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DRAFT GUIDANCE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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Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

I. INTRODUCTION

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

- Prescription drugs controlled under the Controlled Substances Act (CSA)[4]
- Prescription drugs not controlled under the CSA for which there is important information to convey to health care providers related to abuse and dependence

This guidance discusses and provides recommendations on the following:

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

[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).

- What information to include in the DRUG ABUSE AND DEPENDENCE section, including common terminology and definitions related to abuse and dependence

- How to write, organize, and format the information within the DRUG ABUSE AND DEPENDENCE section

- How information related to topics presented in the DRUG ABUSE AND DEPENDENCE section should be distributed elsewhere in labeling

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

In general, FDA's guidance documents 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.

II. GENERAL PRINCIPLES

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

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

A. Distribution of Information Among Labeling Sections

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

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

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

B. Updating the Section

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

C. Terminology

The concepts of abuse, misuse, addiction, physical dependence, and tolerance are important for health care providers to understand to facilitate the safe and effective use of drugs associated with the development of these behaviors or conditions. However, these terms are commonly confused or misinterpreted. FDA recommends that definitions of these terms be included in the DRUG ABUSE AND DEPENDENCE section of labeling to ensure common understanding and 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).

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

III. CONTENT AND FORMAT OF THE DRUG ABUSE AND DEPENDENCE SECTION

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

A. 9.1 Controlled Substance

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

1. Prescription Drugs Scheduled Under the Controlled Substances Act

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

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

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

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

For some drug products that are controlled substances, there may be additional legal 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.

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

2. Prescription Drugs for Which Controlled Substance Scheduling Is Pending

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

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

Once DEA has issued a scheduling decision assigning a controlled substance schedule, the 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

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

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

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

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[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.

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

- Active ingredient-Y is not a controlled substance.

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

B. 9.2 Abuse

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

1. Information on Abuse

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

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

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

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

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

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

[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).

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

- Abuse of DRUG-X poses a risk of overdosage, which may lead to death, central nervous system and respiratory depression, hypotension, and seizures.

OR

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

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

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

a. Product-specific risks related to abuse

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

- Inappropriate manipulation (e.g., chewing, crushing, dissolving) or self-administration by an inappropriate route (e.g., snorting or injecting) enhances release of active ingredient-Y and increases the risk of overdose or death.

- Inappropriate intravenous, intramuscular, or subcutaneous use of DRUG-X can result in death, local tissue necrosis, infection, pulmonary granulomas, and an increased risk of endocarditis and valvular heart injury.

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

b. Abuse potential studies

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

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

c. Products with abuse-deterrent properties

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

2. Information on Misuse

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

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

Examples of misuse include:

- Patients intentionally using a prescription drug for a condition different from the condition for which the drug is prescribed
- Patients intentionally taking a drug for therapeutic purposes at a higher dose or taking the drug at a different dosing interval than prescribed
- Individuals intentionally using a drug for therapeutic purposes when the drug is not prescribed for them

Misuse is defined in the context of *therapeutic* use, while abuse is defined in the context of *non-therapeutic* use. The terms misuse and abuse are similar in that they both represent the intentional intake of a drug in a way other than prescribed or by an individual for whom the drug is not prescribed. If the drug is used for therapeutic purposes, other than as prescribed, either for 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).

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

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

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

3. Information on Addiction

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

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

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

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

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[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*.

C. 9.3 Dependence

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

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

1. Information on Physical Dependence and Withdrawal

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

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

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

In a person who is physically dependent on a drug, a withdrawal syndrome is normally 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*.

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

- Physical dependence can occur in patients treated with DRUG-X. Abrupt cessation or dose reduction following chronic use can result in withdrawal symptoms, including extreme fatigue and depression.

- If DRUG-X is abruptly discontinued in a physically dependent patient, a withdrawal syndrome may occur, typically characterized by restlessness, lacrimation, rhinorrhea, perspiration, chills, myalgia, and mydriasis.

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

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

2. Information on Tolerance

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

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

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

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

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

IV. FORMATTING THE DRUG ABUSE AND DEPENDENCE SECTION

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

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

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

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

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

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

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

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