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CDER SBIA Webinar Series

**Writing the Indications and Usage Section  
of Labeling: FDA's New Draft Guidance  
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Center for Drug Evaluation and Research (CDER)

# Writing the *Indications and Usage* Section of Labeling: FDA's New Draft Guidance

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# Outline

- General principles
- What information to include
- When to include limitations of use (LOU)
- How to write, organize, and format the Indications and Usage (I&U) section

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

**Guidance for Industry**

*DRAFT GUIDANCE*

This guidance document is being distributed for comment purposes only.

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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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)

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# FDA Draft Guidance

- When finalized, will represent FDA's current thinking on this topic
- Should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited
- Notes the option of proposing an alternative approach if that approach satisfies requirements of applicable statutes and regulations

# This FDA Draft Guidance

- Applies to prescription drugs and biological products regulated as drugs
- Retains flexibility in presenting indications
- Recommends regular communications with FDA staff

# Indications and Usage Section

- Enables health care practitioners to readily identify appropriate therapies 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

# Evidentiary Standards for Indications

- Governed by regulation
- For drug products, indications “must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies\*”  
(§ 201.57(c)(2)(iv))
- For biological products, indications “must be supported by substantial evidence of effectiveness”  
(§ 201.57(c)(2)(v))

\* As defined in 21 CFR 314.126(b)

# Scope of an Indication Relative to the Population Studied



- I&U section should clearly communicate scope of the approved indication
  - i.e., the population to which the determination of safety and effectiveness is applicable
- Applicants should discuss scope of a proposed indication with the applicable review division



# Scope of an Indication Relative to the Population Studied

- Indication may mirror the studied population (e.g., in terms of patient demographics or severity of disease), but can sometimes differ
- In some cases, FDA may conclude that available evidence supports approval of an indication broader or narrower in scope than the precise population studied

# Broader than Studied

- An indication for a broader population than was studied 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 may include patient populations that were absent or specifically excluded from clinical studies supporting approval
  - e.g., geriatric patients, pregnant women, patients taking certain concomitant drugs

# Example of a Broader Indication

- Trial evaluating a drug 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 adults outside that age range or in those taking the other drugs

# Example of a Broader Indication

In this scenario:

- Indication should be worded to reflect broader age group (i.e., “in adults”), rather than exact ages studied, and
- Unless available evidence suggests otherwise, indication should not exclude use in patients taking the concomitant drugs

# Another Example of a Broader Indication

- Drug was studied only in patients with a moderate stage of a disease
- There is reason to believe -- based on generalizability of the data, consistencies in disease process, and drug's benefits and risks -- that drug would be safe and effective in a broader group of patients with the condition

# Another Example of a Broader Indication

In this scenario:

- An indication covering a broader population with the disease may be appropriate
- In some cases, an indication covering the overall disease population can be considered

# Example of a Narrower Indication

- A randomized trial that stratified patients by presence/absence of a specific genomic marker
- Benefit seen only in patients positive for the marker

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



# Indications Matching the Studied Population

- Some study designs may identify population in which the benefits outweigh the risks or the only population in which effectiveness is reasonably likely
- In such cases, indication should reflect only the population studied, unless and until evidence is available supporting determination that broader safety and effectiveness can be expected

# Indications Matching the Studied Population - Examples

- Prognostic enrichment
  - e.g., enrolls only people with prior myocardial infarction in study of an antiplatelet drug
- Predictive enrichment
  - e.g., enrolls only people with a specific genomic marker

# Pediatric Considerations

- ***Not*** appropriate to generalize across pediatric populations or between adult and pediatric populations because of:
  - Unique clinical considerations in children (e.g., differences in drug metabolism, different safety risks, and need for different dosing regimens)
  - Statutory requirements related to pediatric assessments

# Inclusion of Age Groups in Indications

For these reasons, indications 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”

# Other Related Labeling Regulations

- Indications or uses must not be implied or suggested in other sections of labeling if not included in I&U (§ 201.57(c)(2)(iv) and (v))
- FDA may require specific warning about an unapproved use in *Warnings and Precautions* if drug is commonly prescribed for that use and if such use has a clinically significant risk or hazard (§ 201.57(c)(6)(i))

# Updating the I&U Section

- Labeling must be updated when new information becomes available that causes the labeling to be inaccurate, false, or misleading (§ 201.56(a)(2))

# Updating the I&U Section

- Application holders should:
  - Review I&U regularly to ensure it reflects current science and, to extent possible, maintains consistency within a drug class
  - Discuss with FDA staff

# Content and Format of I&U Section

The I&U section includes:

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



# Details to Include in the Indication



- For many drugs, indication will be sufficiently conveyed by stating
  - Disease or condition being treated, prevented, mitigated, cured, or diagnosed, and
  - Age group(s)

# Details to Include in the Indication



- In such circumstances, endpoints and descriptions of benefit should be summarized in *Clinical Studies* and should not be included in I&U

# Details to Include in the Indication

- Other scenarios may warrant inclusion of more information in the indication
- For example:
  - Drug targets a different aspect of a disease (e.g., in multiple sclerosis)
  - Endpoints are not well-standardized (e.g., in heart failure)

# Examples of Endpoints in Indications



## Drug for the treatment of insomnia

- Indication should state whether drug affects sleep onset, sleep maintenance, or both
- Will facilitate appropriate prescribing

# Examples of Endpoints in Indications



Outcome study with overall effect on composite endpoint

- Indication should identify components of composite (e.g., cardiovascular death, myocardial infarction, and stroke)

# Details to Avoid in Indications

- I&U is not a description of data supporting determination of effectiveness
- Inclusion of such details could suggest short-term use of a drug indicated for a chronic condition

# Details to Avoid in Indications

- Descriptions of the basis for approval
  - e.g., statement that effectiveness was demonstrated in two 12-week trials in patients with FEV<sub>1</sub> less than 60% of predicted
- Discussions of disease definitions
  - e.g., diagnostic criteria for major depressive disorder

# Components of the Indication

- Indications should begin with:  
    “DRUG-X is indicated”
- **And** must include certain elements required under 21 CFR 201.57(c)(2)(i)



# Required Elements Under 21 CFR 201.57(c)(2)(i)

- Disease
- Condition
- or
- Manifestation of disease or condition (e.g., symptoms)

being

- Treated
- Prevented
- Mitigated
- Cured
- or
- Diagnosed

# Required Elements Under 21 CFR 201.57(c)(2)(i)

- **And**, when applicable, other information necessary to describe the approved indication

# Descriptors or Qualifiers

- Patients previously treated with other therapies (e.g., hormone-refractory prostate cancer)
- Patients with a certain classification of a disease (e.g., WHO Group I pulmonary arterial hypertension)
- Patients with other important identifying variables (e.g., immunocompetent patients)

# Descriptors or Qualifiers

- **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.
- **DRUG-X** is indicated for the treatment of **moderate to severe active rheumatoid arthritis in adult patients** who have had an inadequate response to TNF antagonist 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.**

# Tests for Appropriate 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.

# Outcomes, Endpoints, and Benefits

- Not usually necessary to describe how benefit was measured in clinical trials (i.e., identifying outcomes or endpoints) when treatment affects broad range of manifestations of the disease
  - e.g., an indication for the relief of symptoms of allergic rhinitis

# Outcomes, Endpoints, and Benefits

- In some cases, however, a broad disease indication may not be appropriate



# Include Outcomes/Endpoints/Benefits

- Clinical trials evaluated only one or some disease manifestations
- Drug's effect on overall disease not well understood
- Different drugs have different effects on various manifestations of the diseases
- Endpoints are different from typical effectiveness measures

# Including an Outcome or Endpoint

- DRUG-X is indicated **to improve walking** in adult patients with multiple sclerosis.

# Including an Outcome or Endpoint

- For outcome studies, indication may be to reduce the risk of significant morbidity and mortality
- Describes the demonstrated benefit more accurately than would an indication for the treatment for the condition itself

# Including an Outcome or Endpoint

DRUG-X is indicated to reduce the risk of nonfatal myocardial infarction, fatal and nonfatal stroke, and revascularization procedures in adult patients with clinically evident coronary heart disease.

# When to Consider *Limitations of Use*

- Sufficient uncertainty exists about the drug's benefits in certain clinical situations to suggest it generally should not be used in those settings
- Evidence falls short of requiring a contraindication, but suggests use of drug may be inadvisable
- Awareness of such information is important for practitioners to ensure the safe and effective use of the drug

# LOUs and Contraindications

- Contraindications “describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit” (§ 201.57(c)(5))
- To avoid redundancy, contraindications should not be restated as limitations of use

# LOU or Part of the Indication

- LOUs will most often identify a patient population in which drug should generally *not* be used (i.e., discouraging its use)
- Information that specifies patient population in which drug *should* be used (i.e., encouraging its use) should, wherever possible, be incorporated in the indication

# LOU or Part of the Indication

- Drug to be used only after failure of or as an adjunct to another drug or treatment modality
  - Indication should include this information rather than using a separate LOU



# Reasonable Concern or Uncertainty About Effectiveness or Safety



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)*].

# How LOUs Should *Not* Be Used

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

# How 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 risk of rejection in patients receiving a heart transplant, there should not be a LOU about the lack of data on use in lung transplants

# Required or Recommended Language

- Some products have required or recommended language for I&U section
  - Required statement in I&U for systemic antibacterials about reducing the development of drug-resistant bacteria (§ 201.24)

# Required or Recommended Language



- Other FDA guidances recommend specific wording for I&U for certain indications
  - e.g., Clinical/medical guidances, accelerated approval products

## “Reduce the risk of” vs. “Prevent”

- Generally recommend using “reduce the risk of” or “reduce the incidence of” rather than using “prevent” in an indication
- *Prevent* may imply a guarantee of success that is not supported by the data

## “Reduce the risk of” vs. “Prevent”

- The terms *prevent* or *prophylaxis* may sometimes be appropriate because, in a given context, these terms are well established and understood by the clinical community
  - Preventive vaccines
  - Drugs for post-exposure prophylaxis



## “Only”

- Indications should be worded clearly, making inclusion of the word “only” unnecessary
  - i.e., indication should **not** state “DRUG-X is indicated only for...”

# Preferred Wording/Wording to Avoid



## “Also indicated”

- When a new indication is added, the phrase “also indicated” should ***not*** be used because it may imply a hierarchy among indications

# Preferred Wording/Wording to Avoid



## Product identification

- Indication should include proprietary (trade) name
- If none, include the nonproprietary name (established or proper name)
- Established pharmacological class appears in the indication only in Highlights

# Format for Multiple Indications

- Assign a subsection to each indication
  - 1.1 Disease-A
  - 1.2 Disease-B
  
- Present distinct indications using bullets
  - DRUG-X is indicated for:
    - Disease-A
    - Disease-B

# Format for LOUs

- Present separately from indication under the heading *Limitations of Use*
- If drug has multiple indications and LOU applies to all, may consider a separate numbered subsection for LOUs

# Recap

- General principles
- What information to include
- When to include LOUs
- How to write, organize, and format I&U

# Final Thoughts



- Remember the role of I&U section
  - Clearly convey uses for which drug shown to be safe and effective
  - Reflect scientific evidence accurately using terminology that is clinically relevant, scientifically valid, and understandable to practitioners
- Seek regular communication with FDA staff

# Q&A and Resources



Click for:

- [The draft guidance](#)
- [PLR Requirements for Prescribing Information website](#)
- [CDER guidances website](#)
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