of rescue medication may be informative when  
considering dosing interval for the investigational drug and supplement knowledge of the drug's



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209 pharmacokinetic properties. If the time to second use of rescue medication is earlier than  
210 expected based upon drug exposure, waning efficacy can be considered a potential issue.

### 211 Endpoints Associated with Reducing or Eliminating Opioid Use

212  
213 As discussed further below, total elimination of opioid or a numerical reduction in the number of  
214 doses, dose per day, or duration of opioid use may support the efficacy of the investigational  
215 drug in alleviating pain. In order to support a clinical benefit of a reduction in opioid use that  
216 would be described in labeling, sponsors should demonstrate a direct patient benefit, such as  
217 clinically meaningful reduction in the incidence and/or severity of opioid-induced adverse  
218 reactions. See section III. B. below.

### 219 Biomarkers

220  
221  
222 FDA is not aware of any biomarkers that are useful in developing pain management products,  
223 but we welcome feedback on this issue. If sponsors identify a way to use biomarkers in any  
224 aspect of a clinical trial associated with non-opioid analgesics for acute pain, we are interested in  
225 engaging on this topic.

#### 226 227 228 *4. Safety Considerations—Clinical Trial Elements*

229  
230 When monitoring safety during clinical trials, sponsors should consider the nature of the drug  
231 and the trial population. Sponsors may also need to include subject discontinuation and/or study  
232 stopping criteria in protocols, depending on the expected safety profile of a non-opioid analgesic.

233  
234 Appropriate assessment of both effectiveness and safety relies on accurate and complete capture  
235 of the reason for subject discontinuation. Sponsors should assure that when a subject  
236 discontinues study drug or withdraws from the trial that the specific reason is obtained.  
237 Investigators should be prompted to provide detailed information, with specific causes rather  
238 than report terms such as “other,” “subject request,” “investigator decision,” or other such  
239 nonspecific categories. Sponsors also should ensure that case report forms are designed to  
240 accurately capture the reason for patient discontinuation.

241  
242 The size of the safety database needed to support approval for an acute pain indication depends  
243 on a number of factors, including whether the drug is a new molecular entity or a reformulation  
244 of an approved drug substance. In addition, a nonclinical safety finding or safety data from early  
245 clinical studies suggesting a potential serious adverse reaction may necessitate enlargement of  
246 the safety database to better define the safety profile of the proposed product. Safety  
247 assessments should continue as appropriate after dosing is completed, with consideration of  
248 patient population and setting (i.e., inpatient versus outpatient).

249  
250 Early in development, sponsors should discuss safety considerations, including the safety  
251 database requirements, with FDA.

252

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253 **B. Potential Claims in Labeling for Non-Opioid Analgesic Products for Acute**  
254 **Pain That Eliminate or Reduce Opioid Use and Data Needed to Support**  
255 **Those Claims**  
256

257 *1. FDA Thinking Regarding Concept of “Opioid-Sparing”*  
258

259 Consistent with the feedback of the Anesthetic and Analgesic Drug Products Advisory  
260 Committee on November 15, 2018, FDA believes the term “opioid-sparing” as a statement in  
261 labeling is unlikely to be sufficiently descriptive to be meaningful. Instead, FDA recommends  
262 labeling that more clearly and specifically explains the benefits provided by eliminating or  
263 reducing the need for opioid analgesics as discussed in section III. B. 2. below.<sup>7</sup> For drugs that  
264 are already approved and for those that are seeking initial approval, considerations in describing  
265 elimination or reduction in the need for opioid analgesics are similar.  
266

267 *2. Reductions in the Use of Opioid Analgesics That May Merit Description in*  
268 *Labeling*  
269

270 There are several ways in which a non-opioid analgesic may show benefit in reducing opioid use  
271 that would merit description in labeling:  
272

- 273 • Eliminating patient use of opioid analgesics in some or all patients in a pain setting in  
274 which use of opioids would typically be required to alleviate pain  
275
- 276 • Providing adequate analgesia such that the patient can be discharged from the health care  
277 facility without opioid analgesics when patients would be expected to be discharged with  
278 opioid analgesics  
279
- 280 • Showing a direct patient benefit related to reduced opioid analgesic use, such as a  
281 clinically meaningful reduction in opioid-associated adverse reactions or earlier  
282 functional recovery (e.g., earlier ability to participate in physical therapy with earlier  
283 regain of ambulation)  
284

285 In each of these scenarios, data should support a finding that the non-opioid and opioid have  
286 comparable effects on pain.  
287

288 *a. Product eliminates patient use of opioid analgesics*  
289

290 Exposure to an opioid analgesic presents a risk of addiction, misuse, or abuse. In addition to the  
291 risk of addiction, opioid use also may cause serious adverse reactions, including overdose, and  
292 death. Therefore, a non-opioid analgesic for acute pain that completely eliminates the need for  
293 an opioid in a setting in which opioid-level analgesic would be otherwise necessary would have  
294 the greatest impact on reducing the risk of opioid addiction. In addition to reducing the risk for

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<sup>7</sup> This view is consistent with feedback provided at the November 15, 2018, Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee. See <https://www.fda.gov/advisory-committees/advisory-committee-calendar/november-15-2018-meeting-anesthetic-and-analgesic-drug-products-advisory-committee-meeting>.

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295 the patient, the absence of opioid analgesics in the home lessens access to others in the same  
296 residence who may seek opioid analgesics for misuse or abuse.

297  
298 If a sponsor can show that a product eliminates the need for an opioid analgesic in a statistically  
299 significant number of patients in a setting in which opioids are routinely required for adequate  
300 acute pain control, this finding could be sufficient to support description in labeling. In such  
301 circumstances, labeling that describes analgesia comparable to or better than the comparator  
302 opioid may be appropriate.

303  
304 b. Product enables patient discharge without opioid analgesics

305  
306 As with products that eliminate opioid use, if a sponsor demonstrates that a non-opioid analgesic  
307 product eliminates the need for an opioid to manage acute pain at discharge from a health care  
308 facility or other outpatient settings, when opioid use post-discharge is routinely needed, this also  
309 could be considered adequate to support description in labeling. Additional assessments after  
310 discharge would be required to confirm patients' pain can be managed without opioids.  
311 Reducing the supply of prescription opioid analgesics in the home reduces the risks of misuse  
312 and abuse by both the patient and others within the home. Labeling that describes these findings  
313 may be appropriate.

314  
315 c. Product reduces patient exposure to opioid analgesics with direct clinical  
316 benefit to the patient

317  
318 Apart from discharge by a health care facility without opioids, reduction in dosage and/or  
319 duration of opioid use alone is not likely to be adequate to support description in labeling. To  
320 include a reduction in opioid use in labeling, the reduction claim should be associated with a  
321 direct patient benefit such as (1) reduced time to recovery of function, such as more rapid  
322 mobility and/or earlier ability to participate in rehabilitation or other clinically meaningful  
323 functional outcomes, or (2) a relevant decrease in opioid-related adverse reactions such as less  
324 sedation, fewer gastrointestinal side effects (such as constipation), or other adverse reactions. If  
325 these types of clinical benefits are adequately demonstrated in clinical trials, language in the  
326 labeling delineating these benefits could be included.

327  
328 3. *Data to Support Language in Labeling Describing Clinically Meaningful*  
329 *Reductions in Opioid Analgesic Use*

330  
331 To support language describing clinically meaningful reductions in opioid analgesic use in  
332 product labeling for any of the categories described above, sponsors should provide data from at  
333 least two adequate and well-controlled trials. As described in section III. B. 2. above, examples  
334 of clinically meaningful outcomes include not requiring opioids for a pain model where opioid  
335 use is usually required, or, where use of opioids is still needed, showing reduced opioid dose  
336 requirements in concert with either a shortening of time to mobility (e.g., following orthopedic  
337 surgery) or a reduction in the frequency of major complications of opioid treatment, such as  
338 delirium in an elderly population or a reduction in opioid-related adverse reactions.

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340 FDA also encourages sponsors to include open-label extensions with follow-up assessment of  
341 opioid analgesic utilization (e.g., 30 days after discharge following a surgical procedure) to  
342 assess whether patients have been taking opioid analgesics during the period of extension.  
343

344 FDA does not recommend observational study designs or exclusive use of electronic health care  
345 data (e.g., electronic health record or administrative claims data) to support labeling language  
346 describing clinically meaningful reductions in opioid analgesic use. Electronic health care data  
347 are not sufficiently able to measure factors that may drive selection of patients for the  
348 investigational versus the control treatment. Likewise, routinely collected health care data (e.g.,  
349 administrative claims data) are insufficient to ascertain primary endpoints, such as pain control,  
350 level of function, actual opioid use, and adverse effects.  
351

352 However, incorporating electronic health care data may be useful in other respects. For instance,  
353 such data may be valuable (1) in assessing opioid analgesics dispensed at discharge and  
354 persistent prescribed opioid analgesic dispensing, (2) in understanding current practices and  
355 standards of pain management in specific clinical settings, and (3) in identifying patients who  
356 may be eligible for study participation. We remain interested in feedback on ways in which  
357 these data could be useful to support the development of non-opioid analgesic products.  
358

359 We recognize that we are not addressing all aspects of clinical trial design for products that may  
360 reduce the use of opioid analgesics in a way that may merit description in product labeling, and  
361 we invite comment on this area of clinical trial design in response to this guidance. We also  
362 encourage sponsors of any non-opioid analgesic for acute pain seeking a claim of opioid  
363 replacement or reduction in labeling to have early and regular discussions with FDA to help  
364 ensure the use of adequate and interpretable assessments of treatment benefits that are consistent  
365 with a drug's mechanism of action.  
366

### **C. Expedited Programs**

367  
368  
369 FDA encourages the development of non-opioid analgesic products and novel study designs.  
370 Non-opioid analgesic development programs designed to replace or reduce the use of opioid  
371 analgesics may be eligible for one or more of FDA's expedited review programs, as applicable.  
372 FDA encourages early discussion of products that could eliminate or reduce opioid analgesic use  
373 and may be suitable for expedited reviews.  
374

375 These expedited programs and their relevant criteria are described in the guidance for industry  
376 *Expedited Programs for Serious Conditions—Drugs and Biologics* (May 2014). The applicable  
377 expedited programs include fast track, breakthrough therapy, priority review, and accelerated  
378 approval. Although each program differs, they all offer some form of expedited review and  
379 guidance for sponsors for drug development programs.<sup>8</sup>

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<sup>8</sup> In addition to the programs outlined above, the Breakthrough Devices Program may be available for certain nonaddictive medical products to manage pain. (Federal Food, Drug, and Cosmetic Act § 515B (21 U.S.C. 360e-3)). The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. The guidance for industry and Food and Drug Administration staff *Breakthrough Devices Program* (December 2018) outlines the criteria for designation as a breakthrough device as well as the policies FDA

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380 FDA has not had experience with an analgesic approval based on a surrogate or intermediate  
381 endpoint that is reasonably likely to predict clinical benefit, as would be consistent with  
382 accelerated approval.<sup>9</sup> Given that pain intensity is a subjective experience that can only be  
383 directly reported by the patient, it is difficult to envision how surrogate or intermediate endpoints  
384 could be used to predict analgesic effect. However, consistent with applicable statutory criteria,  
385 FDA will consider a non-opioid analgesic's abuse or misuse potential and its risk profile relative  
386 to available opioid analgesics to determine if the application qualifies for fast track or  
387 breakthrough designation during development, or for priority review upon receipt of the  
388 marketing application.

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intends to use to implement the program. The considerations set forth in that guidance document apply to FDA's review of devices as nonaddictive methods to manage pain.

<sup>9</sup> See FD&C Act 506(c) and 21 CFR 314.500 et seq. For drugs granted accelerated approval, postmarketing trials have been required to verify and describe clinical benefit.