

Draft Guidances on the Indications and Usage & Drug Abuse and Dependence Sections of Labeling

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Disclaimer



- The views and opinions expressed in this presentation represent those of the presenter, and do not necessarily represent an official FDA position.
- The labeling examples in this presentation are provided only to demonstrate current labeling development challenges and should not be considered FDA recommended templates.
- Reference to any marketed products is for illustrative purposes only and does not constitute endorsement by the FDA.

Learning objectives



- Describe recommendations for prescription drug labeling outlined in draft guidances on the Indications and Usage & Drug Abuse and Dependence sections
- Identify labeling information discussed today that is relevant for your organization

Draft Guidance on the Indications and Usage Section of Labeling

Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Guidance for Industry

DRAFT GUIDANCE

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Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to <https://www.regulations.gov>. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Iris Masucci at 301-796-2500 or (CBER) the Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

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 2018
Labeling

Indications and Usage section



- Primary role is to enable health care practitioners to readily identify appropriate therapies for patients by clearly communicating the drug's approved indication(s)
- Should be clear, concise, useful, and informative and, to the extent possible, consistent within and across drug and therapeutic classes

Scope of an indication relative to the population studied



- Section should clearly communicate the scope of the approved indication, including the population to which the determination of safety and effectiveness is applicable
- Indicated population may mirror the studied population (e.g., in terms of patient demographics or severity of disease or condition), but can sometimes differ

Broader than studied



An indication for a broader population than the patient population studied in controlled trials may be appropriate after careful consideration of:

- Generalizability of the evidence
- Consistencies in the disease process across different groups
- Drug's overall benefits and risks

Broader than studied



Indications cover patient populations that were absent or specifically excluded from the clinical studies supporting approval

- e.g., geriatric patients, pregnant women, patients taking certain concomitant drugs, patients with a different severity or stage of a disease

Example of a broader indication



- A study in adults enrolled patients of a certain age range and excluded patients taking certain concomitant drugs
- Available evidence does not suggest drug would be unsafe or ineffective in adult patients outside that age range or in those taking the other drugs

Indication should be worded to reflect a broader age group (i.e., “in adults”), rather than the exact ages studied.

And unless available evidence suggests otherwise, the indication should not exclude use in patients taking the concomitant drugs.

Example of a narrower indication



- A study enrolled and randomized patients, but then also stratified participants by the presence or absence of a specific genomic marker
- The study demonstrated benefit only in patients who had tested positive for the marker

FDA may conclude that the available evidence supports approval of an indication in a population that is narrower in scope than the population that was studied.

Pediatric considerations



Approach noted earlier about generalizing among adult populations is generally not appropriate across pediatric populations or between adult and pediatric populations because of:

- Statutory requirements related to pediatric assessments
- Unique clinical considerations for pediatric patients (e.g., differences in drug metabolism, different safety risks)

Inclusion of age groups in indications



An indication should state that a drug is approved, for example:

- “in adults”
- “in pediatric patients X years of age and older”
- “in adults and pediatric patients X years of age and older”

Content and format of the section



Indications and Usage section includes:

- The indication
- And, as appropriate, any identified limitations of use

Details to include in the indication



- For many drugs, the indication will be sufficiently conveyed by stating the disease or condition being treated, prevented, mitigated, cured, or diagnosed, and the approved age group(s)
- In such circumstances, endpoints and descriptions of benefit should be summarized in the Clinical Studies section of labeling and should not be included in the indication

Details to include in the indication



- However, other scenarios may warrant the inclusion of more information in the indication
- For example:
 - When a drug may target different aspects of a disease (e.g., in multiple sclerosis)
 - When endpoints are not well-standardized (e.g., in heart failure)

In these scenarios, the specific benefits of the drug should be stated within the indication.

Example of endpoints within indications



- For a drug indicated for the treatment of insomnia, the indication should state whether the drug affects sleep onset, sleep maintenance, or both, in order to facilitate appropriate prescribing for an individual patient

Example of endpoints within indications



- For many outcome studies, when there is an overall effect on a composite endpoint, the indication should identify the components of the composite (e.g., cardiovascular death, myocardial infarction, and stroke)

Components of the indication



The indication should begin “DRUG-X is indicated” and must include the following elements required under 21 CFR 201.57(c)(2)(i):

- The disease, condition, or manifestation of the disease or condition (e.g., symptoms) being treated, prevented, mitigated, cured, or diagnosed
- When applicable, other information necessary to describe the approved indication

Selected patient subgroups



DRUG-X is indicated for the treatment of **adult and pediatric patients 12 years of age and older with moderate to severe** plaque psoriasis **who** are candidates for phototherapy or systemic therapy.

Adjunctive or concomitant therapies



DRUG-X is indicated in adults for the treatment of high-grade malignant glioma **as an adjunct to surgery and radiation.**

Specific tests needed for proper patient selection

DRUG-X is indicated for the treatment of adult patients with metastatic non-small cell lung cancer whose tumors are anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test.

Overview of “limitations of use”



Are included when:

- The evidence falls short of requiring a contraindication, but suggests that use of the drug may be inadvisable
- There is sufficient uncertainty about the drug’s benefits in certain clinical situations to suggest that the drug should generally not be used in those settings
- The awareness of such information is important for practitioners to ensure the safe and effective use of the drug

Reasonable concern or uncertainty about effectiveness or safety in a certain clinical situation



DRUG-X is indicated for the treatment of hypertension in adults and pediatric patients 1 year of age and older.

Limitations of Use

In patients younger than one year of age, DRUG-X can adversely affect kidney development [see *Warnings and Precautions (5.X) and Use in Specific Populations (8.4)*].

Drugs with dose, duration, or long-term use considerations



DRUG-X is indicated for the treatment of severe spasticity in adult patients with spinal cord injury, brain injury, or multiple sclerosis.

Limitations of Use

Prior to implantation of a device for chronic intrathecal infusion of DRUG-X, confirm a positive clinical response to DRUG-X in a screening phase [*see Dosage and Administration (2.X)*].

LOUs should not be used ...



- To restate information already included in the indication
 - e.g., if an indication is clearly worded for use in combination with another drug, there is no need for a limitation of use stating that the subject drug should be used only in combination and not as monotherapy

LOUs should not be used ...



- To address an absence of data in populations in which the drug was not studied
 - e.g., if a drug is approved to reduce the risk of rejection in patients receiving a heart transplant, there should not be a limitation of use about the lack of data on use in lung transplants

Format for multiple indications



- Can assign a subsection to each indication
 - 1.1 DiseaseA
 - 1.2 DiseaseB
- Can present distinct indications using bullets
 - DRUG-X is indicated for:
 - DiseaseA
 - DiseaseB

Format for limitations of use



- Presented separately from the indication a Limitations of Use heading and not usually under a separate numbered subsection
- If a drug has multiple indications and the LOU applies to all of them, it may be preferable to use a separate numbered subsection for limitations of use within the section

Draft Guidance on the Drug Abuse and Dependence (DAD) Section of Labeling

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

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Labeling

DAD guidance applies to:



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

Distribution of information



- Detailed information about drug abuse and dependence is included in the DAD section of labeling
- Other relevant sections should:
 - Discuss only those aspects of the information that are pertinent to those sections' scopes and purposes
 - Not repeat the identical content or level of detail found in the DAD section

Distribution example



For products that have abuse or dependence information in both the Warnings and Precautions and DAD sections:

- DAD section will have the detailed abuse or dependence information (e.g., description of study designs and results of abuse liability studies)
- Warnings and Precautions section will have the succinct description of the adverse reaction or risk, the clinical implications, and recommendations for managing risks related to abuse or dependence

Drug Abuse and Dependence section

Composed of three subsections:

- 9.1 Controlled Substance
- 9.2 Abuse
- 9.3 Dependence

9.1 Controlled Substance subsection



- If a drug is scheduled under the CSA, the 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))
- Should identify the proprietary name (if a proprietary name exists) and the active ingredient(s) or drug substance(s) that is (are) controlled

Guidance examples

- DRUG-X contains xxxxxx, a Schedule II controlled substance.

[typical presentation]

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

[for product without a proprietary name]

- DRUG-Z contains zzzzzzz. (Controlled substance schedule to be determined after review by the Drug Enforcement Administration.)

[when scheduling is pending]

Non-scheduled drugs with information in 9.2 or 9.3



Examples:

- 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
- 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

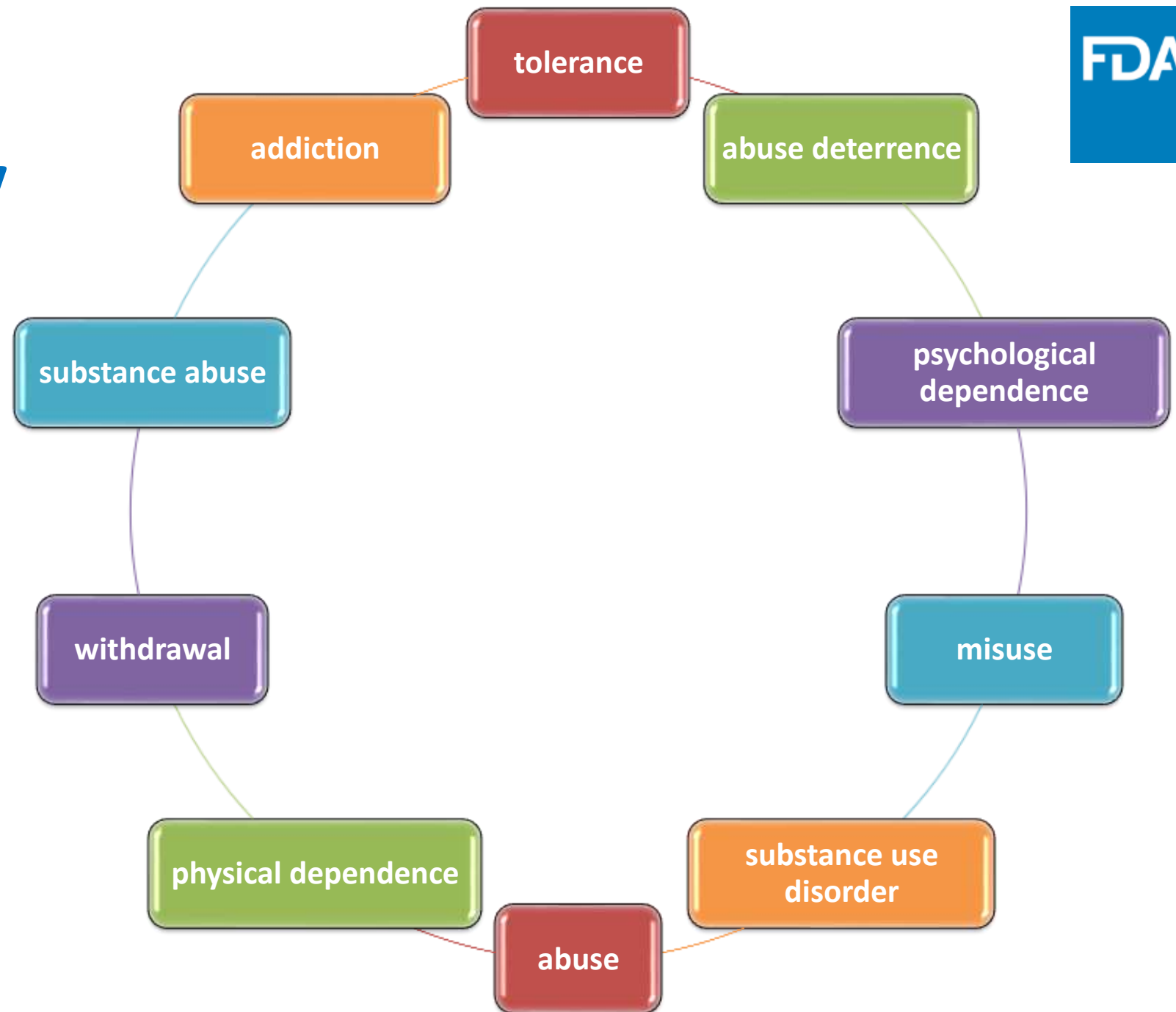
Non-scheduled drugs with information in 9.2 or 9.3



Include a subsection 9.1 with a single sentence stating that the active ingredient(s) or drug substance(s) is (are) not controlled

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

Terminology



Terminology

Five major concepts for the DAD section:

- Abuse
- Misuse
- Addiction
- Physical dependence
- Tolerance

Terminology – What goes where?

9.2 Abuse

Abuse

Misuse

Addiction

9.3 Dependence

Physical dependence

Tolerance

Terminology

- These terms are commonly confused and misinterpreted
- Guidance recommends that definitions of these terms be included in the DAD section
 - To ensure common understanding
 - To facilitate the diagnosis and management of substance use disorders

9.2 Abuse subsection



- Contains information related to **abuse, misuse, and addiction** that is important for prescribers to consider
- 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))

9.2 Abuse subsection



- Should summarize information that supports recommendations on how to prevent or mitigate risks associated with abuse
- Should include risks specific to abuse of the product, such as those related to a product's particular formulation
- May include information on risks resulting from inappropriate routes or methods of administration

9.2 Abuse subsection



- Should summarize results from human abuse potential studies that adequately characterize the abuse potential of the drug product
- Should summarize studies conducted to evaluate the abuse-deterrent properties of a drug product

9.2 Abuse subsection



- For drugs with a risk of abuse, include the following definition:

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

9.2 Abuse subsection



- For drugs with a risk of misuse that would negatively impact health or functioning, include the following definition:

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.

9.2 Abuse subsection



- For drugs with a risk of addiction, include the following definition:

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.

9.3 Dependence subsection

- Must contain information about the drug related to **physical dependence**, withdrawal, and **tolerance**
- 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

§ 201.57(c)(10)(iii)

9.3 Dependence subsection

- Should summarize signs and symptoms of withdrawal after chronic use or abuse of the drug
- 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

9.3 Dependence subsection

- For drugs to which patients may develop physical dependence, include the following definition:

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.

9.3 Dependence subsection

- For drugs to which patients may develop tolerance, include the following definition:

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).

What not to include in DAD section



- Speculative or promotional language
- Detailed information on 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

Challenge question #1

When compared to the population studied in the main registration trials, an indication may:

- a) Exactly match the studied population
- b) Be broader than the studied population
- c) Be narrower than the studied population
- d) a and c
- e) a, b, and c

Challenge question #2

True or false: For drugs that are not controlled substances, the Drug Abuse and Dependence section should always be omitted from labeling.

- a) True
- b) False

Questions?