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# Guidance for Industry

## Assessment of Abuse Potential of Drugs

### *DRAFT GUIDANCE*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)  
January 2010**

**Clinical Medical**

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# Guidance for Industry

## Assessment of Abuse Potential of Drugs

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**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
January 2010**

**Clinical Medical**

## TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND .....</b>	<b>2</b>
<b>III.</b>	<b>DETERMINING A DRUG'S ABUSE POTENTIAL .....</b>	<b>4</b>
	<b>A. Definitions.....</b>	<b>4</b>
	<b>B. When Should an Abuse Potential Assessment Be Submitted to FDA? .....</b>	<b>4</b>
	<b>C. What Should Be Included in an Abuse Potential Submission?.....</b>	<b>5</b>
<b>IV.</b>	<b>APPROACHES AND METHODS FOR ABUSE POTENTIAL ASSESSMENTS....</b>	<b>6</b>
	<b>A. Preclinical Screening .....</b>	<b>6</b>
	<b>B. Chemistry and Manufacturing .....</b>	<b>7</b>
	<b>C. Animal Behavioral Pharmacology Studies .....</b>	<b>9</b>
	<b>D. Application of Good Laboratory Practice (GLP) .....</b>	<b>12</b>
	<b>E. Pharmacokinetics/Pharmacodynamics .....</b>	<b>12</b>
<b>V.</b>	<b>HUMAN LABORATORY STUDIES .....</b>	<b>12</b>
	<b>A. Human Abuse Potential Study in Recreational Drug Users .....</b>	<b>13</b>
	<b>B. Related Pharmacology Studies .....</b>	<b>16</b>
	<b>C. Clinical Trial Data Relative to Abuse Potential Assessments .....</b>	<b>17</b>
<b>VI.</b>	<b>POSTMARKET EXPERIENCE/DATA .....</b>	<b>18</b>
<b>VII.</b>	<b>LABELING AND DRUG SCHEDULING .....</b>	<b>19</b>
	<b>ABBREVIATIONS.....</b>	<b>20</b>
	<b>BIBLIOGRAPHY.....</b>	<b>21</b>

1  
2  
3  
4  
5  
6  
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## Guidance for Industry<sup>1</sup>

### Assessment of Abuse Potential of Drugs

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

#### I. INTRODUCTION

This guidance is intended to assist sponsors who are developing drug products with the potential for abuse that may need to be scheduled under the Controlled Substances Act (21 U.S.C. 811(b), 811(c)). Examples of products that are addressed in this guidance include new molecular entities and new dosage forms of drug substances already controlled under the Controlled Substances Act (21 U.S.C. 812(c)). Drugs with abuse potential generally include drugs that affect the central nervous system, drugs that are chemically or pharmacologically similar to other drugs with known abuse potential, and drugs that produce psychoactive effects such as sedation, euphoria, or mood change.<sup>2</sup>

Specifically, the guidance discusses the following:

- The definition of *abuse potential*
- Information on submitting an abuse potential assessment, including a proposal for scheduling
- A description of what constitutes an adequate abuse potential assessment
- Information for sponsors performing an assessment, including (1) the design and conduct of appropriate studies and investigations and (2) general administrative recommendations for submitting a proposal for scheduling

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

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<sup>1</sup> This guidance has been prepared by the Controlled Substance Staff (CSS) in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> Comprehensive Drug Abuse Prevention and Control Act of 1970, H.R. Rep. No. 91-1444, 91st Cong., Sess. 1 (1970), reprinted in 1970 U.S.C.A.N. 4566, 4603.

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**II. BACKGROUND**

The purpose of scheduling substances under the CSA is to minimize abuse and diversion while affording appropriate therapeutic access. Each schedule under the Controlled Substances Act includes a set of regulations that are most restrictive for the Schedule I and II substances and are relatively less restrictive for the Schedule III to V drugs, respectively. Drugs in Schedule I have no accepted medical use in the United States. Depending on the Schedule (II-V), controls may include manufacturing and production quotas, varying degrees of manufacturing and distribution site security requirements, dispensing and prescribing limitations, a range of record-keeping and reporting requirements, and import/export regulations. Prescribers, dispensers, drug manufacturers, and distributors are required to register with the Drug Enforcement Administration (DEA).

Before a drug with a potential for abuse is controlled under the Controlled Substances Act (CSA), the Secretary, Department of Health and Human Services (HHS), must make a recommendation for scheduling under the CSA to the DEA. The regulatory responsibilities for this process are described in 21 U.S.C. 811 and 812, as well as in 21 CFR parts 1300-1316.

Under 21 U.S.C. 811(b) of the CSA, the Secretary of HHS is required to consider, in a scientific and medical evaluation, eight factors determinative of control under the CSA. Following consideration of the eight factors, the Secretary must make three findings and a recommendation for scheduling a substance in the CSA. The eight factors are set out in 21 U.S.C. 811(c) as follows:

1. Its actual or relative potential for abuse
2. Scientific evidence of the drug's pharmacological effects
3. The state of current scientific knowledge regarding the drug or other substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled.

The findings relate to a substance's abuse potential, legitimate medical use, and safety or dependence potential, which are factors considered in scheduling drugs under 21 U.S.C. 812.

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86 When a sponsor submits a new drug application (NDA) to the FDA for review, if the drug has a  
87 potential for abuse, the sponsor must submit “a description and analysis of studies or information  
88 related to abuse of the drug, including a *proposal for scheduling* (emphasis added) under the  
89 Controlled Substances Act.” (21 CFR 314.50(d)(5)(vii)). In addition, a description must be  
90 submitted “of any studies related to overdose, . . . including information on dialysis, antidotes,  
91 or other treatments, if known” (id.).

- 92  
93 1. The Controlled Substance Staff evaluates the drug’s abuse potential. The Controlled  
94 Substance Staff prepares a scientific analysis, including a recommendation for  
95 scheduling, based on a scientific and medical evaluation of all relevant and available data  
96 (including the public health risk and the sponsor’s proposal for scheduling), as required  
97 by the CSA.  
98
- 99 2. FDA provides the analysis to the National Institute on Drug Abuse (NIDA) for review  
100 and comment, as described in the Memorandum of Understanding (MOU) of March 8,  
101 1985 (50 FR 9518-20).  
102
- 103 3. The FDA analysis is reviewed and approved by the Office of Chief Counsel, the Center  
104 Director, and the FDA Commissioner.  
105
- 106 4. FDA then forwards the FDA proposed scheduling recommendation to the Assistant  
107 Secretary for Health, who makes the HHS recommendation for scheduling that is  
108 transmitted to the DEA.  
109
- 110 5. In accepting the HHS recommendation to schedule a drug, DEA publishes a notice of  
111 proposed rulemaking in the Federal Register wherein DEA proposes scheduling,  
112 describes the proposal and requests comments from the public. After the comment period  
113 (usually of 30 to 60 days) has expired, DEA reviews any comments, objections, and  
114 requests for a hearing that they have received, and publishes another FR notice, either  
115 finalizing the scheduling action with an effective date or responding to the objections and  
116 hearing requests.  
117

118 If the DEA determines that a drug requires scheduling, the sponsor must follow specific  
119 regulations related to drug labeling, manufacturing, storage, ordering, prescribing and  
120 dispensing. See generally 21 CFR parts 1300-1316. Sponsors are encouraged to contact the  
121 DEA early in the drug development process if they believe their drug may have abuse potential  
122 and may be controlled and to discuss with the DEA issues related to CSA researcher registration  
123 requirements, quotas, and other rules and regulations that concern controlled substances that may  
124 be relevant to their product.  
125

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126 **III. DETERMINING A DRUG'S ABUSE POTENTIAL**

127

128 **A. Definitions**

129

130 The Controlled Substances Act refers to the assessment of “potential for abuse,” “addiction-  
131 sustaining liability,” and “dependence” 21 U.S.C. 802(1),(9),(18),(29). The Controlled  
132 Substances Act does not define these terms. *Abuse potential* and *addiction-sustaining*, or *abuse*  
133 *liability*, can be understood to encompass similar concepts and, as such, are often used  
134 interchangeably.<sup>3,4</sup>

135

136 *Abuse potential* refers to a drug that is used in nonmedical situations, repeatedly or even  
137 sporadically, for the positive psychoactive effects it produces. These drugs are characterized by  
138 their central nervous system (CNS) activity. Examples of the psychoactive effects they produced  
139 include sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood  
140 changes. Drugs with abuse potential often (but not always) produce psychic or physical  
141 dependence and may lead to the disorder of *addiction*.

142

143 The concept of *abuse potential* encompasses all the properties of a drug, including, for example,  
144 chemical, pharmacological, and pharmacokinetic characteristics, as well as fads in usage and  
145 diversion history.

146

147 *Addiction* is defined as a chronic, neurobiological disorder with genetic, psychosocial, and  
148 environmental aspects, characterized by one or more of the following: impaired control over  
149 drug use, compulsive use, continued use despite harm, and craving (American Academy of Pain  
150 Medicine, American Pain Society, and American Society of Addiction Medicine consensus  
151 document, 2001).

152

153 **B. When Should an Abuse Potential Assessment Be Submitted to FDA?**

154

155 A sponsor must submit in the NDA an assessment of studies and other information related to the  
156 potential abuse of a drug and include a *proposal for scheduling* if the drug affects the central  
157 nervous system (CNS), is chemically or pharmacologically similar to other drugs with known  
158 abuse potential, or produces psychoactive effects such as sedation, euphoria, and mood changes.  
159 See 21 CFR 314.50(d)(5)(vii).

160

161 An assessment of abuse potential may be needed for new drugs, including new molecular entities  
162 (NME). An abuse potential assessment might also be necessary for a marketed drug product that  
163 presents an unexpected adverse event profile that includes events that are related to abuse  
164 potential or that is being re-evaluated for a new route of administration that could affect the  
165 abuse potential of the drug.

166

---

<sup>3</sup> See the DEA Web site for the schedules of drugs, contact information, pertinent information regarding the Controlled Substances Act, and related topics (<http://www.deadiversion.usdoj.gov>).

<sup>4</sup> “Conference on Abuse Liability Assessment of CNS Drugs,” *Drug Alcohol and Dependence*, 70:3 Suppl. 2003.

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167 **C. What Should Be Included in an Abuse Potential Submission?**  
168

169 The abuse potential assessment must be submitted as a section of the NDA or a supplement. The  
170 section must contain all pertinent preclinical, pharmacological, chemistry, biochemical, human  
171 laboratory, and clinical studies, drug formulation data, and a proposal for scheduling, if  
172 appropriate (21 CFR 314.50(d)(5)(vii)). The abuse potential section should also include  
173 proposed labeling that describes the drug’s abuse potential and dependence liability.  
174

175 The Controlled Substance Staff evaluates all abuse-related data to help FDA review divisions to  
176 determine the suitability of a drug’s label and labeling and accordingly may make additional  
177 recommendations to the sponsor that relate to the CSS evaluation.  
178

179 Contents of an abuse potential section include the following:  
180

181 For NMEs, the NDA should include an abuse potential section with the following:  
182

- 183 1. A summary, interpretation, and discussion of abuse potential data provided in the NDA
- 184 2. A proposal and rationale for placing (or not placing) a drug into a particular schedule of  
185 the Controlled Substances Act
- 186 3. All primary data related to the abuse potential characterization of the drug, organized  
187 under the following subheadings:
  - 188 a. Chemistry
  - 189 b. Preclinical Pharmacology
  - 190 c. Animal Behavioral and Dependence Pharmacology
  - 191 d. Pharmacokinetics/Pharmacodynamics
  - 192 e. Human Abuse Potential Laboratory Studies
  - 193 f. Clinical Trial Data Relative to Abuse and Dependence Potential
  - 194 g. Integrated Summaries of Safety and Efficacy
  - 195 h. Foreign Experience with the Drug (Adverse Events, Abuse Potential, Marketing  
196 and Labeling)
- 197 4. Electronic submissions  
198

199 For an NDA submitted in electronic format, the common technical document (CTD) should  
200 address points 1, 2, and 3a-h (above) under the appropriate Modules 1, 2, 3, 4 and 5. These  
201 sections should contain links to the summary of abuse data in Module 2 and the proposal for  
202 scheduling and product labeling in Module 1. The data and studies supporting sections 3 a-g  
203 (above) should be placed in the appropriate sections of the CTD: Chemistry (Module 3),  
204 preclinical and animal pharmacology (Module 4), pharmacokinetics/pharmacodynamics  
205 (Modules 4 and 5), human abuse and clinical studies (Module 5), and integrated summaries  
206 of safety and efficacy (Module 5). Foreign experience has no specific designated location,  
207 but would fit most appropriately under Module 5, postmarket experience.  
208

- 209 5. Paper submissions  
210

211  
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213 An NDA that will be submitted in paper form should contain the above listed information  
214 clearly identified as an abuse potential section.

215  
216 The scientific overview of the drug’s pharmacological activity should include consideration of  
217 the drug’s pharmacology, a description of its chemical structure and class, its profile of  
218 biochemical activity, its pharmacokinetics and metabolism, the production of any active  
219 metabolites (and their pharmacological activity profile), and a description of any adverse  
220 reactions.

221  
222 Sponsors are encouraged to consult with the Controlled Substance Staff through the appropriate  
223 FDA centers, offices, or divisions responsible for the overall review of the application about the  
224 design of studies and data to be included in an abuse potential section. Discussions between the  
225 Controlled Substance Staff and sponsors regarding the proposed studies and data can facilitate  
226 adequate data submission and full characterization of the abuse potential of the drug substance or  
227 product.

228  
229

230 **IV. APPROACHES AND METHODS FOR ABUSE POTENTIAL ASSESSMENTS**

231

232 A variety of approaches that can be used to assess the abuse potential of a drug product are  
233 discussed in the following sections of the guidance.

234

235 **A. Preclinical Screening**

236

237 In vitro receptor binding studies are an important part of the preclinical screening of new drugs  
238 with abuse potential because they are very useful in interpreting the results of other animal and  
239 human studies, as well as in the planning of future investigations.

240

241 In vitro binding studies should be conducted to determine the pharmacological site of action of  
242 the drug and active metabolites in the brain (e.g., receptor, transporter, ion-gated channel  
243 system). Novel drug mechanisms of action may be associated with previously unrecognized  
244 abuse potential in humans.

245

246 Although a drug may have a single high-affinity site, it is important that direct and indirect  
247 actions and effects of the drug on other neurotransmitter systems associated with abuse potential  
248 be assayed. Examples of neurotransmitter systems of interest include the following:

249

- 250 • Dopamine
- 251 • Norepinephrine
- 252 • Serotonin
- 253 • Gamma-aminobutyric acid (GABA)
- 254 • Acetylcholine
- 255 • Opioid
- 256 • N-methyl-D-aspartate (NMDA)
- 257 • Cannabinoid

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259 The application of general scientific principles, including the use of appropriate regional brain  
260 tissue, positive controls, and internal standards, should be ensured. High selectivity radioligands  
261 should be used whenever they are available. Binding sites can also be analyzed using  
262 complementary DNA (cDNA), encoding a specific receptor that is expressed in a homogeneous  
263 system.

264  
265 In vivo binding techniques, such as positron emission tomography (PET) or single photon  
266 emission computed tomography (SPECT), can also provide information about the localized  
267 action of drugs. Studies using these techniques can contribute important information about the  
268 whole body pharmacokinetic and pharmacodynamic properties of the drug in question.

269  
270 Knowledge of the binding profile may suggest which functional in vitro assays can help  
271 determine whether the drug is an agonist, antagonist, partial agonist, or mixed agonist-antagonist  
272 at specific binding sites. Based on the biochemical pharmacology, behavioral tests relevant to  
273 the specific mechanism of action will be more apparent.

274  
275 Receptor binding data should be submitted as a part of the pharmacology-toxicology section of  
276 the NDA and should also be included in, or hyperlinked to, the abuse potential assessment  
277 section of the NDA.

278  
279 **B. Chemistry and Manufacturing**

280  
281 *1. Consideration of Chemistry Data*

282  
283 Data from the chemistry, manufacturing, and controls (CMC) section of the NDA that are  
284 relevant to the abuse potential of the drug under investigation should be submitted as part  
285 of, or be hyperlinked to, the abuse potential section. The assessment of abuse potential  
286 should include information related to the synthesis of the drug, data on the physical and  
287 chemical properties of the substance and proposed drug product, and data related to  
288 alternate synthetic pathways and drug characteristics, including yields and impurity  
289 profiles.

290  
291 In addition to the information submitted as part of the CMC section of the NDA, the  
292 abuse potential assessment should include an evaluation of the physicochemical  
293 properties of the drug substance and product. Information on extractability and solubility  
294 of a drug is relevant to the drug's abuse potential and should be addressed.

295  
296 Assessment of such data is especially relevant when the new drug product is a new  
297 formulation of a drug substance, such as a 505(b)(2) NDA submission, of recognized  
298 abuse potential, that presents additional safety concerns. Examples of drugs with the  
299 highest relative abuse potentials can be found in Schedule II (see 21 CFR 1308.12 for the  
300 most current listing). Additional information on the ease or risk of extraction of the drug  
301 substance, that is, the active pharmaceutical ingredient (API), from the product  
302 formulation should be obtained. In particular, sustained- or extended-release  
303 formulations and transdermal systems (patches or mechanical devices containing drugs)  
304 that are expected to contain large quantities of a controlled substance should be assessed

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305 to determine the ease of extracting or altering the drug for abuse and diversion.  
306 Transdermal and transmucosal drug products in which excess unused drug substance  
307 remains after use are a major concern, and the safe disposal of these products should be  
308 addressed in the abuse potential assessment.

309  
310 Studies should be performed that provide information on the performance of the drug  
311 product under different conditions, such as application of bandages or heat or multiple  
312 applications of a transdermal system. Information should be obtained on how much drug  
313 substance might be released and any changes that could take place in the rate of release of  
314 the drug from the drug product if it is misused either intentionally or unintentionally. The  
315 effects of pH, temperature, and solvent polarity on disruption or destruction of the drug  
316 product matrix should be evaluated. Additional experimental variables may include  
317 exposure times to the solvent, agitation, varying the surface area (such as from intact to  
318 being ground, crushed, or cut up into pieces), and ease of crushing tablets or destroying  
319 the dosage form matrix. In general, assay procedures for drug content already reported  
320 under CMC may indicate the best conditions for drug extraction and analysis.

321  
322 *2. Abuse Deterrent Formulations*

323  
324 Formulations that deter abuse may be useful in ensuring access to drugs for purposes of  
325 medical treatment while limiting abuse and the consequences of abuse. For example, a  
326 combination product might be developed that contains an FDA-approved drug with abuse  
327 potential and a second FDA-approved drug without abuse potential that causes an adverse  
328 effect (e.g., sometimes a sponsor may add a substance to limit or reduce abuse of the  
329 narcotic). Several different types of abuse deterrent formulations have been proposed in  
330 the scientific literature, including formulations with physical barriers to tampering,  
331 combinations of an agonist with an antagonist, components that cause adverse events, and  
332 alternative methods of administration.<sup>5,6</sup>

333  
334 Currently, the concept of *abuse deterrence* is viewed as the introduction of some limits or  
335 impediments to abuse, as opposed to the outright elimination of abuse. For all dosages of  
336 such products, extractability and solubility studies should be designed to determine  
337 whether any of the drugs present in the combination might be differentially solubilized  
338 and extracted, and thus separated from the API.

339  
340 A new formulation that is designed with a possible claim of abuse deterrent qualities  
341 should be studied for relative abuse potential in human pharmacology studies. The abuse  
342 potential of the new formulation should be compared to a previously approved product  
343 that serves as a positive control. The positive control in these studies may be an  
344 immediate release product, an extended-release product, and possibly an extract of the  
345 new formulation that is believed not to be abusable (see section V.A below). In addition  
346 to the above assessments, robust assessments of efficacy, safety, biopharmaceutics

---

<sup>5</sup> N. Katz. "Abuse-Deterrent Opioid Formulations: Are They a Pipe Dream?" *Curr. Rheumatol. Rep.* 10(1): 11-8, 2008.

<sup>6</sup> N. Katz et al., "Challenges in the Development of Prescription Opioid Abuse-deterrent Formulations," *Clin. J. Pain*, 23(8), pp 648-60, Oct 2007.

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347 (including alcohol interaction), and epidemiologic studies should be performed to  
348 demonstrate that a new formulation is an abuse deterrent. Long-term epidemiological  
349 studies may also be necessary to support an abuse deterrent claim.

350

351 **C. Animal Behavioral Pharmacology Studies**

352

353 The behavioral assessment of drugs in animals is a continually evolving field that seeks to assess  
354 drugs using the latest scientific advances. The main goal of animal studies is to provide an  
355 indication early in drug development of a drug's abuse potential. The information gained can  
356 guide the sponsor and FDA in determining what additional studies should be conducted in  
357 animals and humans. The recommendations in the sections that follow address the conduct of  
358 animal abuse potential studies, recognizing that new methodologies may be developed.

359

360 *1. Principles in Study Design*

361

362 Animal abuse potential studies use *several species*, usually rodents and primates.  
363 Sponsors should provide (1) justification for the selection of an animal model and (2) the  
364 prior drug history of the animals selected. The *sample size* in animal studies should be  
365 adequate to accurately characterize the ability of the drug to induce the particular  
366 behavior of interest. The number of animals included in a study depends on the  
367 anticipated effect size and the desired power of the statistical test used.

368

369 *Route of administration* can significantly affect behavior because of psychophysiological  
370 and pharmacodynamic effects. Given that drugs are commonly abused by more than one  
371 route, the proposed clinical route of administration as well as other routes should be  
372 tested when feasible.

373

374 A determination of *plasma levels* of the parent drug and its major metabolites in animals  
375 over a time course are important when assessing similarities to human plasma levels.  
376 Pharmacodynamic and pharmacokinetic considerations should guide the selection of *time*  
377 *points for measurements*, including appropriate pretreatment times. A correlation  
378 between the pharmacokinetic profile and the appearance and resolution of behavioral  
379 effects for parent and psychoactive metabolites is often observed in abuse potential  
380 assessments.

381

382 The experimental design should include appropriate *negative and positive control groups*,  
383 with suitable justification provided. A negative control could include a drug without  
384 abuse potential that is approved for treatment of the same condition proposed for the new  
385 drug. The positive control should be in the same pharmacological class as the test drug  
386 when possible. Doses for negative and positive controls should be behaviorally  
387 equivalent to the test drug. For drugs that are new molecular entities or are not  
388 pharmacologically similar to a known drug of abuse, an appropriate comparator can be a  
389 drug approved for treatment of the same condition for which the new drug is proposed.

390

391 Generally, studies should explore the behavioral effects of a *range of doses*, including  
392 high doses that produce plasma levels that are multiples of the therapeutic dose. Doses

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393 should be chosen on the basis of the drug's characteristics as the plasma levels of the drug  
394 increase. Additional principles of dose selection can be found in the DHHS/Public  
395 Health System document entitled *Policy on Humane Care and Use of Laboratory*  
396 *Animals*.<sup>7</sup> Information resulting from adverse effects or other safety concerns should be  
397 used to set dose level limits or indicate that further investigation is appropriate.

398  
399 ***2. Types of Animal Abuse Potential Studies***  
400

401 A variety of approaches exist to study the abuse potential of drugs in animals. When  
402 choosing a behavioral test, the chemical and pharmacological properties of the drug, its  
403 pharmacological class, and existing knowledge about its abuse potential should be  
404 considered.

405  
406 ***Self-administration*** tests assess the rewarding properties of a drug. If animals actively  
407 work at a behavioral task to receive a dose of the drug, it is likely that the drug will be  
408 rewarding in humans.

409  
410 ***Conditioned place preference*** is a method related to self-administration in which animals  
411 choose to spend time in one of two distinct environments, that is, the site where they  
412 previously received a drug or where they previously received placebo. Conditioned place  
413 preference is not as rigorous a behavioral test as self-administration in determining the  
414 rewarding properties of a drug.

415  
416 A positive result with a drug in self-administration or conditioned place preference tests  
417 in animals can have some predictive value in identifying drugs that might have abuse  
418 potential in humans. However, a negative result does not necessarily mean that the drug  
419 does not have abuse potential. This is because certain classes of drugs used by humans  
420 do not induce self-administration or conditioned place preference in animals. Examples  
421 of such drug classes include 5-HT<sub>2</sub> agonist hallucinogens, cannabinoids, NMDA  
422 antagonists, and other drugs that produce effects broadly characterized as “psychedelic.”  
423 When a drug could produce effects that are similar to these classes of drugs, other  
424 behavioral tests should be relied on to assess abuse potential.

425  
426 ***Drug discrimination*** is a method in which animals indicate whether a test drug produces  
427 physical or psychic perceptions similar to those produced by a known drug of abuse. In  
428 this test, an animal learns to press one bar when it receives the known drug of abuse and  
429 another bar when it receives placebo. A challenge session with the test drug determines  
430 which of the two bars the animal presses more often, as an indicator of whether the test  
431 drug is recognized or perceived by the animal as the known drug of abuse.

432  
433 ***Psychomotor tests*** assess the effects of the test drug on motor functioning in comparison  
434 with the effects of well-characterized drugs of abuse.  
435

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<sup>7</sup> This document is available on the Internet at <http://grants1.nih.gov/grants/olaw/references/phspol.htm>.

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436 ***Dependence potential*** of a substance is the propensity of a substance, as a consequence  
437 of its pharmacological effects on physiological or psychological functions, to give rise to  
438 a need for repeated doses of the substance. Physical dependence is often characterized by  
439 withdrawal symptoms.<sup>8</sup> Psychological or psychic dependence refers to impaired control  
440 over drug use, such as craving.

441  
442 Dependence potential can be determined by measuring the pharmacological properties  
443 during animal and human drug testing. Tests for *tolerance* and *physical dependence*  
444 examine the responses to repeated administration of a drug. Repeated doses over a wide  
445 range are needed to attain the same effects observed at starting doses or, as an alternative,  
446 to avoid symptoms of *withdrawal* or “bad feelings.” Studies should start at doses, as  
447 compared to placebo, showing no behavioral effects, and doses should be increased  
448 several times to produce a dose-effect curve. Correlation of results with plasma  
449 concentration measurements can provide useful insight when interpreting the studies. An  
450 assessment of *tolerance* or *physical dependence* should be performed as part of the safety  
451 assessment of a drug and should be considered in drug scheduling. The demonstration of  
452 dependence in animals can influence the human safety and the abuse potential  
453 evaluations.<sup>9</sup>

454  
455 **3. *Timing of Studies During Preclinical Development***

456  
457 Sponsors are encouraged to consult with the Agency early in the development of new  
458 molecular entities about the need for, and optimal timing of, animal abuse potential  
459 studies. The consultation will be most useful before the end of phase 2 of the  
460 development to facilitate planning of late stage clinical trials. Conducting any necessary  
461 animal abuse potential studies early in development will provide the sponsor with more  
462 information for consideration in the overall development of the drug. However, during  
463 phase 1, a drug’s clinically effective dose may not be known, and animal abuse potential  
464 studies that do not use an appropriate dose may not be useful for assessing abuse  
465 potential or in the design of human abuse potential studies later in development. See  
466 section V.A below.

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<sup>8</sup> Physical dependence is a state of adaptation manifested by a drug class-specific withdrawal syndrome produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug and/or administration of an antagonist. Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time. The presence of tolerance does not determine whether a drug has abuse potential, in the absence of other abuse indicators such as rewarding properties (American Academy of Pain Medicine, American Pain Society and American Society of Addiction Medicine consensus document, 2001).

<sup>9</sup> M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonized Tripartite Guideline, current *Step 2* version, July 15, 2008, pp. 16-17.

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**D. Application of Good Laboratory Practice (GLP)**

The good laboratory practice (GLP) principles described in the guidance for industry *S7A Safety Pharmacology Studies for Human Pharmaceuticals* (ICH S7A) and in FDA regulations, 21 CFR part 58, apply to abuse potential studies in animals.<sup>10</sup> The scope of ICH S7A includes new chemical entities and biotechnology-derived products for human use. Sponsors should find ICH S7A useful in ensuring quality and reliability of animal safety studies.

**E. Pharmacokinetics/Pharmacodynamics**

Characterization of the pharmacokinetic (PK)/pharmacodynamic (PD) properties of a substance and product is important for determining the abuse potential of a drug or product. Measures of systemic exposure to the drug product from preclinical and clinical studies should be considered when assessing the abuse potential of the drug.<sup>11</sup> Data should include information on maximum concentration ( $C_{max}$ ), time to onset, time to maximum concentration ( $T_{max}$ ), area under the curve ( $AUC_{0-\infty}$ ), and the terminal elimination half-life ( $T_{1/2}$ ) of the parent drug and any psychoactive metabolites. In addition, data on bioavailability, distribution volume, and drug clearance should be included. The PK information relevant to abuse potential and described in the abuse potential section of the NDA should include or be hyperlinked to data that have also been submitted under the PK section of the NDA.

Information on PD should also be included if available. This information will be of value because it can help to correlate psychoactive drug effects with achieved plasma concentrations.

Information on factors that might change the properties of a product, such as crushing a tablet or taking the product with alcohol and inducing rapid release and absorption of the active drug, should be collected not only to characterize the abuse potential of the product, but also to identify any safety concerns associated with misuse of the product (see section IV.B.1).

**V. HUMAN LABORATORY STUDIES**

The abuse potential assessment of a new drug should be based on a composite analysis of chemistry, pharmacology, and clinical data, and the public health risk that the drug presents. One study alone generally would not be considered sufficient for an adequate abuse potential assessment. Data from human abuse potential studies will contribute to the development of product labeling and drug scheduling recommendations. If the human abuse potential studies and the adverse events profile from clinical studies do not show the presence of rewarding effects or other abuse-related behaviors or similar pharmacology, a recommendation for scheduling would be unlikely. (General information on conducting clinical studies can be

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<sup>10</sup> We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/cder/guidance/index.htm>.

<sup>11</sup> See FDA's guidance on *Format and Content of the Human Pharmacokinetics and Bioavailability Section of an Application*, available on the CDER guidance page.

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508 obtained from the FDA guidance on *General Considerations for the Clinical Evaluation of*  
509 *Drugs*.<sup>12)</sup>

510

511 **A. Human Abuse Potential Study in Recreational Drug Users**

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513 The human abuse potential study consists of pharmacology assessments that provide unique  
514 information relevant to central nervous system-active drugs, especially opioids, stimulants,  
515 depressants, cannabinoids, and hallucinogens (see also section IV.B.2). The objectives of such  
516 studies are to provide information on the relative abuse potential of a new drug in humans and to  
517 contribute to predicting the likelihood of abuse when the drug becomes available. The studies  
518 are typically conducted in a population experienced in using drugs recreationally after sufficient  
519 data related to safety and efficacy in a patient population have been acquired. Sponsors are  
520 encouraged to proactively interact with FDA in planning and conducting such studies, often by  
521 the end of phase 2. Sponsors are encouraged to submit protocols to FDA for review and advice  
522 on design, as well as safety issues, before beginning the study.

523

524

*1. Subjects*

525

526 Human abuse potential studies are usually conducted in experienced, recreational drug  
527 users who have a recent or current history of using a drug in the pharmaceutical class of  
528 the test drug. The subjects in the study should have experience with drugs with similar  
529 psychoactive properties, regardless of the pharmacologic mechanism of action.

530

531 The characteristics of the study population with respect to past and current drug use and  
532 abuse should be presented in detail with respect to drugs abused, preferred drug(s) of  
533 abuse, and duration of abuse and abstinence. Screening for substance abuse during the  
534 study is often necessary to ensure that subjects are not currently abusing other substances.  
535 Exclusion criteria should include a current diagnosis of substance dependence, current  
536 abuse, and current treatment for a substance-related disorder.

537

538 Recently, some abuse potential studies have also been conducted in drug naïve healthy  
539 subjects and this is an area of needed research. These two populations may differ in  
540 important ways, including in their ability to identify subtle differences in drug effects that  
541 are relevant to abuse assessment.

542

543 For the study to be interpretable, the subjects should be able to reliably report “drug-  
544 liking” and be able to provide ratings of drug experiences related to the drug’s subjective  
545 effects and similarity to specific classes of known drugs of abuse. Study subjects should  
546 be able to distinguish the effects of the test drug and similar drugs and should be able to  
547 demonstrate that they can discriminate the effects of the positive control from the  
548 placebo. Some investigators may consider prescreening subjects for their ability to detect  
549 and report subjective drug effects, and to distinguish the effects of the appropriate  
550 positive control. Other factors that influence the significance of study results include

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<sup>12</sup> Available on the Internet at  
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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551 demographic range with respect to age, sex, and race, drug of choice, frequency of  
552 participation in drug abuse studies, duration of drug abuse, variety of drugs used, and  
553 duration of drug abstinence.<sup>13</sup>

554  
555 2. *Design*

556  
557 The design of the study should be based on the study objective and statistical analysis  
558 model. The human abuse study measures repeated single-dose administrations over a  
559 period of time, determined by the time course of the drug's effects. Doses should range  
560 from minimally effective to supratherapeutic, if safety is known and precautions are  
561 taken to deal with safety concerns.

562  
563 Human abuse potential studies are usually double blind, double dummy, placebo, and  
564 positive comparator controlled, and are crossover designs. The abuse potential of the test  
565 drug is assessed by comparing responses of the test drug with those of placebo and with  
566 those of the positive control. A result of *no abuse potential* should be validated by  
567 showing a significant difference in response between the positive control and the placebo.  
568 All subjects are tested under all drug conditions. Drug conditions would typically  
569 involve placebo and multiple doses of the new drug and positive control. A repeated  
570 Williams square design is recommended. Subjects should be randomly assigned to one  
571 of the sequences in the Williams square. Thus, the number of replicates of the Williams  
572 square depends on the desired sample size. The assessment of abuse potential can  
573 include co-primary endpoints and some secondary endpoints of interest, if appropriate.  
574 However, no more than three primary measures should be recommended. Although the  
575 use of 12 to 25 subjects has been seen in past studies, in some recent studies as many as  
576 40 subjects have been used. We don't recommend a specific number of subjects for a  
577 study; however, the study should be sufficiently powered such that we can determine the  
578 statistically significant relationship of the test drug to placebo and positive control to the  
579 primary and secondary outcome measures. The investigator and the staff who interact  
580 with subjects should not know the sequence of substances administered.

581  
582 Procedures for managing adverse events should be explicit and appropriate for the drug  
583 class being tested. The washout period of a crossover designed study should be at least  
584 five times the maximum  $t_{1/2}$  of the longest acting drug in the study.

585  
586 3. *Study Site*

587  
588 Studies should be conducted under controlled laboratory settings, preferably in a closed  
589 residential unit. The subject population is at risk for abuse of the same type of drugs  
590 being tested, and subjects with histories of drug abuse may be more likely to dropout or  
591 miss visits. Therefore, it is recommended that subjects stay overnight following  
592 administration of each dosage. The laboratory setting should provide control over  
593 variables related to sleep and nutrition that can lead to greater variability in outcome.  
594 The controlled setting also provides greater safety at the higher than therapeutic doses

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<sup>13</sup> "Conference on Abuse Liability Assessment of CNS Drugs," *Drug and Alcohol Dependence*, 70:3 Suppl., 2003.

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595 that are usually administered and can help prevent other forms of drug abuse and possible  
596 drug carryover effects.

597  
598 *4. Selection of Doses and Controls*

599  
600 Study protocols should be specific as to proposed dosing and monitoring of subjects. The  
601 test drug should be compared to the positive control under identical conditions for assay  
602 of abuse potential. The positive control should have measurable abuse potential  
603 previously established through experimental studies and epidemiological data. The  
604 positive control should be a drug of abuse in the same pharmacological class as the test  
605 drug. Additional useful information can be obtained if the positive control has the same  
606 medical indication as the test drug. Limits of sensitivity of the assay to lower doses  
607 should be determined. Slopes of the dose effect functions across different measures  
608 should be determined. Within a given study, a positive control should have its  
609 anticipated effects on the parameters of abuse potential that are being studied. Failure to  
610 demonstrate the expected effects would invalidate the study.

611  
612 A dose run-up pilot study in a drug abuser population can provide an empirical basis for  
613 dose selection. This preliminary study potentially provides an opportunity to evaluate  
614 and modify procedures in subsequent dose effect studies.

615  
616 *5. Outcome Measurements*

617  
618 The primary method for evaluating the subjective effects of drugs is through the use of  
619 standardized questionnaires. Study participants are asked to rate their response to a drug  
620 that has been administered to them in a laboratory in terms of whether the drug produces  
621 sensations such as “good,” “high,” or “spacey.” The “drug liking” rating can be  
622 measured on a Visual Analog Scale during a drug session or at the end of the drug  
623 session.

624  
625 Measures most directly related to likelihood of abuse include the following:

- 626  
627
- 628 • Ratings of liking (“Do you like the drug?”) and other subject-rated effects
  - 629 • Determining the subjects’ disposition to take the drug again
  - 630 • Drug identification (that is, subjects are able to categorize the effects of the test drug as  
631 similar to those of numerous classes of psychoactive drugs)

632 Measures of drug effect typical of drug class include the following:

- 633  
634
- 635 • Subject-rated strength of drug effect
  - 636 • Behavioral and cognitive performance assessment
  - 637 • Measurement of relevant physiological effects
  - 638 • Assessment of mood state changes using Profile of Mood States (POMS) and the  
639 Addiction Research Center Inventory (ARCI)

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640                   6.     *Analysis of Data*

641  
642                   If the study consists of a heterogeneous population of identifiably unique groups,  
643 analyses of the data subsets corresponding to each group should be conducted. For  
644 example, a population of recreational users of central nervous system depressants could  
645 include individuals who prefer to abuse sedative-hypnotic drugs over alcohol. In a study  
646 evaluating a new central nervous system stimulant, the study population could include  
647 individuals identified as cocaine abusers, for example. These individuals are often  
648 polydrug abusers and may prefer to abuse drugs from other pharmacological classes. The  
649 differences in preference of each population group to the drug class could yield different  
650 results. Further research in this area of analysis would help determine under what  
651 circumstances these subgroup analyses can be performed and are useful.

652  
653 Information about the subjective effects of drugs in humans can also be obtained through drug  
654 discrimination studies, in which subjects are first trained to recognize the effects of a known drug  
655 of abuse compared to placebo. Subjects then receive a blind challenge with different doses of a  
656 test drug to determine whether they can identify the effects of the test drug as being similar to  
657 those of the known drug of abuse.

658  
659 Self-administration studies in humans can be a useful method for determining the probability of  
660 abuse potential. In this test, subjects are given the opportunity to request additional doses of a  
661 drug after initial exposure to that drug, often in conjunction with a requirement for a certain  
662 amount of work before the subsequent dose is offered. The major advantage of self-  
663 administration in humans compared to that in animals is that human subjects can communicate  
664 the reasons a drug is desirable to them, and specifics about the full range of sensations that a  
665 drug induces.

666  
667  
668                   **B.     Related Pharmacology Studies**

669  
670 Other aspects of human pharmacology of the test drug (e.g., cognitive and performance  
671 impairment) should be investigated.

672  
673 Certain tests that might be conducted during clinical studies to assess the therapeutic potential of  
674 a new drug can give indications of similarities between the new drug and known drugs of abuse.  
675 Psychomotor tests that determine whether the effects of a drug increase or decrease normal  
676 motor functioning can suggest that a drug may be like a known stimulant or depressant.  
677 Similarly, cognitive tests that assess whether memory, perception, attention, language ability, or  
678 consciousness are altered by a drug can indicate the presence of certain effects that drug abusers  
679 might find desirable.

680  
681 As with animal tests, human investigations with new drugs should assess whether a drug  
682 produces tolerance upon repeated administration, as well as whether a drug produces withdrawal  
683 symptoms following discontinuation of drug administration, which is indicative of physical  
684 dependence.

686           **C.       Clinical Trial Data Relative to Abuse Potential Assessments**

687  
688       The evaluation of the adverse events profile of a drug from clinical trials can provide a signal of  
689       abuse potential. The systematic categorization, tabulation, and analysis of safety data for mood  
690       elevation, sedation, and psychotomimetic events can provide useful information. The incidence  
691       of euphoria-type adverse events (including euphoria, euphoric mood, elevated mood, mood  
692       alteration, feeling drunk, feeling abnormal) and hallucination (visual and auditory) are a few of  
693       the more prominent MedDRA terms that should be considered. MedDRA 12 terms for  
694       inappropriate affect, which include the following lower level terms: elation inappropriate,  
695       exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate  
696       elation, inappropriate laughter, inappropriate mood elevation, should also be considered. A  
697       prospective evaluation of withdrawal adverse events after abrupt discontinuation of treatment  
698       can provide information relevant to dependence. Various quantitative measurements will be  
699       useful in providing objective data to assess dependence (e.g., opioid and benzodiazepine  
700       withdrawal scales and psychiatric rating scales). Data related to serious psychiatric and  
701       neurological adverse events and the need for hospitalization is relevant to the public health risks  
702       and abuse potential of the drug.

703  
704       Phase 3 clinical trials evaluate the safety and efficacy of a product for a specific condition in  
705       large multi-center trials involving the intended patient populations. Phase 3 trials provide  
706       support for therapeutic dose recommendations; dose response data; and data relevant to abuse,  
707       dependence potential, drug diversion, and accountability, as related to study subjects (completers  
708       and dropouts).

709       Sponsors should make every effort to do the following:

- 710
- 711           1. Set criteria, collect data, and tabulate the abuse, misuse, noncompliance, and diversion  
712           cases across the studies and study sites with special attention to aberrant drug behaviors  
713           that may be indicative of drug abuse, misuse and/or diversion.<sup>14,15</sup>  
714
  - 715           2. Provide complete information, including case report forms and final outcomes, on all  
716           instances of addiction, abuse, misuse, overdose, drug diversion/drug accountability,  
717           discrepancies in amount of the clinical supplies of the study drug, noncompliance,  
718           protocol violations, lack of efficacy, individuals lost to follow-up, and any other reasons  
719           why subjects dropped out of the study.  
720
  - 721           3. Provide information on the risks of addiction, abuse, misuse, overdose, and drug  
722           diversion in the study populations.  
723

724       Pertinent data can include measurements of drug accountability, tolerance, physical dependence,  
725       or withdrawal symptoms, and the presence of signs or symptoms of drug abuse, misuse,

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<sup>14</sup> S.D. Passik, K.L. Kirsh, K.B. Donaghy, R.K. Portenoy, “Pain and Aberrant Drug-Related Behaviors in Medically Ill Patients With and Without Histories of Substance Abuse,” in *J. Pain*, 2(2):173-81, Feb 2006.

<sup>15</sup> <http://sbirt.samhsa.gov/> Screening and brief intervention (SBI) can identify the severity of the “problem” in study participant and identify the appropriate level of intervention.

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726 overdose, or drug diversion. Evidence from clinical trials suggesting that a drug has reinforcing  
727 effects can warrant a prospective abuse potential study (as described above, under section V.A).  
728

729 Abuse-relevant adverse event data for non-patient healthy populations can be obtained from  
730 single and multiple dose pharmacokinetic studies and electrocardiographic studies.  
731

732

733 **VI. POSTMARKET EXPERIENCE/DATA**  
734

735 Foreign postmarket experience and epidemiological data regarding misuse and abuse of a drug  
736 under review by the FDA may be useful in decisions about scheduling a substance under the  
737 CSA and labeling a drug under the Food, Drug, and Cosmetic Act (FDCA). Information from  
738 countries outside the United States can contribute to the abuse potential assessment of a drug,  
739 especially if there has been substantial postmarket experience. Adverse events reports associated  
740 with appropriate medical use, misuse, or illicit use, as well as data on abuse and diversion of a  
741 drug can be relevant. In addition, English translations of labels approved in other countries can  
742 provide relevant information regarding safe use, abuse, and dependence.  
743

744 For active pharmaceutical ingredients that are formulated into new drug products, postmarket  
745 data on abuse, misuse, overdose, and diversion in the United States provide valuable insight.  
746 Sponsors should search publicly available databases, including the Drug Abuse Warning  
747 Network (DAWN), the National Survey on Drug Use and Health (NSDUH), the Treatment  
748 Episode Data Set (TEDS), Monitoring the Future (MTF), and other databases, to characterize  
749 and monitor risks associated with the misuse and abuse of a drug and to estimate the extent of  
750 use and abuse of a particular drug.<sup>16</sup> Because these databases have limitations, the scope of each  
751 individual database should be described to clarify the applicability and limitations of the data that  
752 are provided.  
753

754 Raw counts and weighted estimates from the above databases should be put into the context of  
755 relative exposure, especially for purposes of comparisons and assessing trends. The ratio of the  
756 number of abuse events (*numerator*) relative to the number of prescriptions or number of patients  
757 or amount of drug produced during the specified time period (the *denominator*) should be  
758 calculated to provide an abuse indication corrected for exposure. Such a calculated ratio for a  
759 test drug can provide useful information when compared with pharmacologically similar drugs  
760 covering the same time period. This calculation would be relevant to the overall assessment of  
761 relative abuse for a drug and may be useful in providing meaningful trends over a period of  
762 several years.  
763

764 Information from other sources that is neither systematically acquired nor statistically significant  
765 can provide only anecdotal information that a substance is being illicitly used, purchased, sold,  
766 or diverted. Such sources include substance abuse clinics, poison control centers, state boards of  
767 pharmacy, medical examiners (ME), police diversion units, local departments of public health,

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<sup>16</sup> More information and statistics on substance abuse are available from the Substance Abuse and Mental Health Services Administration Web site at <http://www.oas.samhsa.gov> and the National Institute on Drug Abuse Web site at <http://www.nida.nih.gov>.

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768 and national or field offices of the DEA. DAWN ME data can provide important information  
769 related to drug mortality. Determining whether there are increasing or decreasing trends in abuse  
770 can provide valuable information about the postmarket experience with a drug product.

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772

773 **VII. LABELING AND DRUG SCHEDULING**

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775 Labeling and drug scheduling play different roles in encouraging safe and appropriate use of  
776 drugs with abuse potential, as well as in minimizing the actual abuse, misuse, and diversion that  
777 may result from their availability.

778

779 Information on the abuse potential of a drug is generally conveyed to healthcare professionals  
780 and patients through appropriate labeling. The *Drug Abuse and Dependence* section of the label  
781 should describe the abuse potential and symptoms of withdrawal of the drug and provide  
782 information on its safe use. The label may not reflect that a drug is scheduled, or that it will be  
783 scheduled, until the scheduling process is complete. When the scheduling process is completed,  
784 a supplement must be submitted to reflect the schedule. The regulations require that the label of  
785 a drug that has been scheduled bear the C-X symbol, where X is the schedule II, III, IV or V (21  
786 CFR 201.57(a)(2)). Labeling is the cornerstone of risk minimization efforts for most of the  
787 drugs approved by FDA.

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**ABBREVIATIONS**

AERS	Adverse Events Reporting System
ASH	Assistant Secretary of Health
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CNS	Central nervous system
CSA	Controlled Substances Act
CSS	Controlled Substance Staff
DAWN	Drug Abuse Warning Network
DEA	Drug Enforcement Administration
DHHS	Department of Health and Human Services
DOJ	Department of Justice
FDA	Food and Drug Administration
IND	Investigational New Drug
NDA	New Drug Application
NSDUH	National Survey on Drug Use and Health
NIDA	National Institute on Drug Abuse
SAMHSA	Substance Abuse and Mental Health Services Administration
U.S.C.	United States Code

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