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U.S. FOOD & DRUG ADMINISTRATION

Considerations for Developing the INDICATIONS AND USAGE Section of Prescription Drug Labeling

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Outline

- Background – Basics
- The Indication
- “Limitations of Use”
- Examples
- Challenges
- Format and Other Considerations

INDICATIONS AND USAGE (I&U) Section

- Statute: Food, Drug, & Cosmetic Act (FD&C Act)
- Regulations: 21 CFR 201.57(c)(2)
- Guidance (under development):

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

Federal Food, Drug, and Cosmetic Act

Section 502 [21 U.S.C. 352]

A drug or device ***shall be deemed to be misbranded****—*

(a)(1) ***If its labeling is false or misleading*** *in any particular...*

(f) ***Unless its labeling bears*** *(1)* ***adequate directions for use****;* ***and*** *(2) such adequate warnings* ***against use*** *in those pathological conditions or by children* ***where its use may be dangerous to health****, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users…*

INDICATIONS AND USAGE Section

- 1st step in providing directions for use, but...
- Labeling should be considered in toto for full conditions of use to inform individual patient use
  - (Whole) labeling provides "*summary of the essential scientific information needed for the safe and effective use of the drug*" [1]
  - I&U section: **what** / **when** / **in whom**
    - Reflects regulatory determination/FDA-approved usage
  - Other sections: how / when / why

[1] 21 CFR 201.56(a)(1)

I&U Section Also Sets Bounds for Other Sections of the PI:

- Section 1 limits what may be implied or suggested about drug use within the PI

> *Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section. (§ 201.57(c)(2)(iv) and (v))*[1]

- Exception: when there are important risks to convey

  A specific warning relating to a use not provided for under the I&U section may be required by FDA in accordance with sections 201(n) and 502(a) of the FD&C Act if the drug is commonly prescribed for a disease or condition and such usage is associated with a clinically significant risk or hazard. (§ 201.56(c)(6)(i))

[1]See also §§ 201.56(a)(3) and 201.57(c)(15)(i)

Features of a Good I&U Section

- Concise but clear; no ambiguity (specificity when needed)
- Allows ready identification of approved indication(s)
- Reflects scientific evidence accurately *(review issue)*
- Uses current terminology that is clinically relevant, scientifically valid, understandable
- Consistent within/across drug and therapeutic class, where possible
  - Aids the indexing of indications in electronic drug databases, medical information systems

➢ Supports prescribing decisions

The Indication

Basic structure and required elements: [1]

DRUG-X is indicated
..... for the **treatment**, **prevention**, **mitigation**, **cure**, or **diagnosis**
(or relief of symptoms)
..... of a **disease** or **condition** (or manifestation thereof)
..... in *{**age group**, e.g., adults and pediatric patients age Y years and older}*.

Include:

- **Age group**
- **Other information necessary to describe appropriate use**
  - **Descriptors identifying indicated population** (patient/disease subgroup)[2]
  - **Adjunctive or concomitant therapy, if part of indicated use**[3]
  - Specific **tests needed for patient selection** for therapy[4]

[1]See 21 CFR 201.57(c)(2); [2]§201.57(c)(2)(i)(B) , [3](A), and [4](C)

Examples of Including Descriptors –

Required Adjunctive or Concomitant Therapy and Patient/Disease Subgroup

1 INDICATIONS AND USAGE

DRUG-X is **indicated in combination with an aromatase inhibitor** as initial endocrine-based therapy for the treatment of **postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer**.

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of carcinoid syndrome diarrhea **in combination with somatostatin analog (SSA) therapy** in **adults inadequately controlled by SSA therapy**.

Example of Including Descriptors –

Patient/Disease Subgroup; and
Tests Needed for Patient Selection

1 INDICATIONS AND USAGE

1.1 Acute Myeloid Leukemia

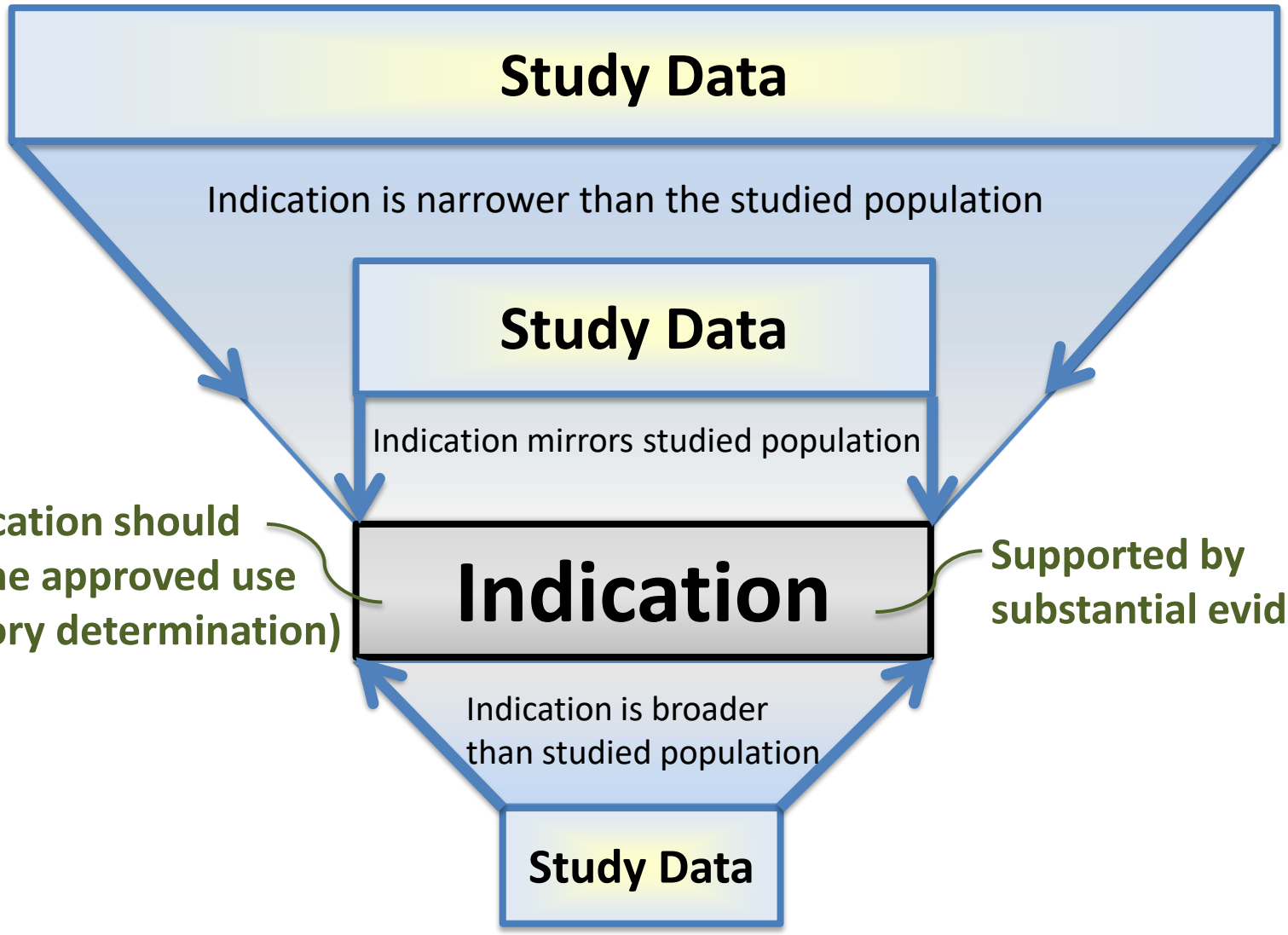
DRUG-X is indicated for the treatment of adult patients with **relapsed or refractory** acute myeloid leukemia (AML) **with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test.**

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of AML with DRUG-X based on the presence of IDH2 mutations in the blood or bone marrow *[see Indications and Usage (1.1) and Clinical Studies (14.1)]*. Information on FDA-approved tests for the detection of IDH2 mutations in AML is available at http://www.fda.gov/CompanionDiagnostics.

The Indication



[1] 21 CFR 201.57(c)(2)(iv) and (v); see also § 314.126(b) for drugs

Limitations of Use (LOU) –

When to Use this Heading?

- **Circumstances in which drug use inadvisable**; reasonable concern or uncertainty about risk-benefit profile
- Only certain non-recommended use(s). LOU **generally based on (some) evidence** suggesting that drug use in a population would be:
  - **Unsafe**; and/or
  - **Ineffective**

Limitations of Use:

DRUG-X is not recommended in ..... subpopulation A or clinical setting B ..... because of increased risk of toxicity X ..... and/or decreased therapeutic effect in these patients.

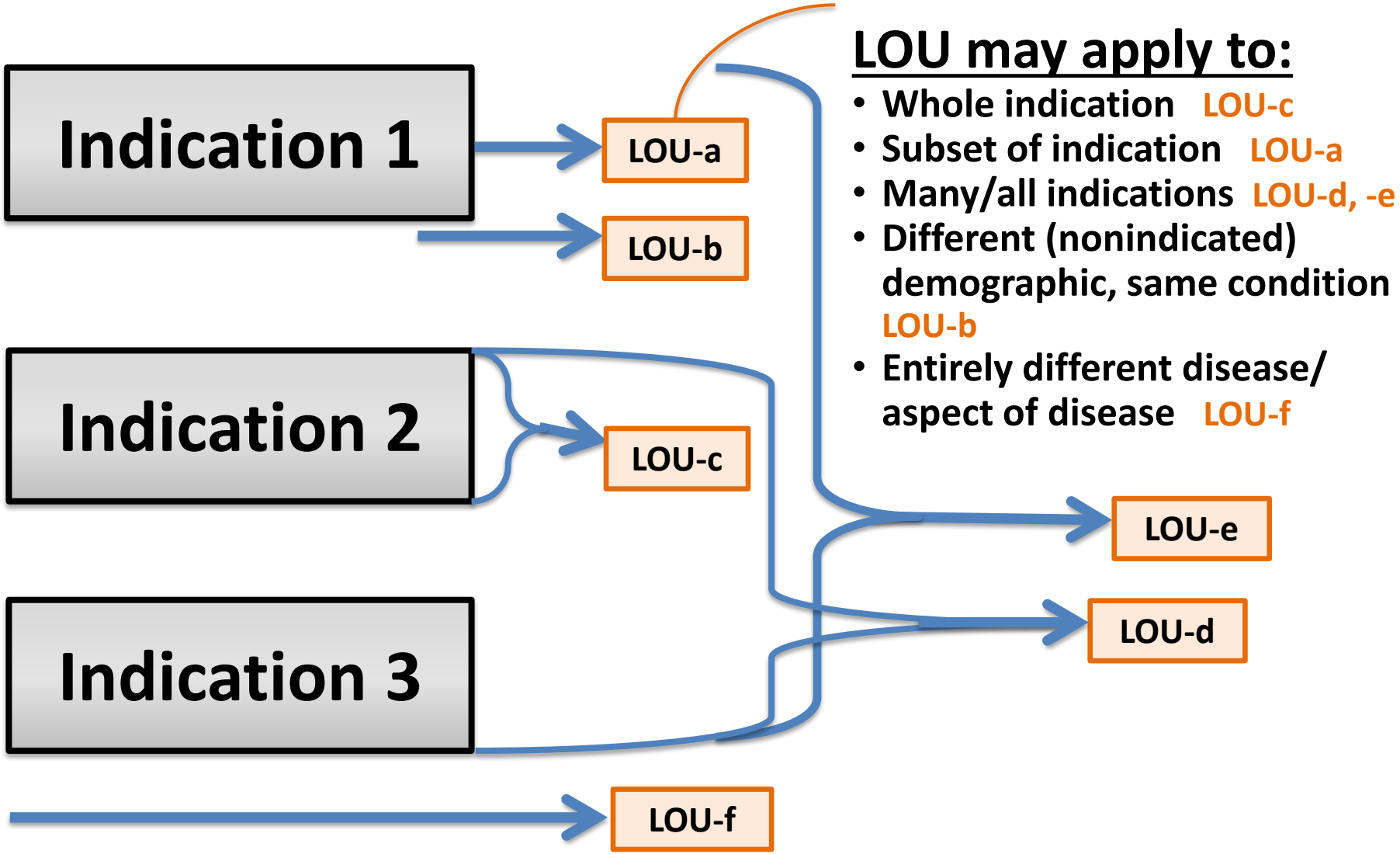
LOU vs. Contraindication –
How Do They Differ?

Limitation of Use (LOU)	Contraindication
• Drug use inadvisable (not recommended, but not contraindicated either) • May derive from safety *and/or* efficacy concern • Suggestive data on the subgroup often was part of planned investigations/drug development	• Never use (risk of use clearly outweighs any possible benefit; no potential benefit makes the risk acceptable)[1] • Typically harm-based (have substantial risk of being harmed by drug)[1] • Dataset typically very small (e.g., fatal ARs would preclude further study in a contraindicated population)

[1]See 21 CFR 201.57(c)(5)

Scope of Limitations of Use (LOU)

(Drug Use Inadvisable)



LOU may apply to:

- Whole indication LOU-c
- Subset of indication LOU-a
- Many/all indications LOU-d, -e
- Different (nonindicated) demographic, same condition LOU-b
- Entirely different disease/ aspect of disease LOU-f

Some Situations to Include LOU

- **Concern about effectiveness or safety** in a clinical setting
- **If there is a common belief** that drug may be effective for a certain use, **but** preponderance of evidence related to the use or condition suggests otherwise (shows drug is ineffective or that the therapeutic benefits do not generally outweigh its risks) (201.57(c)(2)(ii))
- Drugs approved **without evidence of long-term benefits known to occur with related drugs** in same class
- Drugs with duration or **long-term use considerations**

LOU Example #1

Safety concern

LOU #1 is for different demographic, same condition

1 INDICATIONS AND USAGE

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

Limitations of Use

DRUG-X is not indicated for the treatment of hypertension in **pediatric patients less than 1 year of age** because **its direct activity on the renin-angiotensin system can adversely affect kidney development** *[see Warnings and Precautions (5.X) and Use in Specific Populations (8.4)]*

LOU Example #2

Reasonable uncertainty about drug's benefit-risk

LOU #2 is a subset of one indication

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of patients with multicentric Castleman's disease (MCD) who are human immunodeficiency virus (HIV) negative and human herpesvirus-8 (HHV-8) negative.

Limitations of Use

DRUG-X was not studied and is not recommended in **patients with MCD who are HIV positive or HHV-8 positive** because DRUG-X did not bind to virally produced IL-6 in a nonclinical study.

LOU Example #3

Demonstrated lack of efficacy and increased toxicity

LOU #3 is outside the indication (different type of cancer)

1 INDICATIONS AND USAGE
DRUG-X is indicated, in combination with gemcitabine and cisplatin, for first-line treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC). Limitations of Use DRUG-X is **not recommended for treatment of patients with non-squamous NSCLC. Increased toxicity and lack of efficacy was observed in these patients receiving DRUG-X in a clinical trial** *[see Warnings and Precautions (5.6) and Clinical Studies (14.2)]*.
5.6 Non-Squamous NSCLC - Increased Toxicity and Increased Mortality
DRUG-X is not recommended in patients with non-squamous NSCLC. In a study of DRUG-X plus pemetrexed and cisplatin (PC) versus PC alone, patients treated with DRUG-X + PC experienced more serious (51% vs. 41%) and fatal toxicities (16% vs. 10%) and cardiopulmonary arrest/sudden death within 30 days of the last study drug (3.3% vs. 1.3%) compared to patients who received PC alone *[see Clinical Studies (14.2)].*
14.2 Non-Squamous NSCLC - Lack of Efficacy
Lack of efficacy of DRUG-X in combination with pemetrexed and cisplatin for the treatment of patients with metastatic non-squamous NSCLC was determined in one randomized, open-label, multicenter trial. The study was closed prematurely after 633 patients were enrolled due to increased incidence of death due to any cause and of thromboembolic events in the DRUG-X arm.

LOU Example #4

Without evidence of long-term benefits of related drugs

LOU #4 pertains to entire indication

1 INDICATIONS AND USAGE

DRUG-X is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease (CVD), who require additional lowering of LDL cholesterol.

Limitations of Use

The effect of DRUG-X on cardiovascular morbidity and mortality has not been determined.

LOU Example #5

Duration or long-term use considerations (e.g., efficacy)

LOU #5 pertains to entire indication

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of elevated plasma uric acid levels in adult patients with tumor lysis syndrome.

Limitations of Use

The activity of DRUG-X may be neutralized by the development of anti-drug antibodies if more than a single course of treatment is administered *[see Dosage and Administration (2.X) and Warnings and Precautions (5.X)].*

LOU Example #6

Duration or long-term use considerations (e.g., safety)

LOU #6 pertains to entire indication

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture…..

Limitations of Use

Because of the unknown relevance of the **rodent osteosarcoma findings** to humans, **cumulative use** of DRUG-X and parathyroid hormone analogs (e.g., teriparatide) **for more than 2 years during a patient's lifetime is not recommended** *[see Warnings and Precautions (5.1)].*

Limitations of Use (LOU) Heading

- **Not** for identifying contraindications
- **Not** for listing all settings with absence of data
- **Not** a wastebasket for all possible disclaimers
- Generally **not** for explaining why an indication wasn't granted (e.g., regulatory standard for approval not met) if otherwise no suggested significant safety/efficacy concern
- Limitations of Use ≠ discussion of "limitations of data"
- Generally **not** for further defining an intended use
  (not a substitute for sufficient detail within the indication)
- Generally **not** for describing benefit differences between subgroups if overall safety/effectiveness determination (i.e., approval) applies to all of those subgroups

→ Consider if information better placed elsewhere

Some Non-Recommended Uses Typically NOT Identified as LOU

Example Scenarios	Recommended Language
• PK/PD differences in a subgroup (e.g., increased exposures in severe renal/hepatic impairment); clinical data limited • No data (e.g., ESRD ± dialysis); exposure could be higher	Describe risk in other sections (e.g., sections 5, 8); state recommendation, e.g., Use of Drug-X in these subgroups – is "**not recommended**"; or – "**No recommendation can be made**"
• Drug interaction- significantly increased exposures but clinical implication uncertain	Describe risk in other sections (e.g., sections 5, 7); state recommendation, e.g., "Concomitant use is "**Not recommended**" or "avoid…"
• Pediatric assessments pending	State in section 8.4: **"Safety and effectiveness in pediatric patients have not been established"**
• Other diseases (or disease subtypes) or patient populations not studied	**No statement** (silent), in the absence of concern

LOU Exceptions – *Rarer Uses*

Critical Clarifications

- In rare circumstances, LOU language may help prevent misunderstanding of usage where such misunderstanding would have significant consequences
  - E.g., sufficient doubt about drug's benefit in clinical situation requiring immediate, effective treatment
- **LOU should not substitute for clearly defined indication**

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of hyperkalemia.

Limitations of Use

DRUG-X **should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action** *[see Clinical Pharmacology (12.2)]*.

LOU Exceptions – *Rarer Uses*

Example LOU not about inadvisable use –

Presents criteria for further indicated use (long-term use)

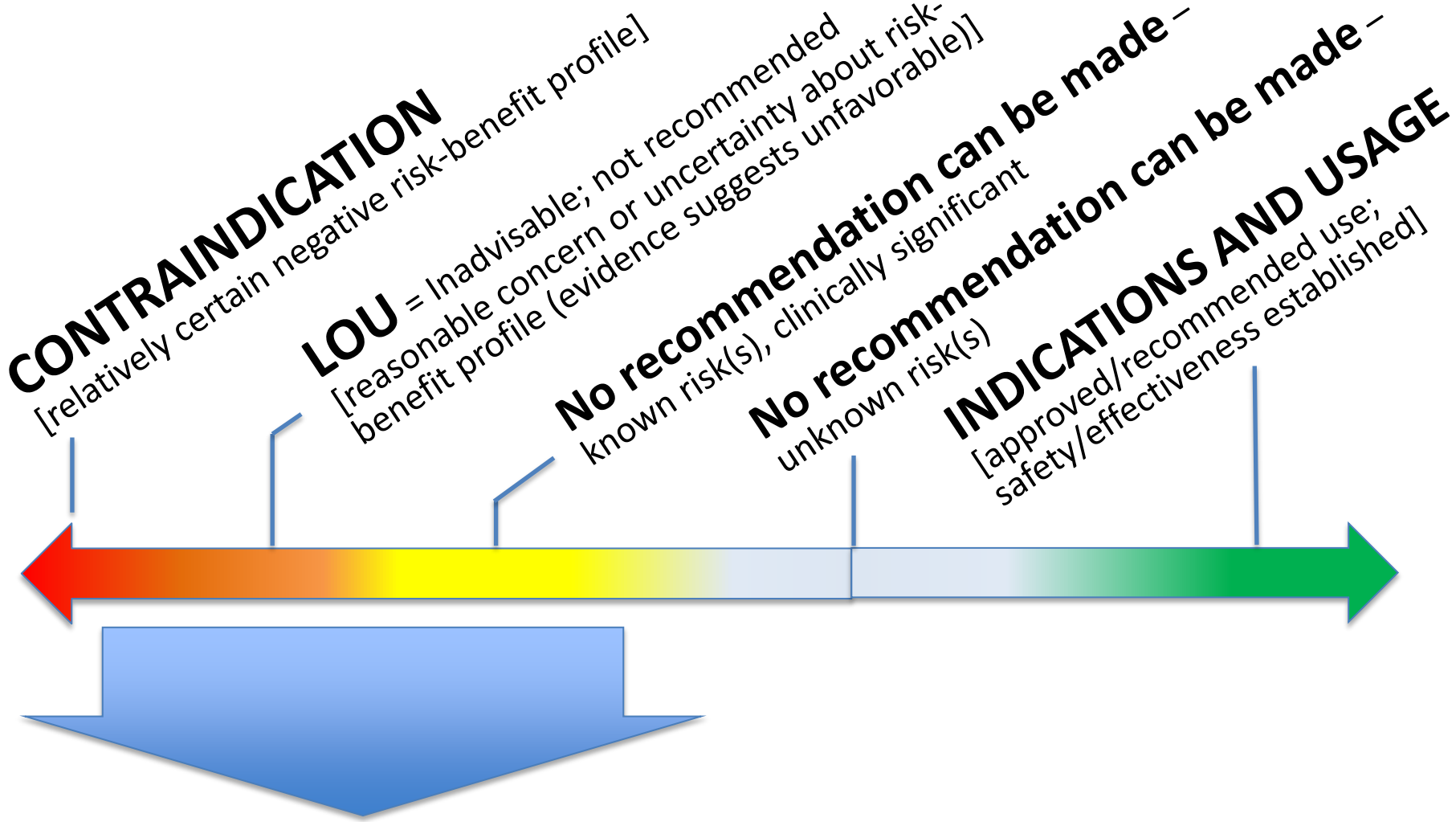
1 INDICATIONS AND USAGE

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)].*

Challenges with LOU



WARNINGS AND PRECAUTIONS

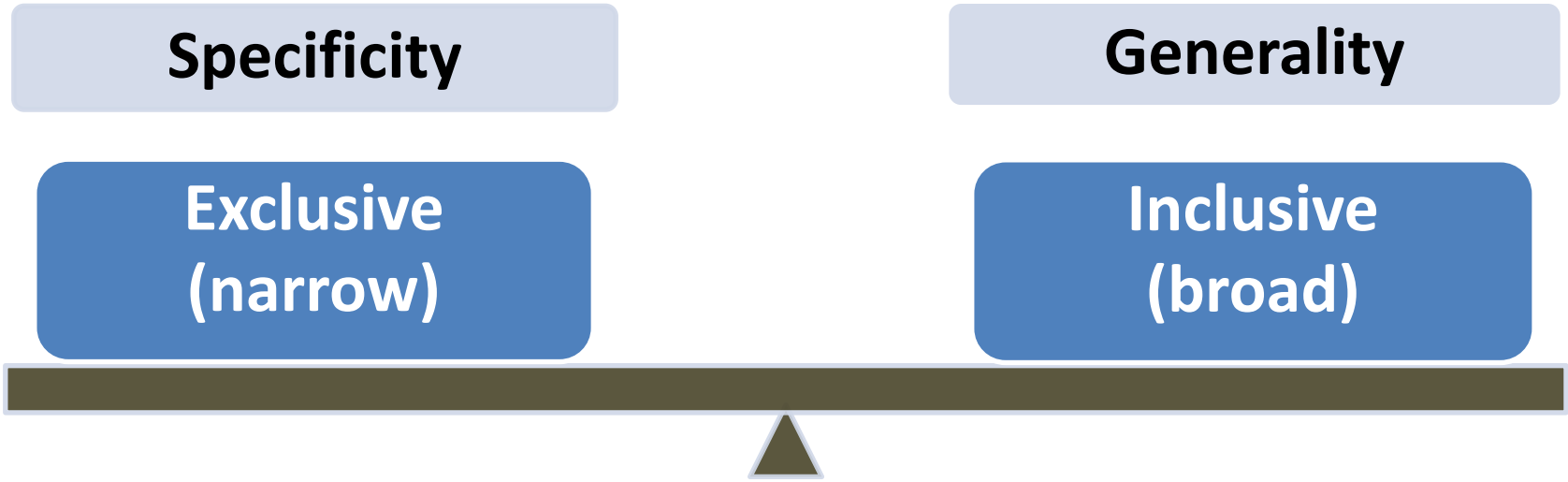
Challenges with LOU

- Data falls on a spectrum; clinical recommendations more distinct *(review issues)*
- Limited data-- How large a safety signal/concern or trend of reduced efficacy to justify recommendations? *(review issues)*
- LOU heading sometimes overused/underutilized

  → **Consider if information better placed under different section:**
  - WARNINGS AND PRECAUTIONS
  - USE IN SPECIFIC POPULATIONS
  - CLINICAL STUDIES
- LOU (e.g., in Highlights) sometimes unclearly associated with respective indication(s) → **Address with format/language**

Challenges of Writing the Indication

When to Elaborate ?



Specificity vs. generality on each of the following:

- Population (demographic)
- Disease or condition
- Circumstance/clinical setting
- Description of effect/outcomes

Challenges of Writing the Indication – When to Elaborate ?

Disease or condition

- **Drug targets specific aspect of disease** (specify which), e.g.,
  - Acute vs. chronic disease
  - Relapsing vs. primary progressive multiple sclerosis
  - Sleep onset vs. sleep maintenance (for insomnia)
- **Disease criteria are unclear**/varied/poorly understood and there is concern about inappropriate therapy (consider defining)

Challenges of Writing the Indication – When to Elaborate ?

Population (demographic)

- When evidence **cannot be generalized to broader population** (use necessary descriptors to identify indicated population)
  - Populations with different risk-benefit considerations

Circumstance/clinical setting

- When **drug should be reserved for specific situations** due to safety[1] and/or efficacy considerations (specify circumstances), e.g.,
  - Refractory to standard therapies
  - Intolerant to, or inappropriate for, other earlier-line therapy
- **Drug as adjuvant or concomitant therapy** (in combination regimen or in conjunction w/other treatment modalities)

[1]21 CFR 201.57(c)(2)(i)(E)

Challenges of Writing the Indication – When to Elaborate ?

Description of effect/outcomes

- **Endpoint is a specific major outcome**
  - e.g., cardiovascular death, myocardial infarction, stroke
- **Effect on only some component(s) of composite** primary endpoint (specify component(s) which had effect)
- **Endpoints not standardized** (describe specific benefit)
  - e.g., heart failure
- Different drugs have different effects on disease manifestations
- Drug effect on disease not well understood

Example – When to Elaborate

Drug Use Should Be Reserved for Specific Situation/Population

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (MS). Because of its safety profile, the use of DRUG-X should generally be reserved for patients who have had an inadequate response to two or more drugs indicated for the treatment of MS.

Example – Disease Definition in I&U Section?

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of premenopausal women with **acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to:**

- **A co-existing medical or psychiatric condition,**
- **Problems within the relationship, or**
- **The effects of a medication or other drug substance.**

Acquired HSDD refers to HSDD that develops in a patient who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation or partner.

Limitations of Use

- DRUG-X is not indicated for the treatment of HSDD in postmenopausal women or in men.
- DRUG-X is not indicated to enhance sexual performance.

Example – Composite Endpoint Components Sometimes But Not Always Named in Indication

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

DRUG-X is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

1.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

DRUG-X is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

1.3 Treatment of Deep Vein Thrombosis

DRUG-X is indicated for the treatment of DVT.

1.4 Treatment of Pulmonary Embolism

DRUG-X is indicated for the treatment of PE.

1.5 Reduction in the Risk of Recurrence of DVT and PE

DRUG-X is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

Indication Challenges – Define or Not?

(1) **Does "high risk for fracture" need be defined in I&U? –or— is this practice of medicine?**

(2) **Does identification of endpoints ("vertebral and nonvertebral fractures") in I&U help direct appropriate use?**

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture **defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy.** In postmenopausal women with osteoporosis, DRUG-X **reduces the risk of vertebral fractures and nonvertebral fractures** *[see Clinical Studies (14)]*.

Limitations of Use

Because of the unknown relevance of the **rodent osteosarcoma findings** to humans, **cumulative use** of DRUG-X and parathyroid hormone analogs (e.g., teriparatide) **for more than 2 years during a patient's lifetime is not recommended** *[see Warnings and Precautions (5.1)]*.

Challenges of Writing the Indication

When NOT to Elaborate

- Indication is intentionally broadened based on generalizability of the evidence
- Disease entity is straightforward (most cases)
  - Use high-level terms
- Drug has broad effect on the disease aspects/manifestations
  - Generally no need to describe in I&U how benefit was measured in clinical trials (provide these details in CLINICAL STUDIES section)
- Well-established endpoints
  - State only: DRUG-X is indicated for the treatment of Disease A
  - Instead, describe endpoints in CLINICAL STUDIES section
- Generally, do **not** include details of studies that describe the basis of approval → **goes in CLINICAL STUDIES section**[1]

[1] 21 CFR 201.57(c)(15)

Example – Not Defining Disease in I&U
(Enrollment Criteria in CLINICAL STUDIES Section)

1 INDICATIONS AND USAGE

DRUG-X is indicated for the **treatment of amyotrophic lateral sclerosis (ALS).**

14 CLINICAL STUDIES

The efficacy of DRUG-X for the treatment of ALS was established in a 6-month, randomized, placebo-controlled, double-blind study conducted in Japanese patients **with ALS who were living independently and met the following criteria** at screening:

1. Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R; described below])
2. Normal respiratory function (defined as percent-predicted forced vital capacity values of [%FVC] ≥ 80%)
3. Definite or Probable ALS based on El Escorial revised criteria
4. Disease duration of 2 years or less

Challenges with I&U –

Inconsistencies with Other Sections of Labeling

Inappropriate Inconsistency	vs.	Appropriate "Inconsistency"
Indication is narrower than implied by other sections *Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section* *[§ 201.57(c)(2)(iv)&(v)]*		**Indication intentionally broadened** (based on generalizability of the evidence)
• E.g., 8.4 Pediatric Use describes non-indicated pediatric dosing or use → **Add to I&U if 8.4 Pediatric Use names a pediatric indication** *[§§ 201.57(c)(9)(iv)(B)&(C)]* • E.g., 12.3 Pharmacokinetics describes PK in patients for whom drug is not recommended • E.g., 14 CLINICAL STUDIES describes study arms receiving non-recommended dosage regimen or efficacy results in non-indicated populations		• Indication reflects wider scope than section 14 CLINICAL STUDIES data – Section 14 need not describe rationale for review conclusion • Indication reflects wider scope than data in section 8.4 Pediatric Use →**For pediatric indication, subsection 8.4 should briefly include basis** *[§ 201.57(c)(9)(iv)(D)(1)]*

→ **Remove suggested non-indicated use(s) or qualify with "X is not recommended in Y"**

I&U Section – Other Challenges

Location of "Disclaimers" or Qualifying Statements

- Distinguish between consequences of
  - Including qualifier/disclaimer within indication statement
  - Stating qualifier/disclaimer separately as an LOU or under CONTRAINDICATIONS section
  - Placing disclaimer with data description in CLINICAL STUDIES section
- Best location depends upon the clinical recommendation for use …….

Example – Disclaimers or Qualifying Statements

(Data Disclaimer Not Influencing Usage Recommendation)

1 INDICATIONS AND USAGE

DRUG-X, a combination of lesinurad, a uric acid transporter 1 (URAT1) inhibitor, and allopurinol, a xanthine oxidase inhibitor, is indicated for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a medically appropriate daily dose of allopurinol alone *[see Clinical Studies (14)].*

1.1 Limitations of Use

DRUG-X is not recommended for the treatment of asymptomatic hyperuricemia.

14 CLINICAL STUDIES

Lesinurad in combination with allopurinol has been studied in hyperuricemic gout patients who have not achieved target serum uric acid levels with allopurinol alone.

There have been no phase 3 clinical trials with DRUG-X. Bioequivalence of DRUG-X to co-administered lesinurad and allopurinol was demonstrated, and **efficacy of the combination of allopurinol and lesinurad has been demonstrated** in two phase 3 studies (Study 1 and 2).

Example – Disclaimers or Qualifying Statements

(Information Important for Usage Considerations)

1 INDICATIONS AND USAGE

DRUG-X is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) infection without cirrhosis or with compensated cirrhosis (Child-Pugh A) who have *[see Dosage and Administration (2.2) and Clinical Studies (14)]:*

- genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor.
- genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor.
  - **Additional benefit** of DRUG-X over sofosbuvir/velpatasvir **was not shown in** adults with genotype 1b, 2, 4, 5, or 6 infection previously treated with sofosbuvir without an NS5A inhibitor.

Indications Statement

Format & Other Considerations

- Multiple indications-- 2 format options:
  - Subsection for each indication (1.1 Disease-A, 1.2 Disease-B)
  - Bullets:

    DRUG-X is indicated for:
    - Treatment of…..
    - Treatment of…..
- Omit extraneous information to preserve focus on I&U
  - **Omit:** dosage form(s), strength(s), route(s) of administration, product quality descriptors (e.g., "USP"), FDA established pharmacologic class (except where required in Highlights), clinical trial and nonclinical study data
  - **Omit:** statements that describe regulatory basis for FDA-approval (i.e., biosimilarity) (except accelerated approval statement)
- Cross-reference use is for referencing additional detail.....

  Not a substitute for developing the I&U section

  (Include all I&U required elements within I&U section)

Considerations in Special Situations

- **Accelerated approval**

  "…if the indication is approved based on a surrogate endpoint under §314.510 or §601.41 of this chapter, a **succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the "Clinical Studies" section** for a discussion of the available evidence" (§201.57(c)(2)(i)(B))

  → **incorporated into indication statement**

- **Systemic antibacterial drug products**

  Labeling must include a specific statement in the I&U section about strategies for reducing the development of drug-resistant bacteria and maintaining the effectiveness of the subject drug and other antibacterial drugs (21 CFR 201.24(b))

  → **included within I&U section (e.g., in its own subsection)**

- **Single enantiomer of a previously approved racemic drug**

  Labeling for certain products containing a single enantiomer of a previously approved racemic drug must include a statement that the non-racemic product is not approved, and has not been shown to be safe and effective, for any condition of use of the previously approved racemic drug (FD&C Act, Section 505(u)(2)(B)) → **presented as an LOU**

LOU– Format & Other Considerations

- **Present LOU separately from the main indication**(s), under the heading, Limitations of Use
- **Keep the heading standardized** (Limitations of Use), regardless of how many LOU are identified

  Avoid creating variations such as: Limitation of Use; Important Limitations, etc.
- Formatting should follow that of either a:
  - Heading (e.g., Limitations of Use); OR
  - Subsection title (e.g., **1.X Limitations of Use**)
- Begin LOU content on next line beneath heading

  (not trailing after, or sharing, the same line as LOU heading)
  i.e., not "Limitations of Use: DRUG-X is not indicated for…"
- Keep LOU concise
  - **Identify the safety/efficacy concern**
  - **Cross-reference to greater detail elsewhere** (e.g., WARNINGS AND PRECAUTIONS; CLINICAL STUDIES)

LOU Format Example

1 INDICATIONS AND USAGE

1.1 Bile Acid Synthesis Disorders due to Single Enzyme Defects

DRUG-X is indicated for the treatment of bile acid synthesis disorders due to single enzyme defects (SEDs) *[see Clinical Trials (14.1)].*

1.2 Peroxisomal Disorders Including Zellweger Spectrum Disorders

DRUG-X is indicated for adjunctive treatment of peroxisomal disorders (PDs) including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea or complications from decreased fat soluble vitamin absorption *[see Clinical Trials (14.2)].*

1.3 Limitations of Use

The safety and effectiveness of DRUG-X on extrahepatic manifestations of bile acid synthesis disorders due to SEDs or PDs including Zellweger spectrum disorders have not been established.

LOU Format Example

1 INDICATIONS AND USAGE

1.1 Relapsed Chronic Lymphocytic Leukemia

DRUG-X is indicated, in combination with rituximab, for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL) for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

Limitations of Use

DRUG-X is not indicated and is not recommended for first line treatment of patients with CLL.

1.2 Relapsed Follicular B-cell non-Hodgkin Lymphoma

DRUG-X is indicated for the treatment of patients with relapsed follicular B-cell non-Hodgkin lymphoma (FL) who have received at least two prior systemic therapies.

Accelerated approval was granted for this indication based on Overall Response Rate *[see Clinical Studies (14.2)]*. An improvement in patient survival or disease related symptoms has not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Limitations of Use

DRUG-X is not indicated and is not recommended for first line treatment of patients with FL.

1.3 Relapsed Small Lymphocytic Lymphoma

DRUG-X is indicated for the treatment of patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies.

Accelerated approval was granted for this indication based on Overall Response Rate *[see Clinical Studies (14.3)]*. An improvement in patient survival or disease related symptoms has not been established. Continued approval for this indication may be contingent upon verification of clinical benefit in confirmatory trials.

Limitations of Use

DRUG-X is not indicated and is not recommended for first line treatment of patients with SLL.

Updating I&U Section Post-Market

In accordance with §§314.70 and 601.12 … the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading [§ 201.56(a)(2)]

- Ensure I&U reflects current science/understanding
- Consider updating I&U when there is change in current practices for writing indication, e.g.,
  - More information becomes available on drug/drug class or disease/condition
  - Endpoints become better established

Summary

- INDICATIONS AND USAGE section reflects the FDA-approved usage of a drug, including any limitations of use
- Indications are uses determined to be safe and effective and for which the regulatory standard of "substantial evidence of effectiveness" was met
- When developing the indication, weigh the merits of specificity against generality (use descriptors/ qualifiers as appropriate)
- Ensure that the I&U language is both clear and scientifically/clinically appropriate to support prescribing decisions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