
Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

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

**July 2019
Labeling**

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1 **Drug Abuse and Dependence Section of Labeling for Human**
2 **Prescription Drug and Biological Products —**
3 **Content and Format**
4 **Guidance for Industry¹**
5
6

7
8 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
9 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
10 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
11 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
12 for this guidance as listed on the title page.
13

14
15
16
17 **I. INTRODUCTION**
18

19 This guidance is intended to assist applicants in writing the DRUG ABUSE AND
20 DEPENDENCE section of labeling, as described in the regulations for the content and format of
21 labeling for human prescription drug and biological products (21 CFR 201.57(c)(10)).^{2,3} This
22 guidance applies to:
23

- 24 • Prescription drugs controlled under the Controlled Substances Act (CSA)⁴
- 25
- 26 • Prescription drugs not controlled under the CSA for which there is important information
27 to convey to health care providers related to abuse and dependence
28

29 This guidance discusses and provides recommendations on the following:
30

- 31 • The general principles to consider when drafting the DRUG ABUSE AND
32 DEPENDENCE section of the labeling
33

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² This guidance applies to drugs, including biological drug products. For the purposes of this guidance, *drug product* or *drug* will be used to refer to human prescription drug and biological products that are regulated as drugs.

³ See the final rule “Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products,” (71 FR 3922, January 24, 2006) and additional labeling guidances at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

⁴ The complete list of all scheduled substances can be found at 21 CFR part 1308, which is updated following publication in the *Federal Register* of a drug scheduling action by the Drug Enforcement Administration (DEA).

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- 34 • What information to include in the DRUG ABUSE AND DEPENDENCE section,
35 including common terminology and definitions related to abuse and dependence
36
- 37 • How to write, organize, and format the information within the DRUG ABUSE AND
38 DEPENDENCE section
39
- 40 • How information related to topics presented in the DRUG ABUSE AND DEPENDENCE
41 section should be distributed elsewhere in labeling
42

43 The recommendations in this guidance are intended to help ensure that the DRUG ABUSE AND
44 DEPENDENCE section is useful, informative, and, to the extent possible, consistent in content
45 and format within and across drug and therapeutic classes. Applicants should follow the
46 recommendations in this guidance when developing the DRUG ABUSE AND DEPENDENCE
47 section for a new drug and when revising this section for a currently approved drug.
48

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

55 **II. GENERAL PRINCIPLES**

57 Information on a drug’s potential for abuse, misuse, addiction, physical dependence, and
58 tolerance is generally conveyed to health care providers in the DRUG ABUSE AND
59 DEPENDENCE section of labeling. Information about a product’s abuse-deterrent properties
60 should also be presented in this section.

61 The primary role of the DRUG ABUSE AND DEPENDENCE section of labeling is to convey
62 information about a drug’s potential for abuse, misuse, addiction, physical dependence, and
63 tolerance in order to help inform prescribing decisions and facilitate the safe and effective use of
64 prescription drug products. This section should be concisely and clearly written to include the
65 information that accurately summarizes the product’s abuse potential, signs and symptoms of
66 withdrawal, and abuse-deterrent properties (if applicable) and to provide information that is
67 important for the safe and effective use of the product.
68

69 **A. Distribution of Information Among Labeling Sections**

70

71 Generally, detailed information about drug abuse and dependence is included in the DRUG
72 ABUSE AND DEPENDENCE section of labeling. Other relevant sections should discuss only
73 those aspects of the information that are pertinent to those sections’ scopes and purposes and
74 should not repeat the identical content or level of detail found in the DRUG ABUSE AND
75 DEPENDENCE section. To the extent possible, redundancies in text should be avoided in
76 labeling, and cross-referencing among sections should be used instead.
77

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78 For example, labeling for opioid products typically includes information on abuse, misuse, and
79 addiction in the BOXED WARNING and WARNINGS AND PRECAUTIONS sections, in
80 addition to the DRUG ABUSE AND DEPENDENCE section. For products that have drug
81 abuse or dependence information in both the WARNINGS AND PRECAUTIONS and DRUG
82 ABUSE AND DEPENDENCE sections, detailed abuse or dependence information (e.g.,
83 description of study designs and results of abuse liability studies) should generally be included in
84 the DRUG ABUSE AND DEPENDENCE section, with the succinct description of the adverse
85 reaction or risk, the clinical implications, and recommendations for managing risks related to
86 abuse or dependence appearing in the WARNINGS AND PRECAUTIONS section.

87
88 The labeling for Schedule II controlled substances typically includes a BOXED WARNING
89 providing information on abuse and dependence, as well as a related discussion in the
90 WARNINGS AND PRECAUTIONS subsection for abuse and dependence information. As
91 appropriate, labeling for Schedule III, IV, and V products may also include discussions related to
92 abuse and dependence in a BOXED WARNING or in the WARNINGS AND PRECAUTIONS
93 section.⁵

B. Updating the Section

94
95
96
97 Holders of marketing applications for drugs have an ongoing obligation to ensure their labeling
98 is accurate and up to date (21 CFR 201.56(a)(2)). For example, when new information becomes
99 available that causes information in labeling to become inaccurate, false, or misleading, the
100 application holder must take steps to change the content of its labeling, in accordance with
101 § 201.56(a) and, as applicable, 21 CFR 314.70, 314.97, and 601.12. The DRUG ABUSE AND
102 DEPENDENCE section must be updated as new information about the abuse of and dependence
103 on the product that warrants inclusion in product labeling becomes available.⁶

C. Terminology

104
105
106
107 The concepts of abuse, misuse, addiction, physical dependence, and tolerance are important for
108 health care providers to understand to facilitate the safe and effective use of drugs associated
109 with the development of these behaviors or conditions. However, these terms are commonly
110 confused or misinterpreted. FDA recommends that definitions of these terms be included in the
111 DRUG ABUSE AND DEPENDENCE section of labeling to ensure common understanding and
112 to facilitate the diagnosis and management of substance use disorders. This guidance provides

⁵ For recommendations on when boxed warnings and warnings/precautions are warranted, see the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* (October 2011). We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁶ See 21 CFR 201.56(a)(2).

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113 recommendations for definitions for abuse- and dependence-related terminology that should be
114 included in this section of labeling (see sections III.B and C of this guidance).⁷

115

116

117 **III. CONTENT AND FORMAT OF THE DRUG ABUSE AND DEPENDENCE** 118 **SECTION**

119

120 The DRUG ABUSE AND DEPENDENCE section is composed of three subsections
121 (§ 201.57(c)(10)). The following information provides recommendations for the content of each
122 subsection.

123

124 **A. 9.1 Controlled Substance**

125 Under the CSA, controlled substances are placed in one of five schedules based on their potential
126 for abuse, whether they have a currently accepted medical use in the United States, and the
127 degree of dependence that abuse of the drug or other substance may cause.⁸ Drugs in each
128 schedule are subject to a set of requirements governing their manufacture, distribution, and
129 dispensing, among other things. In general, the requirements that are most restrictive apply to
130 drugs scheduled in Schedule I and II; and those that are relatively less restrictive cover drugs
131 scheduled in Schedule III, IV, and V.

132 *1. Prescription Drugs Scheduled Under the Controlled Substances Act*

133 If a drug is scheduled under the CSA, the *Controlled Substance* subsection must state that the
134 drug is a controlled substance and identify the schedule under which the drug is controlled
135 (§ 201.57(c)(10)(i)). This subsection should identify the proprietary name (if a proprietary name
136 exists) and the active ingredient(s) or drug substance(s) that is (are) controlled. This information
137 should be conveyed in a single sentence. For example:

- 138 • DRUG-X contains active ingredient-Y, a Schedule II controlled substance.

139

140 If the drug product does not have a proprietary name, this subsection should identify the active
141 ingredient(s) or drug substance(s) that is (are) controlled. For example:

142

- 143 • Active ingredient-Y is a Schedule II controlled substance.

144

145 For some drug products that are controlled substances, there may be additional legal
146 requirements that should be noted in labeling because they are relevant to prescribers. For

⁷ Not all definitions recommended in this guidance for use in labeling are the same as the definitions used for the purposes of making a clinical diagnosis, such as those in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5).

⁸ See Section 202 of the Controlled Substances Act (21 U.S.C. 812(b)), which describes the five schedules for controlled substances. All controlled substances with approved U.S. marketing applications have a currently accepted medical use in treatment in the United States and fall within Schedules II through V.

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147 example, these would include the requirements under the CSA (as amended by the Drug
148 Addiction Treatment Act of 2000)⁹ for the use of buprenorphine products for the treatment of
149 opioid dependence. In such instances, information about the legal requirements should be briefly
150 stated in the *Controlled Substance* subsection following the sentence about the controlled
151 substance scheduling.

2. *Prescription Drugs for Which Controlled Substance Scheduling Is Pending*

152
153
154
155 If scheduling of the controlled substance is pending when the application is approved under
156 section 505(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the initial labeling
157 should reflect that the schedule will be determined after the Drug Enforcement Administration
158 (DEA) has issued a final scheduling decision.¹⁰ For example:

- 159
160 • DRUG-X contains active ingredient-Y. (Controlled substance schedule to be
161 determined after review by the Drug Enforcement Administration.)

162
163 Once DEA has issued a scheduling decision assigning a controlled substance schedule, the
164 labeling must be updated with the controlled substance scheduling information.¹¹

3. *Prescription Drugs Not Controlled Under the Controlled Substances Act That Have Information in Subsection 9.2 or 9.3*

165
166
167
168
169 In some situations, even though a drug is not scheduled as a controlled substance, its labeling
170 may include information to convey to health care providers in subsection 9.2 *Abuse* or 9.3
171 *Dependence*. For example, a demonstrated lack of abuse potential for a new drug in a
172 therapeutic category in which most other products are controlled substances may be relevant
173 information to include in subsection 9.2. Additionally, labeling for a non-controlled drug may
174 include information on physical dependence in subsection 9.3 when discontinuation of the drug
175 has been shown to cause a withdrawal syndrome.

176
177 When information is included in subsection 9.2 or 9.3 of labeling for non-controlled drugs,
178 subsection 9.1 should include a single sentence stating that the active ingredient(s) or drug
179 substance(s) is (are) not controlled. For example:

- 180
181 • DRUG-X contains active ingredient-Y, which is not a controlled substance.

⁹ See 21 U.S.C. 823(g).

¹⁰ With the enactment of the Improving Regulatory Transparency for New Medical Therapies Act in 2015, FDA approval of a new drug may not take effect until DEA issuance of an interim final rule under 21 U.S.C. 811(j) establishing schedule placement for the drug, in accordance with 21 U.S.C. 355(x). See Public Law 114-89, 129 Stat. 698 (Nov. 25, 2015).

¹¹ See 21 CFR 201.57(a)(2), 201.57(c)(10)(i), and 1302.03. To update the labeling following the scheduling action, a supplement to the application must be submitted by the applicant to update product labeling to reflect the DEA scheduling action described in the interim final rule or final rule. See 21 CFR 314.70.

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182
183 If the non-controlled drug does not have a proprietary name, subsection 9.1 should identify the
184 active ingredient(s) or drug substance(s) that is (are) not controlled. For example:

- 185
186
 - Active ingredient-Y is not a controlled substance.

187
188 A statement that a drug is not a controlled substance should *not* be included in labeling when
189 there is no information in subsections 9.2 or 9.3.

190 191 **B. 9.2 Abuse**

192
193 This subsection of labeling should contain, as appropriate, information about the drug related to
194 abuse, misuse, and addiction that is important for prescribers to consider. Sources of information
195 for these topics can include evidence from the clinical development program, human abuse
196 liability or human abuse potential studies, and, in some cases, relevant nonclinical data.

197 198 *1. Information on Abuse*

199
200 Subsection 9.2 must state the types of abuse that can occur with the drug and the adverse
201 reactions pertinent to them and must identify particularly susceptible patient populations, if
202 known (§ 201.57(c)(10)(ii)). This subsection should also summarize the information that
203 supports recommendations on how to prevent or mitigate risks associated with abuse and will
204 typically be cross-referenced in other sections of labeling (e.g., BOXED WARNING or
205 WARNINGS AND PRECAUTIONS).

206
207 The subsection must be based primarily on human data and human experience, but pertinent
208 animal data may also be used (§ 201.57(c)(10)(ii)). If there are pertinent animal data, the clinical
209 implications of those data should be summarized in this subsection, and the relevant details of
210 the animal studies should be presented in the Animal Toxicology and/or Pharmacology
211 subsection of the NONCLINICAL TOXICOLOGY section of labeling.

212
213 For drugs with a risk of abuse, the following single sentence should be included in the *Abuse*
214 subsection:¹²

- 215
216
 - Abuse is the intentional, non-therapeutic use of a drug, even once, for its desirable
217 psychological or physiological effects.

218 Examples of abuse include, but are not limited to, the use of a prescription drug to get “high” or
219 feel euphoric effects.

220 The term *abuse* should not be used to describe accidental or inadvertent exposure to a
221 prescription drug because *abuse* requires intentional administration on the part of the abuser.
222

¹² For this purpose, this guidance uses, with some modifications, the American Psychiatric Association’s definition of *abuse* found in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR).

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223 The *Abuse* subsection should summarize the types of abuse that can occur with the drug based on
224 clinical experience with the drug or drugs within the same class. This discussion should specify
225 the risks of abuse and the types of adverse reactions that may occur, as well as any information
226 about the typical clinical presentation that may occur with non-therapeutic use of the drug. For
227 example:

- 228
- 229 • Abuse of DRUG-X poses a risk of overdose, which may lead to death, central nervous
230 system and respiratory depression, hypotension, and seizures.

231

232 OR

- 233
- 234 • Signs and symptoms of central nervous system stimulant abuse include the following:
235 tachycardia, tachypnea, hypertension, sweating, dilated pupils, hyperactivity, restlessness,
236 insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and
237 abdominal pain.

238

239 This subsection must identify, if known, particularly susceptible patient populations at risk for
240 abuse (§ 201.57(c)(10)(ii)). For example:

- 241
- 242 • Patients at high risk of DRUG-X abuse include those with a history of prolonged use of
243 products containing active ingredient-Y, those with a history of drug or alcohol abuse, or
244 those who use DRUG-X in combination with other abused drugs.

245

246 a. Product-specific risks related to abuse

247

248 The *Abuse* subsection should include risks specific to abuse of the product, such as those related
249 to a product's particular formulation. These discussions may include information on risks
250 resulting from inappropriate routes or methods of administration. For example:

- 251
- 252 • Inappropriate manipulation (e.g., chewing, crushing, dissolving) or self-administration by
253 an inappropriate route (e.g., snorting or injecting) enhances release of active ingredient-Y
254 and increases the risk of overdose or death.
- 255
- 256 • Inappropriate intravenous, intramuscular, or subcutaneous use of DRUG-X can result in
257 death, local tissue necrosis, infection, pulmonary granulomas, and an increased risk of
258 endocarditis and valvular heart injury.

259

260 If there is evidence of abuse of the product when used in combination with another drug product,
261 this information should be included in this subsection.

262

263 b. Abuse potential studies

264

265 Results from human abuse potential studies that adequately characterize the abuse potential of
266 the drug product should be summarized in the *Abuse* subsection. When an assessment of abuse
267 potential is appropriate and the findings do not suggest a potential for abuse, it may be important,
268 in some instances, to include a summary of such data in this subsection of labeling (e.g., when a

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269 drug product is in a therapeutic category of drugs typically known to have abuse potential, but
270 thorough abuse potential studies show no risk of abuse). Under certain circumstances (e.g.,
271 when a human abuse potential study was not conducted because of safety concerns), animal data
272 indicative of the potential for abuse may be summarized.

273

274 c. Products with abuse-deterrent properties

275

276 If studies conducted to evaluate the abuse-deterrent properties of a drug product are included in
277 labeling, summaries of such studies should appear in the *Abuse* subsection. For example, for
278 opioid drug products, when premarket data show that a product's abuse-deterrent properties can
279 be expected to result in a meaningful reduction in that product's abuse, these data, together with
280 an accurate characterization of what the data mean, should generally be included in the *Abuse*
281 subsection of labeling.¹³ FDA presently has limited data correlating the abuse-deterrent
282 properties of certain opioid drug products, as demonstrated by premarket studies, with the impact
283 of those properties on abuse or adverse reactions associated with abuse in the postapproval
284 setting. When postmarketing data become available that provide further information on the
285 impact, if any, of abuse-deterrent properties on abuse liability, these data should be summarized
286 in product labeling.

287

288 2. *Information on Misuse*

289

290 For a drug with a risk of misuse that would negatively impact health or functioning, the
291 following single sentence should be included in the *Abuse* subsection:

- 292 • Misuse is the intentional use, for therapeutic purposes, of a drug by an individual in a
293 way other than prescribed by a health care provider or for whom it was not prescribed.

294 Examples of misuse include:

- 295 • Patients intentionally using a prescription drug for a condition different from the
296 condition for which the drug is prescribed
- 297
- 298 • Patients intentionally taking a drug for therapeutic purposes at a higher dose or taking the
299 drug at a different dosing interval than prescribed
- 300
- 301 • Individuals intentionally using a drug for therapeutic purposes when the drug is not
302 prescribed for them
- 303

304 Misuse is defined in the context of *therapeutic* use, while abuse is defined in the context of *non-*
305 *therapeutic* use. The terms misuse and abuse are similar in that they both represent the
306 intentional intake of a drug in a way other than prescribed or by an individual for whom the drug
307 is not prescribed. If the drug is used for therapeutic purposes, other than as prescribed, either for
308 an approved or unapproved use, the use will represent misuse. If the drug is taken for what could

¹³ For more information, see the guidance for industry *Abuse-Deterrent Opioids — Evaluation and Labeling* (April 2015).

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309 be considered its desirable non-therapeutic effects (e.g., sedative, stimulant, euphoric, mind-
310 altering effects), the use will represent abuse.

311
312 For example, if a person takes a friend's prescription opioid analgesic for a toothache, that usage
313 is considered misuse of the drug. However, if a person takes a friend's prescription opioid
314 analgesic for its desirable non-therapeutic effects (e.g., euphoria), that usage is considered abuse
315 of the drug. Drug misuse is also differentiated from a medication error, in which a patient
316 *mistakenly* (versus *intentionally*) uses a drug in a manner other than prescribed.¹⁴

317 As appropriate, information on misuse should be summarized in the *Abuse* subsection and may
318 include a discussion of the adverse reactions associated with intentional therapeutic use of a drug
319 product in an inappropriate way. A discussion of populations that may be vulnerable to misuse
320 should also be provided, if known.

321 3. Information on Addiction

322
323 Relevant information about addiction to the drug should be summarized in the *Abuse* subsection.
324 This discussion should provide, as available, information regarding the clinical presentation of
325 addiction to the drug, risk factors that may render a patient particularly vulnerable to addiction to
326 the drug, and the adverse effects associated with addiction to the drug.

327
328 For drugs with a risk of addiction, the following single sentence should be included in the *Abuse*
329 subsection:¹⁵

- 330
- 331 • Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that
332 may include a strong desire to take the drug, difficulties in controlling drug use (e.g.,
333 continuing drug use despite harmful consequences, giving a higher priority to drug use
334 than other activities and obligations), and possible tolerance or physical dependence.

335
336 Physical dependence is not synonymous with addiction; a patient may be physically dependent
337 on a drug without having an addiction to the drug. Similarly, abuse is not synonymous with
338 addiction. Tolerance, physical dependence, and withdrawal are all expected biological
339 phenomena that are the consequences of chronic treatment with certain drugs. These phenomena
340 by themselves do not indicate a state of addiction.

341

¹⁴ The National Coordinating Council on Medication Error Reporting and Prevention (NCCMERP) defines a *medication error* as follows: “A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.” This definition can be found at <https://www.nccmerp.org/about-medication-errors>.

¹⁵ For this purpose, this guidance uses, with some modifications, the International Classification of Diseases (ICD-10) definition of *dependence syndrome* as the definition of *addiction*.

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342 C. 9.3 Dependence

343 This subsection of labeling must contain, as appropriate, information about the drug related to
344 physical dependence, withdrawal, and tolerance. Under § 201.57(c)(10)(iii), the subsection must
345 describe characteristic effects resulting from the psychological and physical dependence that
346 occurs with the drug and must identify, if known, the quantity of the drug over a period of time
347 that may lead to tolerance or dependence, or both.¹⁶ The *Dependence* subsection should
348 summarize signs and symptoms of withdrawal after chronic use or abuse of the drug, whereas the
349 *Abuse* subsection should discuss abuse-related adverse reactions. Procedures necessary to
350 diagnose the dependent state and the principles of treating or mitigating the effects of abrupt
351 withdrawal must be described in this subsection (§ 201.57(c)(10)(iii)).

352 This subsection should summarize the information that supports recommendations to health care
353 providers on how to prevent or mitigate risks associated with physical dependence, withdrawal,
354 and tolerance. Other sections of labeling that discuss clinical implications related to dependence
355 (e.g., DOSAGE AND ADMINISTRATION or WARNINGS AND PRECAUTIONS) should
356 cross-reference to the *Dependence* subsection as appropriate.

357 1. Information on Physical Dependence and Withdrawal

358 For drugs to which patients may develop physical dependence, the following single sentence
359 should be included in the *Dependence* subsection:

- 360 • Physical dependence is a state that develops as a result of physiological adaptation in
361 response to repeated drug use, manifested by withdrawal signs and symptoms after abrupt
362 discontinuation or a significant dose reduction of a drug.

363
364 The appearance of a withdrawal syndrome when administration of the drug is terminated or
365 when an antagonist is administered is the only actual evidence of physical dependence. Physical
366 dependence is associated not only with the repeated use of known drugs of abuse, but with drugs
367 with no abuse potential as well. For example, physical dependence to propranolol (a beta-
368 blocker used for the management of hypertension) is known to occur, and abrupt discontinuation
369 may be followed by a “propranolol withdrawal syndrome” resulting in increased blood pressure
370 (temporarily higher than before starting propranolol), headache, chest pain, palpitations, and
371 sweating.

372 In a person who is physically dependent on a drug, a withdrawal syndrome is normally
373 anticipated when the drug is abruptly withdrawn, when the dose is reduced, or when the patient

¹⁶ Terminology used to describe substance-related disorders continues to evolve, and a lexicon is being adopted in which past categories of substance abuse and substance dependence (as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*) are combined into an overarching diagnosis of substance use disorder (as described in DSM-5), which is measured on a continuum from mild to severe. Accordingly, information about substance use disorders is generally parsed out between subsections 9.2 *Abuse* and 9.3 *Dependence*. Although addiction has historically been associated with the concept of psychological dependence, for the purposes of labeling, discussions related to addiction should appear in subsection 9.2 *Abuse* because addiction as it is currently understood relates more closely to abuse than to the subject matter discussed in 9.3 *Dependence*.

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374 is administered an antagonist. The withdrawal syndrome for the drug should be described in the
375 *Dependence* subsection. For example:

- 376 • Physical dependence can occur in patients treated with DRUG-X. Abrupt cessation or
377 dose reduction following chronic use can result in withdrawal symptoms, including
378 extreme fatigue and depression.
379
- 380 • If DRUG-X is abruptly discontinued in a physically dependent patient, a withdrawal
381 syndrome may occur, typically characterized by restlessness, lacrimation, rhinorrhea,
382 perspiration, chills, myalgia, and mydriasis.
383

384 Measures that should be taken to manage symptoms of withdrawal should also be included in
385 this subsection. For example:

- 386 • Discontinue DRUG-X by gradual taper over a 2-week period to reduce the risk of
387 symptoms of withdrawal [*see Dosage and Administration (2.x)*].
388

389 2. *Information on Tolerance*

391 For drugs to which patients may develop tolerance, the following single sentence should be
392 included in the *Dependence* subsection:

- 393 • Tolerance is a physiological state characterized by a reduced response to a drug after
394 repeated administration (i.e., a higher dose of a drug is required to produce the same
395 effect that was once obtained at a lower dose).
396

397 Tolerance may develop to some drug effects much more rapidly than to other effects of the same
398 drug. For example, an individual might develop tolerance to the euphoria that opioids may
399 induce; however, the subject might not develop tolerance to the respiratory depressant effects of
400 the same opioid. This discrepancy in the development of tolerance to different opioid-related
401 effects may lead to overdose and death.
402

403 Relevant information about developing tolerance to the drug, if available, should be provided in
404 this subsection, including a discussion of the dosage or exposure at which tolerance is likely to
405 develop. For example:

- 406 • Tolerance may develop during chronic therapy with DRUG-X.

407 **IV. FORMATTING THE DRUG ABUSE AND DEPENDENCE SECTION**

408 Formatting for the DRUG ABUSE AND DEPENDENCE section must meet the requirements of
409 § 201.57(d) and should follow the general formatting recommendations available in guidance.¹⁷
411

¹⁷ See the guidance for industry *Labeling for Human Prescription Drug and Biological Products — Implementing the PLR Content and Format Requirements* (February 2013).

Contains Nonbinding Recommendations

Draft — Not for Implementation

412 When information within a subsection warrants further delineation, a consistent format for
413 headings and subheadings should be used (e.g., italics or underlining).

414

415

416 **V. WHAT NOT TO INCLUDE IN THE DRUG ABUSE AND DEPENDENCE** 417 **SECTION**

418

419 Labeling may not include speculative or promotional language (§ 201.56(a)).

420

421 FDA recommends that the following information generally *not* be included in the DRUG
422 ABUSE AND DEPENDENCE section of labeling:

423

424 • Detailed information on the proper disposal of controlled substances, which typically
425 appears elsewhere in labeling (e.g., in the PATIENT COUNSELING INFORMATION
426 section).

427

428 • Lengthy definitions — other than those recommended for inclusion in labeling in this
429 guidance — or discussions related to abuse and dependence.