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# Psychedelic Drugs: Considerations for Clinical Investigations 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## *DRAFT GUIDANCE*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)**

**June 2023  
Clinical/Medical**

# Psychedelic Drugs: Considerations for Clinical Investigations Guidance for Industry

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**U.S. Department of Health and Human Services  
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*Contains Nonbinding Recommendations*

*Draft — Not for Implementation*

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44  
45 Because this is an emerging area of drug development, there is limited experience as to the  
46 configuration of programs that may support approval of a psychedelic drug. Rather than  
47 providing specific recommendations on study design, this guidance will present foundational  
48 constructs that all sponsors, including academic sponsor-investigators, studying the therapeutic  
49 potential of psychedelic drugs should consider. Sponsors may also request meetings with FDA  
50 for advice on a specific drug development program.<sup>2</sup>

51  
52 This guidance applies to clinical trials that will be conducted under an investigational new drug  
53 application (IND), including such clinical trials (e.g., research or academic studies) that are not  
54 intended to support marketing applications. The principles in this guidance are intended to  
55 support the ethical conduct of clinical trials as well as to ensure the integrity of the trial and the  
56 reliability of the results.

57

58

### **III. DISCUSSION**

59

60

61 Below, we outline general considerations, by discipline, for drug development programs  
62 evaluating the therapeutic potential of psychedelic drugs. The Agency is open to discussing  
63 various approaches to address these considerations; sponsors should engage divisions early in the  
64 drug development process.

65

#### **A. Chemistry, Manufacturing, and Controls**

66

67  
68 Sponsors must provide sufficient chemistry, manufacturing, and controls information to ensure  
69 proper identification, quality, purity, and strength of the investigational drug substance and drug  
70 product.<sup>3</sup> This is true for all phases of clinical trials.

71

- 72 • Chemistry data submitted by a sponsor to FDA may be proprietary. In general, sponsors  
73 interested in conducting a clinical investigation with a psychedelic drug under an IND  
74 must either submit their own information or incorporate information previously submitted  
75 by a person other than the sponsor when the sponsor has a right of reference for such  
76 information.<sup>4</sup>

77

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<sup>2</sup> See the draft guidance for industry *Formal Meetings Between the FDA and Sponsor or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>3</sup> See 21 CFR 312.23(a)(7).

<sup>4</sup> See 21 CFR 312.23(b).

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- 78 • If using plant material, algae, macroscopic fungi, or a combination of these, the  
79 investigational product may be considered a botanical, as that term is defined in the  
80 guidance for industry *Botanical Drug Development* (December 2016).<sup>5</sup>  
81
- 82 • Although some psychedelic compounds are derived from plants or fungi, drug products  
83 that are genetically modified; produced by fermentation of yeast, bacteria, or plant cells;  
84 or highly purified substances from naturally occurring sources are not considered  
85 botanicals for purposes of this document and the guidance for industry *Botanical Drug*  
86 *Development*.  
87
- 88 • Drugs must be manufactured in compliance with current good manufacturing practice  
89 (CGMP) under section 501(a)(2)(b) of the Federal Food, Drug, and Cosmetic Act. For  
90 most drug products manufactured in support of phase 1 studies, manufacturers should  
91 follow the recommendations in the guidance for industry, *CGMP for Phase 1*  
92 *Investigational Drugs* (July 2008). Certain drug products manufactured in support of  
93 phase 1 studies and drug products manufactured in support of phase 2 studies and beyond  
94 must comply with applicable CGMP regulations in 21 CFR part 211.<sup>6,7</sup> Studies in which  
95 subjects are enrolled to measure the effectiveness of a drug for a particular indication or  
96 indications are generally considered phase 2 studies;<sup>8</sup> therefore, the drug product used in  
97 those phase 2 studies must be manufactured in accordance with CGMP requirements.<sup>9</sup>  
98 Each phase of the investigation requires sufficient information to ensure identification,  
99 purity, and strength of the investigational drug substance and drug product.<sup>10</sup>  
100 Investigators and sponsors are encouraged to refer to the guidance for industry *INDs for*  
101 *Phase 2 and 3 Studies; Chemistry, Manufacturing, and Controls Information* (May 2003)  
102 and the guidance for industry *Content and Format of INDs for Phase 1 Studies of Drugs,*  
103 *Including Well-Characterized, Therapeutic, Biotechnology-Derived Products* (October  
104 2000).<sup>11</sup>

### **B. Nonclinical**

105  
106  
107  
108 The nonclinical program for psychedelic drugs should follow recommendations outlined in the  
109 ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical*

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<sup>5</sup> 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>.

<sup>6</sup> See 21 CFR 210.2(c).

<sup>7</sup> See 21 CFR part 211.

<sup>8</sup> See 21 CFR 312.21(b).

<sup>9</sup> See 21 CFR 210.2(c).

<sup>10</sup> See 21 CFR 312.23(a)(7)(i).

<sup>11</sup> For more general information about the IND process, see <https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application>.

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110 *Trials and Marketing Authorization for Pharmaceuticals* (January 2010).<sup>12</sup> However, the  
111 following considerations may be unique to psychedelic drugs.

- 112
- 113 • It may be reasonable for clinical studies with certain psychedelic drugs to be initiated  
114 under an IND in the absence of the typical animal toxicology testing when extensive  
115 human exposure and information are available from previously conducted clinical studies  
116 and no serious safety concerns were identified. Sponsors should plan to conduct  
117 nonclinical studies to support further drug development after initiation of the IND unless  
118 there are adequate data in the published scientific and medical literature.<sup>13,14</sup>  
119
  - 120 • An IND must include adequate information about pharmacological and toxicological  
121 studies of the drug on the basis of which the sponsor has concluded it is reasonably safe  
122 to conduct the proposed clinical investigations.<sup>15</sup> Therefore, psychedelic drugs without a  
123 history of adequate clinical exposure should not be tested in humans until safety has been  
124 established in nonclinical studies.<sup>16</sup>  
125
  - 126 • Although current psychedelic drug development programs are exploring single-dose or  
127 intermittent-dose treatment paradigms, most of the conditions being studied to date in  
128 these programs are chronic. Nonclinical studies to support chronic or chronic-intermittent  
129 dosing should be provided if the treatment effect is not durable and repeat dosing is  
130 expected.<sup>17</sup> Sponsors should determine the most appropriate dosing paradigm (e.g.,  
131 dosing intervals) for each animal species in the repeat-dose toxicity studies to support  
132 their intended clinical studies. The number and types of nonclinical studies to support  
133 approval of a marketing application will largely depend on treatment paradigm.  
134
  - 135 • Because psychedelic drugs have serotonin (5-HT) activity, a thorough evaluation of  
136 binding to 5-HT receptor subtypes should be conducted. Binding to the 5-HT<sub>2B</sub> receptor  
137 subtype has been linked to heart valvulopathy in humans; therefore, sponsors should  
138 assess functional activity at the 5-HT<sub>2B</sub> receptor subtype. If a psychedelic drug is shown  
139 to be an agonist at 5-HT<sub>2B</sub> receptors, a thorough microscopic evaluation of the heart

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<sup>12</sup> We support the principles of the “3Rs,” to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

<sup>13</sup> See 21 CFR 312, 314, and 601 (for information about the requirements for an IND, a new drug application, or a biologics license application).

<sup>14</sup> See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010).

<sup>15</sup> 21 CFR 312.23(a)(8).

<sup>16</sup> See the guidance for industry *Safety Testing of Drug Metabolites* (March 2020) and ICH M3(R2).

<sup>17</sup> See 21 CFR 312.23(a)(8) (providing information on requirements in INDs. The regulation specifies that “[t]he kind, duration, and scope of animal and other tests required [to conduct the proposed clinical investigation] varies with the duration and nature of the proposed clinical investigations”).

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140 should be conducted to assess for potential heart valve thickening in both rodent and  
141 nonrodent repeat-dose toxicity studies, including sectioning of all heart valves.  
142

### **C. Clinical Pharmacology**

144  
145 Pharmacokinetics and/or pharmacodynamics of psychedelic drugs should be adequately  
146 characterized both in vitro and in vivo. Sponsors should also consider the following clinical  
147 pharmacology aspects when developing psychedelic drugs.  
148

- 149 • Sponsors should evaluate the effect of a high-fat meal on the pharmacokinetics of an oral  
150 psychedelic drug early in development to inform clinical study design and potential  
151 labeling.  
152
- 153 • Sponsors should evaluate potential drug-drug and drug-disease interactions to inform  
154 inclusion and exclusion criteria and prohibited concomitant medications for clinical  
155 studies and to inform potential labeling.<sup>18,19,20</sup>  
156
- 157 • Long-term exposure to 5-HT<sub>2B</sub> agonists may induce cardiac valve stiffening. Currently,  
158 FDA recommends that sponsors exclude subjects with preexisting valvulopathy or  
159 pulmonary hypertension from multiple-dose studies of drugs with this mechanism until  
160 this risk can be better characterized.  
161
- 162 • Known pharmacodynamic interactions to consider include the following:  
163
  - 164 – Chronic use of selective serotonin reuptake inhibitors or monoamine oxidase  
165 inhibitors may reduce the effect of psychedelic drugs.  
166
  - 167 – Chronic use of tricyclic antidepressants or lithium and acute use of selective  
168 serotonin reuptake inhibitors or monoamine oxidase inhibitors use may potentiate  
169 psychedelic effects.  
170
- 171 • The dose-response relationship for most psychedelic drugs is poorly understood.  
172 Sponsors should take appropriate steps to characterize the dose-response relationship,  
173 both for efficacy and for safety.  
174

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<sup>18</sup> See the guidance for industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

<sup>19</sup> See the guidance for industry *Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).

<sup>20</sup> See the guidance for industry *Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications* (March 2023).



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### **D. Abuse Potential Assessment**

The assessment of the abuse potential of a drug product under development is generally conducted as a component of its safety evaluation. Drug products that are assessed for abuse potential include new molecular entities that are active on the central nervous system, as well as those products that contain drugs that are already controlled under the Controlled Substances Act.

- Psychedelic drugs act on the central nervous system, produce psychoactive effects (e.g., mood or cognitive changes, hallucinations), and need to be evaluated for abuse potential during drug development.<sup>21</sup> Data from the abuse potential assessment and a proposal for drug scheduling under the Controlled Substances Act is required to be included in a new drug application submission.<sup>22</sup> Many psychedelic drugs are Schedule I substances under the Controlled Substances Act<sup>23</sup> because they have high abuse potential and do not have a currently accepted medical use in the United States. Should a psychedelic drug that is a Schedule I controlled substance receive FDA approval as a drug product, the abuse potential assessment would assist in determining an appropriate rescheduling action under the Controlled Substances Act. For general information on how to conduct the abuse potential evaluation, including recommended methodologies, and what studies should be included as part of the new drug application submission, see the guidance for industry *Assessment of Abuse Potential of Drugs* (2017).
- For psychedelic drugs that are Schedule I controlled substances, activities associated with investigations under an IND must comply with the applicable Drug Enforcement Administration (DEA) regulations for research, manufacturing, importation/exportation, handling, and storage requirements for a Schedule I drug.<sup>24</sup> This requirement includes DEA registration of the investigator who intends to conduct research, per 21 U.S.C. 823(g) and the implementing regulation 21 CFR 1301.18. A Schedule I registration issued by DEA is required before the initiation of nonclinical and clinical studies. Authorization to conduct the research is required for each specific protocol and may need to be supplemented for amendments made to a protocol.<sup>25</sup> Sponsors should contact DEA to discuss and ensure compliance with all applicable DEA requirements.
- For some psychedelic drugs that are Schedule I controlled substances, there have been numerous investigations of these drugs, as documented in the published scientific literature. When appropriate, sponsors should propose the use of scientifically valid, published investigations to support the abuse potential assessment. For those psychedelic drugs that have not been well-characterized previously in preclinical and clinical studies,

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<sup>21</sup> See 21 CFR 314.50(d)(5)(vii).

<sup>22</sup> Ibid.

<sup>23</sup> See 21 CFR 1308.11.

<sup>24</sup> See 21 CFR part 1301.

<sup>25</sup> 21 CFR 1301.18.

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- 213 sponsors should conduct a full abuse potential assessment, as described in the guidance  
214 for industry *Assessment of Abuse Potential of Drugs*, before submission of a new drug  
215 application.  
216
- 217 • A human abuse potential study should generally be conducted when a drug has shown  
218 abuse-related signals in animal and/or human studies. However, a human abuse potential  
219 study may not be scientifically necessary for certain psychedelic drugs to support the  
220 abuse potential assessment in a new drug application when the subjective effects  
221 predictive of abuse are well characterized from extensive clinical studies and robust  
222 epidemiological data exist to demonstrate that individuals are using the psychedelic drug  
223 for abuse purposes.  
224
  - 225 • An adverse event (AE) for purposes of IND safety reporting means any untoward  
226 medical occurrence associated with the use of a drug in humans, whether or not  
227 considered drug related.<sup>26</sup> An evaluation of psychedelic responses that occur during  
228 clinical studies should be obtained through the inclusion of validated subjective scales  
229 and through monitoring abuse-related AEs, such as euphoria, hallucinations, stimulation,  
230 and emotional lability. Abuse-related AEs are monitored and reported as a safety concern  
231 even if they are hypothesized to be associated with the therapeutic response.<sup>27</sup> Thus, for  
232 psychedelic drugs, investigators and session monitors should be trained to record all  
233 abuse-related AEs, including psychedelic ones. The incidence of these abuse-related AEs  
234 in comparison to placebo or active control in studies should be reported by study,  
235 population, and dose and should be displayed in tabular format. Narratives describing  
236 these events should also be provided. Sponsors are encouraged to discuss their abuse-  
237 related AE monitoring plan early in development with the Controlled Substance Staff  
238 (through the primary review division). For more information about procedures for  
239 monitoring and assessing abuse-related AEs, refer to section V.B. of the guidance for  
240 industry *Assessment of Abuse Potential of Drugs*.  
241
  - 242 • An assessment of the potential for physical dependence with a psychedelic drug may be  
243 appropriate as part of the abuse potential assessment depending on the proposed  
244 conditions of use for which the drug is being studied (e.g., acute intermittent use versus  
245 prolonged continuous use).  
246
  - 247 • For all animal and human abuse potential and dependence-related studies that will  
248 contribute to the abuse potential assessment, it is generally recommended that these  
249 studies be conducted only after the therapeutic dose range is determined, which typically  
250 occurs when phase 2 clinical studies are completed. FDA recommends submitting  
251 proposed protocols to the Agency for review and comment before conducting these  
252 abuse-related studies.  
253

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<sup>26</sup> 21 CFR 312.32(a).

<sup>27</sup> 21 CFR 312.32(c).

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- 254 • Sponsors are encouraged to discuss their plans for an abuse potential assessment with  
255 FDA early in the IND stage of drug development and request (through the primary  
256 review division) review and comment on these plans from the Controlled Substance Staff  
257 in the Center for Drug Evaluation and Research.

### **E. Clinical**

258  
259  
260  
261 The substantial evidence standard for establishing effectiveness of psychedelic drugs is the same  
262 as it is for all other drugs.<sup>28</sup> However, the following considerations may be unique to psychedelic  
263 drugs.

- 264  
265 • Adequate and well-controlled (AWC) clinical studies are generally required to meet the  
266 substantial evidence standard to establish effectiveness in a marketing application.<sup>29</sup>  
267 However, the characteristics of psychedelic drugs present challenges for sponsors in  
268 designing AWC clinical studies.
- 269  
270 – An AWC study uses a design that permits a valid comparison with a control to  
271 provide a quantitative assessment of a drug's effect.<sup>30</sup> In the context of psychedelic  
272 drug development, the use of a traditional placebo as a control can be problematic for  
273 assessing efficacy. Subjects receiving an active drug experience functional unblinding  
274 because of the intense perceptual disturbances that can develop; those who receive a  
275 placebo in the context of high expectancy may experience a *nocebo* effect (i.e.,  
276 worsening symptoms as a result of knowing they did not get active treatment).  
277 However, an inactive control allows for better contextualization of any safety  
278 findings. Alternatives to an inert placebo (e.g., subperceptual doses of a psychedelic  
279 drug, other psychoactive drugs that mimic some aspects of the psychedelic  
280 experience) may be considered as well.
  - 281  
282 – In an AWC study, adequate measures are taken to minimize bias on the part of the  
283 subjects, observers, and analysts of the data.<sup>31</sup> Sponsors should consider the use of  
284 video or central raters blinded to treatment allocation and visit number. The use of a  
285 blinding questionnaire for both subjects and investigators/raters can be helpful to  
286 evaluate the impact of functional unblinding.
  - 287  
288 – Complementary trial designs across phases 2 and 3 could address different challenges  
289 in psychedelic drug development. For example, a trial using a low, middle, and high  
290 dose without a placebo could be paired with a placebo-controlled trial. The trial  
291 without a placebo could provide information about dose-response without the risk of

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<sup>28</sup> See section 505(d) of the FD&C Act; see also the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>29</sup> See section 505(d) of the FD&C Act; 21 CFR 314.126.

<sup>30</sup> See 21 CFR 314.126(b)(2).

<sup>31</sup> See 21 CFR 314.126(b)(5).

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- 292 a placebo effect. The placebo-controlled trial may raise concerns about functional  
293 unblinding but will allow for better characterization of safety signals.  
294
- 295 • Many of the psychedelic drug development programs involve administering the  
296 investigational drug and then engaging in psychological support or psychotherapy either  
297 while the subject is experiencing the acute effects of the drug or in a subsequent session.  
298 This additional variable both complicates the assessment of effectiveness and presents a  
299 challenge for any future product labeling.  
300
    - 301 – As of the publication date of this guidance, the contribution of the psychotherapy  
302 component to any efficacy observed with psychedelic treatment has not been  
303 characterized.  
304
    - 305 – Psychotherapeutic interventions have the potential to increase expectancy and  
306 performance biases. Sponsors should plan to justify the inclusion of a psychotherapy  
307 component and describe any trial design elements intended to reduce potential bias or  
308 to quantify the contribution of psychotherapy to the overall treatment effect. A  
309 factorial design may be useful for characterizing the separate contributions of drug  
310 and psychotherapy to any observed treatment response.  
311
    - 312 – The therapist monitoring the session can usually deduce the treatment assignment by  
313 observing the subject’s behavior. Therefore, it is preferable that the in-session  
314 monitor is not involved in post-session psychotherapy because their knowledge of the  
315 treatment could bias the delivery of subsequent therapy.  
316
  - 317 • FDA may place a study under an IND under clinical hold if it finds, among other reasons,  
318 that human subjects are or would be exposed to an unreasonable and significant risk of  
319 illness or injury.<sup>32</sup> Subjects receiving active treatment with psychedelic drugs remain in a  
320 vulnerable state for as long as 12 hours. Given this concern, so that subjects are not  
321 placed at an unreasonable and significant risk of illness or injury, safety-monitoring  
322 should include the following:  
323
    - 324 – Observation by two monitors for the duration of the treatment session  
325
      - 326 ■ A healthcare provider with graduate-level professional training and clinical  
327 experience in psychotherapy, licensed to practice independently, serving as the  
328 *lead* monitor. Examples of such professional credentials include the following:  
329
        - 330 • Clinical or counseling psychologist (PhD or PsyD)
        - 331 • Psychiatrist or other physician (MD or DO)
        - 332 • Master of Social Work (MSW)
        - 333 • Licensed Clinical Professional Counselor (LCPC)
        - 334 • Licensed Marriage and Family Therapist (LMFT)
        - 335 • Psychiatric Nurse Practitioner (Psychiatric NP).

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<sup>32</sup> 21 CFR 312.42.

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- An *assistant* monitor with a bachelor’s degree and at least 1 year of clinical experience in a licensed mental healthcare setting.
  - If the lead monitor is not a physician, availability of a licensed on-call physician able to reach the clinical site within 15 minutes in the event of a medical emergency.
  - The informed consent should clearly describe that subjects may experience changes in perception, cognition, and judgment that persist for many hours, as well as increased vulnerability and suggestibility during the treatment session.
  - Sponsors should plan to characterize the dose-response relationship for both safety and efficacy early in the drug development program.
  - Sponsors should plan to characterize the durability of response for their drug product, the recommended interdose interval for maintenance of effect, and the safety and efficacy of repeat dosing. At a minimum, for the treatment of a chronic illness such as post-traumatic stress disorder or major depressive disorder, sponsors should evaluate the effect of treatment at 12 weeks. However, sponsors should continue to follow subjects in an open-label extension period for a year beyond the Week 12 endpoint to monitor for symptom recurrence or, potentially, the need for repeat dosing.
  - For drugs that have been shown to have functional activity at the 5-HT<sub>2B</sub> receptor, it is likely that baseline and follow-up echocardiograms to assess valve structure and function and pulmonary artery pressures should be included in the study for drugs that are to be chronically administered. In general, patients with preexisting valvulopathy or pulmonary hypertension should be excluded until the cardiac risk has been characterized. Recommendations for when and how to assess QT interval and blood pressure can be found in the guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2005) and the draft guidance for industry *Assessment of Pressor Effects of Drugs* (February 2022).<sup>33</sup>
  - Sponsors should address how adverse events or serious risks are mitigated during the clinical studies and if similar strategies can be implemented post marketing. Sponsors should consider where the drug would be dispensed and administered if approved and whether the healthcare system would be able to prevent nonmedical use, accidental exposure, and overdose for both patients and nonpatients. Sponsors should also consider if gaps exist in the health care system regarding safe use. For the majority of drugs, routine risk mitigation measures, such as providing health care providers with risk information through FDA-approved prescribing information, are sufficient to preserve benefits while minimizing risks. In some cases, however, FDA may consider whether a

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<sup>33</sup> When final, this guidance will represent the FDA’s current thinking on this topic.

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378 risk evaluation and mitigation strategy may be necessary to ensure that the benefits of the  
379 drug outweigh its risks.<sup>34</sup>

- 380
- 381 • FDA may consider the public health effects of the drug as part of the overall benefit-risk  
382 assessment. Public health effects of the drug include its potential effect on risks that are  
383 related to nonmedical use, substance use disorder, accidental exposure, and overdose for  
384 patients and nonpatients.

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<sup>34</sup> See 505-1(a) of the FD&C Act.