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# Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry

## *DRAFT GUIDANCE*

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For questions regarding this draft document, contact Division of Drug Information at [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov); 855-543-3784 or 301-796-3400.

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

**May 2026  
Clinical/Medical  
Revision 1**

# **Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry**

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1                   **Opioid Analgesic Drugs: Considerations**  
2                   **for Benefit-Risk Assessment Framework**  
3                   **Guidance for Industry<sup>1</sup>**  
4  
5

6  
7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
11 for this guidance as listed on the title page.  
12

13  
14  
15 **I. INTRODUCTION**  
16

17 The purpose of this guidance is to describe the benefit-risk assessment framework that the  
18 Agency uses in evaluating whether applications for opioid analgesic drugs meet the standard for  
19 approval under section 505 of the Federal Food, Drug, and Cosmetic Act. This guidance  
20 summarizes the information that should be included in a new drug application for an opioid  
21 analgesic drug to facilitate the Agency's benefit-risk assessment.  
22

23 In general, FDA's guidance documents do not establish legally enforceable responsibilities.  
24 Instead, guidances describe the Agency's current thinking on a topic and should be viewed only  
25 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
26 the word *should* in Agency guidances means that something is suggested or recommended, but  
27 not required.  
28

29  
30 **II. BACKGROUND**  
31

32 Benefit-risk assessment is the foundation for FDA's regulatory review of human drugs and  
33 biologics. These assessments capture the evidence, uncertainties, and reasoning used by FDA to  
34 arrive at its regulatory decisions. Additionally, these assessments serve as tools for  
35 communicating that information to those interested in a better understanding of FDA's thinking.  
36

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<sup>1</sup> This guidance has been prepared by the Division of Anesthesia, Analgesia, and Addiction Products in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2019-D-1536 (available at <https://www.regulations.gov/docket?D=FDA-2019-D-1536>). See the instructions in that docket for submitting comments on this and other Level 2 guidances.

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37 FDA has developed a benefit-risk assessment framework — a structured, qualitative approach to  
38 FDA’s benefit-risk assessment<sup>2</sup> formatted as a table (see Figure 1 below).<sup>3</sup> In Figure 1, the  
39 factors affecting the benefit-risk assessment are listed on the left side. As reflected in the shaded  
40 boxes, the top two factors (*Analysis of Condition* and *Current Treatment Options*) relate to the  
41 specific therapeutic area — the current state of knowledge regarding the condition to be treated  
42 and the available therapies. The bottom two factors (*Benefit* and *Risk and Risk Management*) are  
43 specific to the drug at issue.

44  
45 FDA assesses risks and benefits of all drugs in the context of the use indicated in the labeling.  
46 However, because of the widespread misuse and abuse of prescription opioid analgesic drugs, for  
47 this class of drugs, FDA also considers the broader public health effect of opioid analgesic drugs;  
48 this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental  
49 exposure, and overdose, for both patients and others. Likewise, FDA considers any properties of  
50 a drug expected to mitigate these risks. This guidance describes the various factors that FDA  
51 will consider in evaluating the benefits and risks of an opioid analgesic drug. FDA encourages  
52 applicants to provide information relevant to these factors.

53  
54 **Figure 1: FDA’s Benefit-Risk Assessment Framework**

55

<b><i>Benefit-Risk Integrated Assessment</i></b>		
<b><i>Benefit-Risk Dimensions</i></b>		
<b>Dimension</b>	<b>Evidence and Uncertainties</b>	<b>Conclusions and Reasons</b>
<b>Analysis of Condition</b>		
<b>Current Treatment Options</b>		
<b>Benefit</b>		
<b>Risk and Risk*</b> <b>Management</b>		

56  
57 \* For purposes of this figure, *Risk and Risk Management* includes not only risks to the patient when used as  
58 indicated but also risks related to the broader public health sometimes described as second-order effects. And, in  
59 assessing risks to the broader public health, the Agency is making an assessment relative to other currently available  
60 analgesic drugs.

61

62

---

<sup>2</sup> See the Enhancing Benefit-Risk Assessment in Regulatory Decision-Making web page available at <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>.

<sup>3</sup> See the Benefit-Risk Assessment in Drug Regulatory Decision-Making implementation plan available at <https://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM602885.pdf>.

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63 **III. BENEFIT-RISK ASSESSMENT**

64

65 The following sections describe the information that FDA will consider in assessing the benefits  
66 and risks of an opioid analgesic drug. Consistent with the benefit-risk assessment framework,  
67 FDA considers the benefits and risks to the patient when the drug is used as labeled, as well as  
68 the benefits and risks relative to other available therapies for pain. Additionally, FDA considers  
69 the public health risks of the drug related to misuse, abuse, opioid use disorder, accidental  
70 exposure, and overdose in both patients and nonpatients, as well as any properties of the drug  
71 that may mitigate such risks. Note that the risk of opioid use disorder can arise even when a  
72 patient is taking an opioid analgesic drug as labeled.

73

74 The sections below provide recommendations for information the applicant should provide to  
75 assist FDA in its assessment.

76

77 **A. Benefits to the Patient Using the Drug as Labeled**

78

79 The Agency will consider questions including the following about benefits to patients who are  
80 prescribed the drug and take it as labeled and directed by their prescribers:

81

- 82 • Analgesic efficacy of the drug when used for its proposed indication

83

- 84 – What is the body of evidence supporting a finding of analgesic drug efficacy?

85

- 86 – In what patient population(s) was efficacy demonstrated? Why was the patient  
87 population chosen for the efficacy study? How does the population studied reflect the  
88 proposed indication (i.e., is the proposed indication broader than the population  
89 studied)?

90

- 91 – What is the body of evidence supporting the proposed duration of use for each  
92 proposed indication?

93

- 94 • Safety of the drug when used for its proposed indication

95

- 96 – Does the drug have characteristics that mitigate adverse events associated with opioid  
97 analgesic drugs, including respiratory depression, sedation, and constipation? What  
98 data support the conclusion that these risks are mitigated?

99

- 100 – Does the drug have characteristics that mitigate the risk of opioid use disorder when  
101 used as labeled? How do the safety data support this?

102

103 **B. Risks to the Patient Using the Drug as Labeled**

104

105 In addition to the already known risks associated with opioid analgesic drugs, the Agency will  
106 also consider questions including the following about risks to patients who are prescribed this  
107 drug and take it as labeled and directed by their prescribers:

108

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- 109 • Does this particular drug have any novel risks not typically associated with opioid  
110 analgesic drugs? How serious are they? Can they be mitigated through monitoring,  
111 patient selection characteristics, or limiting duration of use? Are the novel risks  
112 reversible?  
113
- 114 • Do the formulation and/or excipients pose risks to patients (e.g., tablets that swell in the  
115 gastrointestinal tract, tablets that may adhere to moist mucosal surfaces)? For drugs  
116 formulated to have abuse-deterrent properties, are there any adverse events associated  
117 with the drug product when used as labeled that are attributable to aversive excipients or  
118 excipients intended to impart resistance to manipulation?  
119
- 120 • Are there characteristics of the drug that increase or decrease the risk for respiratory  
121 depression, sedation, or development of opioid use disorder in patients (e.g., large  
122 residual opioid in transdermal systems, high dosage strengths)? Can the risks be  
123 mitigated by particular packaging configurations or storage and disposal conditions?  
124
- 125 • Is there evidence that adverse events typically associated with opioid analgesic drugs  
126 occur at a higher rate or with greater severity with the new drug than expected for similar  
127 drugs based on clinical trials or theoretical risks?  
128

### **C. Effectiveness and Safety Relative to Approved Analgesic Drugs**

130  
131 As part of the benefit-risk assessment for a particular drug and proposed indication, FDA  
132 considers the benefits and risks relative to other available therapies for the condition. FDA will  
133 consider the questions including the following in assessing effectiveness and safety of an opioid  
134 analgesic drug:  
135

- 136 – Do any comparative efficacy data exist for the drug relative to approved opioid or  
137 nonopioid analgesic drugs? Does this analgesic drug offer any advantages relative to  
138 available approved analgesic drugs for each indication, with regard to effectiveness or  
139 duration of response?  
140
- 141 – Do any comparative safety data exist for the drug relative to approved opioid or  
142 nonopioid analgesic drugs? Does this analgesic drug offer any other safety  
143 advantages or disadvantages relative to available approved analgesic drugs for each  
144 indication (e.g., abuse-deterrent properties, less risk of drug-drug interactions)?  
145
- 146 – What is the anticipated benefit-risk balance relative to available approved analgesic  
147 drugs for each indication? Do any comparative safety data exist for the drug relative  
148 to approved opioid or nonopioid analgesic drugs? Does this analgesic drug offer any  
149 other safety advantages or disadvantages relative to available approved analgesic  
150 drugs for each indication (e.g., less risk of drug-drug interactions)?  
151
- 152 – Does the drug have any other advantages over other available approved analgesic  
153 drugs (e.g., can be mixed with food)?  
154

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155 FDA notes that, while the comparative data described above is helpful in applying the benefit-  
156 risk framework, superiority to other available treatments is not a requirement for approval under  
157 FDA's drug approval authorities.

### **D. Broader Public Health Effects: Risks and Mitigation of Risks Related to Misuse, Abuse, Opioid Use Disorder, Accidental Exposures, and Overdose**

161  
162 In the overall benefit-risk assessment of opioid analgesic drugs, FDA will consider the positive  
163 and negative public health effects of the drug, which includes the drug's potential effect on risks  
164 to both patients and nonpatients, such as members of the patient's household (e.g., children,  
165 teenagers, visitors, and others). The risks considered include those related to misuse, abuse,  
166 opioid use disorder, accidental exposure, and overdose. FDA's evaluation of the broader public  
167 health effect of a new opioid analgesic drug is made relative to other currently available  
168 analgesic drugs.

- 169  
170 • In evaluating ways in which an opioid analgesic drug positively or negatively affects  
171 public health FDA will consider the following:  
172
  - 173 – Are there characteristics of the drug that increase or decrease the risk of accidental  
174 exposure in children (e.g., tablet size, color, flavor, packaging configuration,  
175 appearance of topical systems)?  
176
  - 177 – Are there characteristics of the drug that increase or decrease the risk of misuse,  
178 abuse, opioid use disorder, and related adverse outcomes such as overdose and  
179 infectious complications of injection (e.g., abuse-deterrent properties, large residual  
180 opioid in transdermal systems, high dosage strengths)? Can the risks be mitigated by  
181 particular packaging configurations or storage and disposal conditions?  
182
  - 183 – Are there increased or decreased risks associated with the indicated method of  
184 delivery (i.e., delivery device)? For example, does the delivery method affect an  
185 existing risk or introduce a novel risk?  
186
  - 187 – To support the opioid-specific public health benefit-risk evaluation, the applicant  
188 should use traditional epidemiologic data sources (e.g., surveys, emergency  
189 department visits, poison control center calls) and nontraditional sources (e.g.,  
190 internet discussion forums and blogs, social media, qualitative/ethnographic studies,  
191 law enforcement data) to provide information about how this moiety or similar opioid  
192 analgesic drugs are misused and abused in postmarketing settings. These data should  
193 address demographic patterns of abuse, the routes by which these drugs are abused,  
194 concomitant abuse of other substances, as well as risks of related adverse outcomes  
195 (e.g., addiction, fatal and nonfatal overdose, infectious complications of abuse).  
196
- 197 • For abuse-deterrent formulations, in addition to considering any potential benefits of such  
198 drug products, FDA also will consider the following in terms of opioid-specific public  
199 health considerations:  
200

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- 201 – Potential unintended adverse consequences with introduction of the abuse-deterrent  
202 formulation, such as the following:  
203
- 204 ▪ A shift to more dangerous routes of abuse (e.g., nasal to the more dangerous  
205 intravenous) based on properties of the formulation.  
206
  - 207 ▪ Potential tampering methods that could result in harmful effects, including  
208 injection-related harms (e.g., large volume extraction of drug that leads to  
209 increased sharing of drug paraphernalia increasing the risk of human  
210 immunodeficiency virus and hepatitis transmission).  
211
  - 212 ▪ Any other potential safety concerns related to the abuse-deterrent formulation.  
213
- 214 • For safety of excipients by unintended routes of administration, FDA will consider the  
215 following in terms of opioid-specific public health considerations:  
216
    - 217 – Based on a risk assessment of the excipients in the drug, the potential safety concerns  
218 for the drug when administered by unintended routes of administration, including  
219 intravenous, intranasal, and inhalation.  
220
  - 221 • For specific populations that may present distinct benefit-risk profiles, FDA will consider  
222 the following in terms of opioid-specific public health considerations:  
223
    - 224 – The potential for subpopulations where the benefit-risk balance may be unfavorable  
225 (e.g., adolescents, patients with mental health and/or substance use disorders, patients  
226 with certain other comorbidities). The applicant should include a discussion of  
227 anticipated use-specific subpopulations and proposed approaches to mitigate such  
228 risks, if present.  
229

### **E. Risk Management**

230  
231  
232 FDA has determined that a class-wide risk evaluation and mitigation strategy (REMS) is  
233 necessary for all opioid analgesic drugs intended for outpatient use to ensure that the benefits of  
234 these drugs continue to outweigh the risks.<sup>4</sup> The Opioid Analgesic REMS program requires that  
235 training be made available to all health care providers (HCPs) who are involved in the  
236 management of patients with pain, including nurses and pharmacists.<sup>5</sup> To meet this requirement,  
237 drug companies with approved opioid analgesic drugs provide unrestricted grants to accredited  
238 continuing education providers for the development of education courses for HCPs based on

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<sup>4</sup> See the Opioid Analgesic Risk Evaluation and Mitigation Strategy web page at <https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm163647.htm>. Note that certain opioid analgesic drugs are subject to other REMS. Information on the specific REMS associated with each approved opioid analgesic drug can be found on the FDA's Approved Risk Evaluation and Mitigation Strategies (REMS) web page at <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

<sup>5</sup> Ibid.

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239 FDA’s Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the  
240 Treatment and Monitoring of Patients with Pain.<sup>6</sup>

241  
242 To the extent that the safety profile of a drug product may differ from those drug products  
243 covered by the class-wide REMS, a product-specific REMS or REMS element may be required.  
244 For example, an opioid analgesic drug that must be restricted to use in a monitored inpatient  
245 setting may need additional risk mitigation strategies to ensure the drug product does not leave  
246 the hospital. In short, the applicant for an opioid analgesic drug should include any proposed  
247 REMS that the applicant considers necessary to ensure a drug’s benefits outweigh its risks. All  
248 sponsors of opioid analgesic drugs should begin discussions with FDA early during drug  
249 development regarding product-specific risks and the potential need for additional risk  
250 mitigation.

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<sup>6</sup> Available at  
[https://www.accessdata.fda.gov/drugsatfda\\_docs/remis/Opioid\\_analgesic\\_2018\\_09\\_18\\_FDA\\_Blueprint.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/remis/Opioid_analgesic_2018_09_18_FDA_Blueprint.pdf).