Pharmacovigilance Labeling Annotation Guidelines*: Extracting and Categorizing Terms from Drug Labels

* These guidelines were developed for research purposes and do not reflect FDA policy.

Table of Contents

I. Background

A. Evaluation

The Adverse Drug Event Evaluation (ADE Eval) is an evaluation of tools to identify adverse events (AEs) mentioned in publicly available drug labels. The Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Office of Surveillance and Epidemiology (OSE) is sponsoring this ADE Eval. OSE is interested in a tool that would enable pharmacovigilance safety evaluators to automate the identification of labeled AEs which could facilitate triage, review and processing of safety case reports.

This evaluation uses a definition of adverse drug events specific to the business process in the Office of Surveillance and Epidemiology. The task will consist of identifying OSE-defined adverse drug events and mapping them to associated terms in the Medical Dictionary for Regulatory Activities (MedDRA – https://www.meddra.org) for specific sections of drug labels. Evaluation metrics will include precision and recall of mention-level extraction of ADRs and their MedDRA encoding

B. Purpose

The pharmacovigilance-based annotation guidelines reflect FDA Labeling Guidance[1,2] and pharmacovigilance experts' interpretations of drug product labels as well as application of that expertise to FDA case report screening. Labels are reviewed to identify and extract adverse event (AE) terms associated with use of a drug. Each term is evaluated to confirm that it is used in the context of describing an adverse event. The intent is to operationalize pharmacovigilance case report triage practices; all case reports are MedDRA coded and could be triaged by comparing the MedDRA code in the reports to the MedDRA-coded AE discussed in the label. The ultimate purpose is to support efficiency and consistency in triage of adverse event case reports and subsequent signal identification. These data will be used to configure automated or semi-automated natural language processing systems to assist FDA in identifying labeled adverse events and thus subsequently serious, unlabeled adverse events. For this reason, it is critical that adverse events which still require case report review-based safety surveillance not be extracted as labeled events. Therefore, these annotation guidelines provide both rules and examples of terms that should be extracted and categorized. These guidelines were developed for research purposes and do not reflect FDA policy.

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[1] US FDA, Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products: Content and Format, Final January 2006. Website: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf (accessed October 4, 2018).

[2] . US FDA, Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products: Content and Format, Final October 2011, Website: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf (accessed October 4, 2018).

C. Definitions

CFR 314.80 Postmarketing reporting of adverse drug experiences

- *Adverse drug experience.* Any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

- *Unexpected adverse drug experience.* Any adverse drug experience that is not listed in the current labeling for the drug product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

- *Labeling and labeled AEs. FDA* labeling *includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.*[3] An OSE[4]-labeled AE is an adverse event that has been documented in the prescribing information for an associated drug. In these guidelines, *label* refers to the structured product label that accompanies a medication.

- *Annotations.* To avoid confusion with the usage of *label* described above, descriptions added to text to indicate the semantic category of a text span will be referred to as *annotations*.

II. Dataset Annotation Categories

There are three types of annotations described below: OSE_Labeled_AE (adverse events of interest to OSE), NonOSE_AE (adverse events or similar textual elements that are not of interest to OSE), and Not_AE_Candidate (spans that may appear to be adverse events but are not). Only the OSE_Labeled_AE annotations will be scored. The latter two types are provided to performers for reference and diagnostic purposes and will not be scored. They are not exhaustively annotated in the dataset.

[3] Code of Federal Regulation: Title 21 - Food and Drugs. CHAPTER I - FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES. SUBCHAPTER A - GENERAL. PART 1 - GENERAL ENFORCEMENT REGULATIONS. https://www.gpo.gov/fdsys/pkg/CFR-2011-title21-vol1/xml/CFR-2011-title21-vol1-sec1-3.xml

[4] Office of Surveillance and Epidemiology

- OSE_Labeled_AE: adverse event associated with the approved use of a drug. Systems should recognize and extract all terms that fall into in this category (in the indicated sections of the label.

- Not_AE_Candidate: term that describes a condition unrelated to adverse events such as the drug's indication, contraindication, and patient's medical history. Systems should NOT extract terms that fall into this category.

- NonOSE_AE: adverse event other than OSE_Labeled_AE, such as an AE identified in an unapproved use of the drug, an AE that occurs in the context of animal exposure, an AE representing a sign/symptom of an OSE_Labeled_AE, or events resulting from a drug interaction. Some textual elements describing NonOSE_AEs may appear to be adverse events but are not. Systems should NOT extract terms that fall into this category.

The red Not_AE_Candidate and yellow NonOSE_AE categories are also applied to certain terms that resemble an AE but are not used in the context of a green OSE_Labeled_AE or that can never be AEs. Broad application of the Not_AE_Candidate and NonOSE_AE categories was motivated by a desire to reduce the likelihood of false positives. For example, *immunosuppressant*, *hypoglycemic*, and *hypertensive* could be used to describe adverse effects (e.g., *drug A has been associated with immunosuppressant effects*). In this context, *immunosuppressant effects* is annotated OSE_Labeled_AE and should be extracted and MedDRA coded to *immunosuppression*. However, when these terms are used to describe treatments (e.g., *immunosuppressant therapy*, *hypoglycemic drugs*, *hypertensive therapy*), they are not AEs, and in this context, they are annotated NonOSE_AE.

III. Annotation Restrictions Based on Location in Label

A. Annotated Sections

Adverse events should be extracted only from certain sections of a drug label. The sections that occur in a drug label depend on whether the label is in the newer, Physician Labeling Rule (PLR) format or the older non-PLR format. According to FDA, the goal of the PLR content and format requirements (21 CFR 201.56 and 201.57) is to enhance the safe and effective use of prescription drug products by providing health care providers with clear and concise prescribing information (PI) that is easier to access, read, and use. The PLR label format is also intended to make PI more accessible for use with electronic prescribing tools and other electronic information resources.[5] Table 1 shows the sections from which AE terms should be extracted in each type of label .

[5] US FDA. PLR Requirements for Prescribing Information: http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm084159.html. These final regulations were issued in January 2006

Table 1. Sections from which adverse events should be extracted

PLR Format Label Sections to Extract	Non-PLR Format Label Sections to Extract
Boxed Warning	Boxed Warning
Warnings and Precautions	Warnings
	Precautions
Adverse Reactions, including Clinical Trials and Postmarketing Experience	Adverse Reactions

B. Unannotated Sections

Sections not listed in Table 1 are not annotated in the dataset, and systems should not extract text from those sections. Examples of sections from which terms should NOT be extracted include the *Highlights* section of PLR labels, shown in Figure 1, and the *Information for Patients* section, shown in Figure 2.

Figure 1. *Highlights* section of a PLR structured product label

EXCERPT: * Arterial Thromboembolic Events (ATEs): Serious, sometimes fatal ATEs have been reported in clinical trials. Discontinue CYRAMZA for severe ATEs. (5.2)
* Hypertension: Monitor blood pressure and treat hypertension. Temporarily suspend CYRAMZA for severe hypertension. Discontinue CYRAMZA for hypertension that cannot be medically controlled. (5.3)
* Infusion-Related Reactions: Monitor for signs and symptoms during infusion. (5.4)
* Impaired Wound Healing: Withhold CYRAMZA prior to surgery. (5.6)
* Clinical Deterioration in Patients with Cirrhosis: New onset or worsening encephalopathy, ascites, or hepatorenal syndrome can occur in patients with Child-Pugh B or C cirrhosis. (5.7)
* Reversible Posterior Leukoencephalopathy Syndrome: Discontinue CYRAMZA. (5.8)
* Proteinuria Including Nephrotic Syndrome: Monitor proteinuria. Interrupt CYRAMZA for urine protein levels >=2 g/24 hours. Permanently discontinue CYRAMZA for urine protein levels >3 g/24 hours or for nephrotic syndrome. (5.9)
* Thyroid Dysfunction: Monitor thyroid function during treatment with CYRAMZA. (5.10)
* Embryofetal Risk: Can cause fetal harm. (5.11)

Figure 2. *Information for Patients* section of a NonPLR structured product label

Information for Patients

Patients should be advised to immediately report to their physician any signs or symptoms suggesting angioedema (e.g., swelling of face, eyes, lips, tongue, larynx and extremities; difficulty in swallowing or breathing; hoarseness) and to discontinue therapy. (See WARNINGS: HEAD AND HECK ANGIOEDEMA and INTESTINAL ANGIOEDEMA.)

Patients should be told to report promptly any indication of infection (e.g., sore throat, fever), which may be a sign of neutropenia, or of progressive edema which might be related to proteinuria and nephrotic syndrome.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. The causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult with the physician.

Patients should be advised not to use potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes without consulting their physician. (See PRECAUTIONS: GENERAL and DRUG INTERACTIONS; ADVERSE REACTIONS.)

Patients should be warned against interruption or discontinuation of medication unless instructed by the physician.

Heart failure patients on captopril therapy should be cautioned against rapid increases in physical activity.

Patients should be informed that captopril should be taken one hour before meals (see DOSAGE AND ADMINISTRATION).

C. Text Located in Headings

Do NOT extract/annotate any terms in headings, **UNLESS**:

1) the wording of the heading represents an OSE_Labeled_AE,

AND

2) this OSE_Labeled_AE is NOT repeated in the text following and pertaining to the heading.

Example:

5.9 Proteinuria Including Nephrotic Syndrome (heading)

In Study 4, severe proteinuria occurred more frequently in patients treated with CYRAMZA plus FOLFIRI compared to patients receiving placebo plus FOLFIRI. Severe proteinuria was reported in 3% of patients treated with CYRAMZA plus FOLFIRI (including 3 cases [0.6%] of nephrotic syndrome) compared to 0.2% of patients treated with placebo plus FOLFIRI.

Do Not Extract terms from the heading *Proteinuria Including Nephrotic Syndrome* because these OSE_Labeled_AEs (*protenuria, nephrotic syndrome*) are repeated and captured in the text following the heading; *protenuria* and *nephrotic syndrome* have already been captured as OSE_Labeled_AEs.

Extract the OSE_Labeled_AE in the heading when this is the only place it is represented for the section of the label.

Example:

5.9 Worsening of Narrow-Angle Glaucoma (heading) ANORO ELLIPTA should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a healthcare provider immediately if any of these signs or symptoms develops.

In this example, *Worsening of Narrow-Angle Glaucoma* in the heading is to be extracted as an OSE_Labeled_AE because this OSE_Labeled_AE is not captured in the text following that heading. *Narrow-angle glaucoma* is categorized as Not_AE_Candidate and *acute narrow-angle glaucoma*, *eye pain, eye discomfort, blurred vision, visual halos, visual colored images, red eyes, conjunctival congestion, corneal edema* are categorized as NonOSE_AEs (See Section 5 for the distinction between pre-existing conditions and worsening pre-existing conditions.)

D. Text Located in Titles

Do NOT extract/annotate any terms in titles, including *Titles of Study*, *Figure*, *Table*, or *Boxed Warning* **UNLESS:**

1) the wording of the title represents an OSE_Labeled_AE
   AND
2) this OSE_Labeled_AE is NOT repeated in the text following and pertaining to the title.

Note: Not_AE_Candidates and NonOSE_AEs are not extracted from Titles

Examples:
Title of Study:

Bleeding in PLATO (Reduction in risk of thrombotic events in ACS)

Do NOT extract *bleeding* if it is repeated in the text that follows. (Subsequent text not shown for brevity.) Note: *thrombotic events* is a NonOSE_AE.

Title of Figure:

Figure 1 is a plot of time to the first non-CABG major bleeding event.

Do NOT extract *bleeding* if it is repeated in the text that follows. (Subsequent text not shown for brevity.)

Title of Table:

Table 1 – Non-CABG related bleeds (PLATO)

Do NOT extract *bleeds* if it is repeated in the text that follows. (Subsequent text not shown for brevity.)

Box Warning Title:

WARNING: HEMORRHAGE, GASTROINTESTINAL PERFORMATION, AND IMPAIRED WOUND HEALING • Hemorrhage: CYRAMZA increased the risk of hemorrhage, and gastrointestinal hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue CYRAMZA in patients who experience severe bleeding. (2.3, 5.1) • Gastrointestinal Perforation: Permanently discontinue CYRAMZA in patients who experience a gastrointestinal perforation. (2.3, 5.5) • Impaired Wound Healing: Withhold CYRAMZA prior to surgery and discontinue CYRAMZA if a patient develops wound healing complications (2.3, 5.6) INDICATION

Do Not extract/annotate title of box warning such as *Warning: Hemorrhage, Gastrointestinal Perforation, and Impaired Wound Healing.* The terms *Hemorrhage, Gastrointestinal Perforation,* and *Impaired Wound Healing* occur in the following text in that section.

IV. Annotation Extent

A. Modifiers

Adjectives describing severity or frequency of an AE such as *mild, severe*, *grades*, *disabling*, *infrequent, frequent, serious, rare,* are not included in AE annotation and should not be extracted.

Example:

...Severe bleeding

Extract OSE_Labeled_AE *bleeding* but do Not extract *severe*

Adjectives describing the type of AE such as *acute, chronic, hemorrhagic, necrotizing,* are included in AE annotation and should be included in the extracted term.

Example:

Acute renal failure Hemorrhagic pancreatitis

Extract OSE_Labeled_AE *acute renal failure* and *hemorrhagic pancreatitis*.

B. Discontinuous Text

A phrase describing an adverse event may be interrupted by other text. (This situation frequently arises in the context of conjunction, indicated by terms such as *and* and *or*.) In such cases, all and only the text that belongs to the phrase that refers to the adverse event should be extracted.

In the following example, systems should extract *hemorrhagic pancreatitis* (not just *hemorrhagic*) and *necrotizing pancreatitis,* even though *pancreatitis* occurs only once in the text. The coordinating conjunction *or* should not be extracted.

Example:

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with Victoza.

V. Criteria for Annotation Categorization and Extraction

A. Text to be Extracted: OSE_Labeled_AE

Text should be extracted and categorized based on the local context and how it is being used in the sentence; consider the meaning conveyed by the word(s) and/or sentence(s) surrounding that text. Text that is annotated OSE_Labeled_AE in the training data is text that systems should extract.

1. AE associated with the use of a drug

Systems should extract text that describes an AE associated with the use of a drug.

Example 1a.

The most common adverse reactions (incidence >= 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

In Example 1a, systems should extract four OSE_Labeled_AEs:

somnolence
akathisia
extrapyramidal symptoms
nausea

Example 1b.

Hepatocellular liver injury...has been reported in patients treated with MULTAQ in the postmarketing setting.

In example 1b, systems should extract one OSE_Labeled_AE:

hepatocellular liver injury

Example 1c.

Cigarette smoking increases the risk of serious cardiovascular side effects from oral contraceptive use.

In Example 1c, systems should extract one OSE_Labeled_AE:

cardiovascular side effects

Example 1d.

(AEDs), including SABRIL, increase the risk of suicidal thoughts or suicidal behavior in patients taking these drugs for any indication.

In Example 1d, extract two OSE_Labeled_AEs:

suicidal thoughts
suicidal behavior

Example 1e.

In the pool of 5 glycemic control, placebo-controlled clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of VICTOZA-treated patients and 0.5% of placebo-treated patients.

In Example 1e, systems should extract one OSE_Labeled_AE:

gastrointestinal adverse reactions

Example 1f.

As an opioid- containing product, IBUDONE® exposes users to the risks of addiction, abuse, and misuse.

In example 1f, systems should extract three OSE_Labeled_AEs:

addiction
abuse
misuse

Example 1g.

Prolonged use of DILAUDID Oral Solution or DILAUDID Tablets during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated….

In Example 1g, systems should extract one OSE_Labeled_AE:

neonatal opioid withdrawal syndrome

Note: *pregnancy* is Not_AE_Candidate.

Example 1h.

MEKINIST is a kinase inhibitor indicated as a single agent and in combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. Most common adverse reactions (≥20%) for MEKINIST in combination with dabrafenib include pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia.

In Example 1h, a drug is specifically indicated for use in combination with another drug. Therefore, the associated AEs are annotated OSE_Labeled_AE in the training data and the system should extract:[6]

pyrexia
chills
fatigue
rash
nausea
vomiting
diarrhea
abdominal pain
peripheral edema
cough
headache
arthralgia

[6] Note that these events are OSE_Labeled_AEs because Mekinist is indicated to be used in combination with dabrafenib; if the drug did not have an indication to be used in combination with another drug, such as dabrafenib, then they would be labeled as NonOSE_AE drug interaction.

night sweats
decreased appetite
constipation
myalgia

Note: *metastatic melanoma* is Not_AE_Candidate

Example 1i.

Major hemorrhagic events can occur in patients receiving MEKINIST in combination with dabrafenib.

In Example 1i, a drug is specifically indicated for use in combination with another drug. Therefore, the associated AEs are annotated OSE_Labeled_AE in the training data and the system should extract:

hemorrhagic events

Example 1j.

In Trial 2, 13% of patients receiving MEKINIST in combination with dabrafenib at the recommended dose experienced adverse reactions resulting in permanent discontinuation of trial medication(s). The most common adverse reaction resulting in permanent discontinuation was pyrexia (4%). Adverse reactions led to dose reductions in 49% and dose interruptions in 67% of patients treated with MEKINIST in combination with dabrafenib. Pyrexia, chills, and nausea were the most common reasons cited for dose reductions, and pyrexia, chills, and decreased ejection fraction were the most common reasons cited for dose interruptions of MEKINIST and dabrafenib when used in combination.

In Example 1j, a drug is recommended for use in combination with another drug. Therefore, the associated AEs are annotated OSE_Labeled_AE in the training data and the system should extract:

pyrexia
Pyrexia
chills
nausea
pyrexia
chills
decreased ejection fraction

Example 1k.

The use of TRADJENTA in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial [see Adverse Reactions (6.1)]

In Example 1k, systems should extract one OSE_Labeled_AE:

hypoglycemia

Example 1l.

Four of 570 patients (0.7%) who received CYRAMZA as a single agent in clinical trials experienced gastrointestinal perforation.

In Example 1l, systems should extract one OSE_Labeled_AE:

gastrointestinal perforation

Example 1m.

Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

In Example 1m, systems should extract one OSE_Labeled_AE:

gastrointestinal adverse events

Note: *Withdrawal* is a NonOSE_AE.

Example 1n.

Women should avoid becoming pregnant while being treated with FOLOTYN. Inform pregnant women of the potential harm to the fetus.

In Example 1n, systems should extract OSE_Labeled_AE:

harm to the fetus

Note that wording may vary, for example, *hazard to the fetus*, but the system should extract such text as OSE_Labeled_AE. The first occurrence of *pregnant* is a NonOSE_AE and the second occurrence of *pregnant* is Not_AE_Candidate.

2. Lab Results

Systems should extract a lab value or lab result as an OSE_Labeled_AE if the context describes an association between that lab value and the drug. (However, lab values that are solely a manifestation of the primary AE should be treated as NonOSE_AE. See Section 19, Text Related to the Manifestation or Secondary Complication of an AE, for examples.)

Example 2a.

In the Phase III trial, there were transient mean elevations in aminotransferase values in patients treated with SIGNIFOR.

In Example 2a, systems should extract one OSE_Labeled_AE:

elevations in aminotransferase

3. Bulleted Lists

Systems should extract AEs from a bulleted list immediately under Adverse Reactions section.

Example 3a.

6 ADVERSE REACTIONS The following adverse drug reactions are discussed in greater detail in other sections of the label: • Hemorrhage [see Dosage and Administration (2.3) and Warnings and Precautions (5. 1)]. • Arterial Thromboembolic Events [see Dosage and Administration (2.3) and Warnings and Precautions (5. 2)]. • Hypertension [see Dosage and Administration (2.3) and Warnings and Precautions (5. 3)]. • Infusion-Related Reactions [see Dosage and Administration (2.3) and Warnings and Precautions (5. 4)]. • Gastrointestinal Perforation [see Dosage and Administration (2.3) and Warnings and Precautions (5. 5)]

In Example 3a, systems should extract five OSE Labeled AEs:

Hemorrhage

Arterial thrombotic events
Hypertension
Infusion-related reactions
Gastrointestinal perforation

4. Acronym Adjacent to AE Text

When an AE is immediately followed by its acronym, the AE and its acronym should be extracted as a single OSE_Labeled_AE.

Example 4a.

Adverse events from drug use included Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

In Example 4a, systems should extract *Reversible Posterior Leukoencephalopathy Syndrome (RPLS)* as a single AE.

Example 4b.

Patients experienced serious, sometimes fatal, arterial thromboembolic events (ATEs) from drug use.

In Example 4b, systems should extract *arterial thromboembolic events (ATEs)* as a single OSE_Labeled_AE. *Fatal* is a NonOSE_AE.
(Note: Also, extract the AE acronym when it appears alone in the text and meets the definition of an OSE_Labeled_AE.)

5. Worsening Pre-existing Medical Condition

Systems should extract a worsening pre-existing condition as an AE. Note that worsening and/or deterioration is key to determining if the pre-existing condition is an AE; only a worsening or deteriorating pre-existing condition is an OSE_Labeled_AE.

Example 5a.

Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

In Example 5a, systems should extract two OSE_Labeled_AEs:
emotional instability aggravated
psychotic tendencies aggravated

Example 5b.

Worsening of Urinary Retention

In Example 5b, systems should extract one OSE_Labeled_AE:
Worsening of Urinary Retention

6. Medication Errors

A medication error is a preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare provider, patient, or consumer[7]. Examples include administration of incorrect dosage, taking a drug at incorrect frequency, or administering the wrong drug because of easily confused names. A phrase that describes a type of medication error should be extracted as an OSE_Labeled_AE:

Example 6a.

Intra-arterial injection can cause severe necrosis, ischemia or gangrene.

In Example 6a, systems should extract one OSE_Labeled_AE:

Intra-arterial injection

Note: The label states in preceding text that polidocanol is indicated for intravenous use only. Therefore, intra-arterial injection of polidocanol is a medication error and the sequelae of *necrosis, ischemia*, and *gangrene* are NonOSE_AEs.

Example 6b.

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported.

In Example 6b, systems should extract one OSE_Labeled_AE:

Accidental mix-ups between basal insulin products and other insulins

Example 6c.

Dosing errors due to confusion between mg and mL, and other codeine containing oral products of different concentrations can result in accidental overdose and death

In Example 6c, system should extract two OSE_Labeled_AEs:

Dosing errors due to confusion between mg and mL

Dosing errors due to confusion between other codeine containing oral products of different concentrations

Note: *Overdose* and *death* are NonOSE_AEs.

7. Drug Withdrawal Syndrome

An adverse effect associated with discontinuing a medication, often referred to as *withdrawal syndrome* or *discontinuation syndrome*, is an OSE_Labeled_AE and should be extracted.

Example 7a.

Prolonged use of acetaminophen and codeine phosphate tablets during pregnancy can result in withdrawal in the neonate.

In Example 7a, systems should extract one OSE_Labeled_AE:

withdrawal in the neonate

Note that the entire phrase is a medical concept with a specific MedDRA code. *Pregnancy* is Not_AE_Candidate.

[7] National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) https://www.nccmerp.org/consumer-information

Example 7b.

Patients experienced discontinuation syndrome after withdrawing from drug...

In Example 7b, systems should extract one OSE_Labeled_AE
discontinuation syndrome

8. Event-Related Death

If an event-related death is discussed as known for a class of drugs, systems should capture the event. However, death and different causes of death of some of the exposed patients are not considered OSE_Labeled_AEs and should not be extracted. (See Section 23 for additional discussion and examples.)

Example 8a.

LABA, such as vilanterol, one of the active ingredients in ANORO ELLIPTA, increase the risk of asthma-related death.

In Example 8a, systems should extract an OSE_Labeled_AE:
asthma
Note: *death* is a NonOSE_AE in this example.

Other death-related terms that are annotated as OSE_Labeled_AE and that should be extracted are *neonatal death*, *sudden death*, and *cardiovascular death*.

9. AE Modifiers Separated By "And" Or "/"

When AEs include modifiers that are separated by a conjunction such as *and, or*, or a forward slash (/), the interpretation involves distributing the modifier across multiple nominal concepts. Systems should extract complete phrases for each AE.

Example 9a.

Bowel/bladder dysfunction

In Example 9a, systems should extract two OSE_Labeled_AEs:
Bowel dysfunction
bladder dysfunction
Note that the slash should not be extracted.

Example 9b.

Peptic ulcer with possible perforation and hemorrhage

In Example 9b, systems should extract three OSE_Labeled_AEs:
Peptic ulcer
Peptic ulcer perforation
Peptic ulcer hemorrhage

10. AEs Associated with Study Results – Effect Higher than Placebo

AEs mentioned in association with drug study results are OSE_Labeled_AEs if at least one arm of the study drug was higher than placebo.

Example 10a.

Preferred Term	SEROQUEL 400mg (n = 95)	SEROQUEL 600mg (n = 98)	Placebo (n = 90)
Pyrexia	1%	4%	1%
Aggression	1%	3%	0%
Musculoskeletal stiffness	1%	3%	1%
Constipation	4%	2%	0%
Ear Pain	2%	0%	0%
Paraesthesia	2%	0%	0%

In Example 10a, systems should extract six OSE_Labeled_AEs:

Pyrexia
Aggression
Musculoskeletal stiffness
Constipation
Ear pain
Paraesthesia

An AE whose rate is compared with an active comparator drug (i.e., not placebo) is an OSE_Labeled_AE whether or not the rate for the study drug exceeds that of the comparator.

Example 10b.

Table 2
Treatment Emergent Adverse Reactions Occurring in ≥2% of Visceral Leishmaniasis Patients Receiving IMPAVIDO

System Organ Class Preferred Term	IMPAVIDO N = 299	Amphotericin B Deoxycholate N = 99
Gastrointestinal Disorders		
Diarrhea	61 (20.4%)	6 (6.1%)
Vomiting	113 (37.8%)	20 (20.0%)
General Disorders		
Asthenia	19 (6.3%)	4 (4.0%)
Metabolism and Nutrition Disorders		
Decreased Appetite	69 (23.1%)	22 (22.2%)

In Example 10b, IMPAVIDO is the Study Drug and Amphotericin B Deoxycholate is the Active Comparator Drug. Note that the comparator drug can also contribute to that AE. System should extract four OSE_Labeled_AEs:

Diarrhea
Vomiting
Asthenia

Decreased Appetite

Note: *Gastrointestinal Disorders, General Disorders, Metabolism and Nutrition Disorders* are NonOSE_AEs.

Example 10c.

Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were, for Effient and clopidogrel, respectively: epistaxis (6.2%, 3.3%), gastrointestinal hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%), subcutaneous hematoma (0.5%, 0.2%), post-procedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), pericardial effusion/ [hemorrhage] /tamponade (0.3%, 0.2%), and retinal hemorrhage (0.0%, 0.1%).

In Example 10c, systems should extract eleven OSE_Labeled_AEs:

Hemorrhagic events
epistaxis
gastrointestinal hemorrhage
hemoptysis
subcutaneous hematoma
post-procedural hemorrhage
retroperitoneal hemorrhage
pericardial effusion
pericardial hemorrhage
pericardial tamponade
retinal hemorrhage

11. AE Text That States Opposing Effects

When an AE is described as having opposing effects (e.g., both increasing and decreasing an effect on an event, each effect is a distinct OSE_Labeled_AE).

Example 11a.

…both increases and decreases in ejection fraction have been encountered during multidose therapy in patients at usual therapeutic doses.

In Example 11a, systems should extract two OSE_Labeled_AEs:

increases in ejection fraction
decreases in ejection fraction

12. AE Text Listed in Footnotes

AE text that meets the criteria for OSE_Labeled_AEs is annotated even when it appears in footnotes.

Example 12a.

Dyspnea[p] with the following footnotes: [p]Dyspnea includes acute respiratory failure, dyspnea, orthopnea, respiratory distress.

In Example 12a, systems should extract six OSE_Labeled_AEs, five of which appear in a footnote:

Dyspnea (in the text body)

Dyspnea
acute respiratory failure
dyspnea
orthopnea
respiratory distress

13. AEs Associated with Drug Product Components

An AE associated with a*ny* component of a drug product is an OSE_Labeled_AE.

Example 13a.

Benzyl Alcohol Toxicity NATROBA Topical Suspension contains benzyl alcohol and is not recommended for use in neonates and infants below the age of 6 months. Systemic exposure to benzyl alcohol has been associated with serious adverse reactions and death in neonates and low birth-weight infants

In Example 13a, systems should extract three OSE_Labeled_AEs:

Benzyl Alcohol Toxicity
death in neonates
low birth-weight infants

Example 13b.

Nevertheless, treatment with trastuzumab, the antibody component of KADCYLA, during pregnancy in the postmarketing setting has resulted in oligohydramnios…

In Example 13b, systems should extract one OSE_Labeled_AE:

Oligohydramnios

Note: *pregnancy* is Not_AE_Candidate

14. AE Text Related to Class Effect

An AE related to a class effect is an OSE_Labeled_AE if the label specifically states that the AE has been reported/associated with the drug class and the drug of interest is a member of the drug class.

Example 14a.

Corticosteroids [Kenalog] can produce reversible hypothalamic-pituitary-adrenal (HPA) axis suppression

(In Example 14a, systems should extract one OSE_Labeled_AE:

hypothalamic-pituitary-adrenal (HPA) axis suppression

Example 14b.

Seroquel is an atypical antipsychotic…. Atypical antipsychotics have been associated with metabolic changes. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain.

In Example 14b, systems should extract five OSE_Labeled_AEs:

metabolic changes
metabolic changes
hyperglycemia

dyslipidemia
weight gain

B. Text that Should Not Be Extracted: NOT_AE_CANDIDATE

Text that is annotated as NOT_AE_CANDIDATE in the training data is text that describes medical conditions that are not adverse reactions to medications. Systems should not extract this text. Note that this annotation category is not exhaustively annotated in the training data.

15. Drug's Indication

Conditions for which a drug is prescribed, i.e., a drug's indication(s), should not be extracted.

Example 15.

The safety evaluation of dronedarone 400 mg twice daily in patients with AF..." (Multaq).

In Example 15, *AF* is annotated as NOT_AE_CANDIDATE. Neither *AF* nor *atrial fibrillation* should be extracted.

16. Terms Related to Contraindication

Example 16.

VICTOZA is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2

In Example 16, *medullary thyroid carcinoma* and *multiple endocrine neoplasia syndrome type 2* are contraindications. They are annotated as NOT_AE_CANDIDATE and should not be extracted.

17. Pre-existing/Underlying Condition and Medical History

Pre-existing conditions, underlying conditions, and conditions that are stated to be part of a patient's medical history are annotated as NOT_AE_CANDIDATE and should not be extracted. These contexts often coincide with phrases indicating contraindication such as *Risk Factor*, *Avoid Use In*, *Patient Population Not Recommended In, Contraindication*, or *Those Which May Increase Likelihood or Severity of an AE*.

Example 17a.

Avoid the use of CELEBREX in patients with severe heart failure unless the benefits are expected to outweigh the risk."

Example 17b.

If CELEBREX is used in patients with heart failure…

Examples 17a and 17b mention patients with pre-existing heart failure. In this context, the term is annotated as NOT_AE_CANDIDATE and should not be extracted

18. Clinical Trial Exclusion and Inclusion Criteria

Clinical trial exclusion and inclusion criteria are annotated as NOT_AE_CANDIDATE and should not be extracted.

Example 18a.

Study excluded patients with uncontrolled hypertension…or gross hemoptysis within the preceding 2 months.

In Example 18a, *uncontrolled hypertension* and *hemoptysis* are exclusion criteria. They are annotated as NOT_AE_CANDIDATE and should not be extracted.

C. Text that Should Not Be Extracted: NonOSE_AE

Certain types of adverse events are outside of the focus of the research and development with which this task is associated. Such events are annotated NonOSE_AE and should not be extracted. Some textual elements annotated as NonOSE_AE may appear to be adverse events but are not. Note that this annotation category is not exhaustively annotated in the training data.

19. Text Related to the Manifestation or Secondary Complication of an AE

Text that refers to signs, symptoms, or changes in lab results related to the manifestations of the primary AE and the sequelae of the primary AE is annotated NonOSE_AE and should not be extracted.

Example 19a.

Counsel patients regarding the potential risk for MTC with the use of VICTOZA and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

In Example 19a, *mass in the neck*, *dysphagia*, *dyspnea*, and *persistent hoarseness* refer to symptoms of thyroid tumors. Consequently, they are annotated NonOSE_AE in the training data and should not be extracted. Note: *MTC* and *thyroid tumors* are used in the context of instructions; thus, they are also NonOSE_AE.

Example 19b.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia).

In Example 19b, *hyperpyrexia*, *muscle rigidity*, *altered mental status*, and evidence of *autonomic instability* (*irregular pulse, irregular blood pressure*, *tachycardia*, *diaphoresis*, and *cardiac dysrhythmia* refer to manifestations of NMS. They are annotated as NonOSE_AE in the training data and should not be extracted. Note: *NMS* is used in the context of instructions thus, it is a NonOSE_AE.

Example 19c.

Clusters of symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning have occurred in patients treated with MOVANTIK

In Example 19c, *hyperhidrosis chills*, *diarrhea*, *abdominal pain*, *anxiety*, *irritability*, and *yawning* refer to symptoms of opioid withdrawal. They are annotated NonOSE_AE in the training data and should not be extracted. Note: *opioid withdrawal* is a OSE_Labeled_AE.

Example 19d.

Advise patients treated with MULTAQ to report immediately symptoms suggesting hepatic injury (such as anorexia, nausea, vomiting, fever, malaise, fatigue, right upper quadrant pain...)

In Example 19d, *anorexia, nausea, vomiting, fever, malaise, fatigue,* and *right upper quadrant pain* refer to symptoms of hepatic injury. They are annotated NonOSE_AE in the training data and should not be extracted. Note: *hepatic injury* is used in the context of instructions thus, it is a NonOSE_AE.

Example 19e.

The most common signs and symptoms (of hypersensitivity) include rashes, hives, and pruritus.

In Example 19e, *rashes, hives, pruritus* refer to symptoms of hypersensitivity. They are annotated NonOSE_AE and should not be extracted. Note: *hypersensitivity* is used in the context of instructions thus, it is a NonOSE_AE.

Example 19f.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls.

In Example 19f, *headache, difficulty concentrating, memory impairment, confusion, weakness,* and *unsteadiness* refer to symptoms of hyponatremia. They are annotated NonOSE_AE in the training data and should not be extracted. Note: *hyponatremia* is used in the context of instructions thus, it is a NonOSE_AE.

20. AEs Associated with Study Results – Effect Equal to or Lower than Placebo

If an AE rate associated with the Study Drug is equal to or less than AE rate associated with the placebo, it is annotated as NonOSE_AE in the training data and should not be extracted.

Example 20a.

The proportion of patients with prolactin elevations >= 5x upper limit of normal (ULN) was 0.0% for LATUDA-treated patients versus 0.0% for placebo-treated patients.

In Example 20a, *prolactin elevations >= 5x upper limit of normal (ULN)* refers to an AE whose rate equals the rate associated with placebo. Therefore, this term is annotated NonOSE_AE and should not be extracted.

21. AE Observed in Animal Data

Example 21a.

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice.

In Example 21a, *thyroid C-cell tumors* refers to an AEs in rats and mice. Since the OSE task is focused on AEs that occur in humans, this term is annotated NonOSE_AE and should not be extracted.

Example 21b.

Fetal death and teratogenicity occurred in animals administered miltefosine at doses lower than the recommended human dose.

In Example 21b, *Fetal death* and *teratogenicity* refer to AEs in animals. Since the OSE task is focused on AEs that occur in humans, these terms are annotated NonOSE_AE and should not be extracted.

22. AE Associated with Drug-Drug Interaction/Co-administration

AEs associated with the interaction of two or more drugs should be annotated as NonOSE_AE **unless** the drug is specifically indicated for use in combination with the other drug.

Examples 22a.

Hypokalemia/hypomagnesemia may occur with concomitant administration of k-depleting diuretics.

In Example 22a, *hypokalemia* and *hypomagnesemia* refer to AEs associated with the co-administration of the drug with a specified class of drugs (k-depleting diuretics). These terms are annotated NonOSE_AE in the training data and should not be extracted.

23. Non-Specific/General Term or Term Referring to A Body System

An AE candidate that is a non-specific/general term or a term referring to a body system is annotated as NonOSE_AE in the training data and should not be extracted. *Death*, *fatal*, and *nonfatal* generally describe an outcome rather than an AE and in such contexts are annotated as NonOSE_AE.

Example 23a.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

In Example 23a, *death* is annotated as NonOSE_AE and should not be extracted.

Note: *dementia-related psychosis* is Not_AE_Candidate.

Example 23b.

Deaths during double-blind treatment where an adverse event was the primary cause occurred in seven patients on AFINITOR and one patient on placebo. Causes of death on the AFINITOR arm included one case of each of the following: acute renal failure, acute respiratory distress, cardiac arrest, death (cause unknown), hepatic failure, pneumonia, and sepsis.

In Example 23b, *Deaths, death, acute renal failure, acute respiratory distress, cardiac arrest, death, hepatic failure, pneumonia*, and *sepsis* are annotated as NonOSE_AE and should not be extracted. The list includes causes of death, but it is not clear the event was related to the drug.

Terms describing body systems not used in the context of OSE_Labeled_AE are annotated as NonOSE_AE and should not be extracted.

Example 23c.

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects

In Example 23c, *cerebrovascular adverse reactions* is a general description followed by terms that refer to specific AEs. It is annotated as NonOSE_AE and should not be extracted.
Note: *dementia* is Not_AE_Candidate, cerebrovascular accidents and transient ischemic attacks are OSE_Labeled_AEs, and *fatalities* is a NonOSE_AE.

The phrases *abnormal laboratory tests* and *non-hematologic toxicities* are annotated as NonOSE_AE and should not be extracted.

Example 23d.

Investigations [note: Abnormal laboratory tests, which include: Prolonged activated partial thromboplastin time, Bacteriuria NOS present, …

In Example 23d, the phrase *abnormal laboratory tests* is annotated as NonOSE_AE and should not be extracted.

24. AEs Associated with Off-Label or Unapproved Drug Use

AEs associated with off-label use or unapproved drug use, including unapproved indication, dosage, population, or route of administration, are annotated as NonOSE_AE and should not be extracted.

Example 24a.

Adequate studies to demonstrate the safety of Kenalog Injection use by intraturbinal, subconjunctival, sub-Tenons, retrobulbar, and intraocular (intravitreal) injections have not been performed. Endophthalmitis, eye inflammation, increased intraocular pressure, and visual disturbances including vision loss have been reported with intravitreal administration.

In Example 24a, because *endophthalmitis, eye inflammation*, *increased intraocular pressure*, *visual disturbances*, *vision loss* refer to AEs associated with unapproved routes of administration (intravitreal), they are annotated as NonOSE_AE in the training data and should not be extracted.

Example 24b.

Cerebrovascular events, including stroke, in elderly patients with dementia-related psychosis: Risperidone is not approved for use in patients with dementia-related psychosis.

In Example 24b, *cerebrovascular events* and *stroke* refer to AEs associated with an unapproved population (patients with dementia-related psychosis). Therefore, they are annotated as NonOSE_AE in the training data and should not be extracted.
Note: *dementia-related psychosis* is Not_AE_Candidate

25. AEs Associated with Concepts other than the Drug of Interest

There are several contexts in which a term that refers to a medical condition is used to convey information other than an adverse effect of the drug of interest. The term may be mentioned in association with concepts other than medication usage, or it may be associated with a medication other than the drug of interest. Such contexts are typically meant to provide supplementary information to the healthcare professional or patient. Examples of such contexts include the following:

Terms mentioned in instructions

Example 25a.

Temporarily **suspend** Cyramza for severe hypertension until medically controlled. Permanently **discontinue** Cyramza if medically cannot be controlled with antihypertension therapy or in patients with hypertensive crisis or hypertensive encephalopathy.

In Example 25a, *hypertension, hypertensive crisis, hypertensive encephalopathy* occur in the context of instructions. They are annotated as NonOSE_AE in the training data and should not be extracted.

Exception: *hazard to fetus* or similar risk information about fetal harm should be annotated as OSE_Labeled_AE even if it is an instruction. (See Example 1n in Subsection 11)

Additional Exceptions: Medical conditions/risk factors and manifestations stated in the context of instructions take precedence. Frequently text may belong to two context/categories simultaneously such as instructions and manifestations. In cases where text could be categorized as instructional and as medical conditions or risk factors or manifestations, they are annotated in categories other than instructions because these categories are more informative.

Example 25b.

Inform patients of the warning signs and symptoms of hepatoxicity (e.g. nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue CELEBREX immediately, and perform a clinical evaluation of the patient).

In Example 25b, *hepatoxicity* is categorized as a medical condition with manifestations *nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, flu-like symptoms,* and *liver disease* is categorized as a medical condition with manifestations *eosinophilia* and *rash.* These terms are all annotated NonOSE_AE and should not be extracted

Example 25c.

Seek emergency help if any anaphylactic reaction occurs.

In Example 25c, *anaphylactic reaction* is annotated as NonOSE_AE and should not be extracted.

Text used to define, describe, or categorize a concept

Example 25d.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls.

In Example 25d, *hyponatremia* is mentioned in an explanation of the concept and is therefore annotated as NonOSE_AE.
Note: headache, difficulty concentrating, memory impairment, confusion, weakness, *unsteadiness, falls are* NonOSE_AEs.

Terms used to describe a drug's mechanism of action

Example 25e.

The pharmacological activity of CELEBREX in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections.

In Example 25e, *inflammation, fever, infections* occur in the description of a drug's mechanism of action and are therefore annotated as NonOSE_AE:

Text mentioned as monitoring parameters

Example 25f.

Like adults, pediatric patients should be carefully observed for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis.

In Example 25f, *infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, osteoporosis* are mentioned as problems for which the patient should be monitored. They are annotated as NonOSE_AE and should not be extracted.

Example 25g.

Monitor patients for signs of worsening heart failure (Celebrex)

In Example 25g, *heart failure* is mentioned as a condition for which the patient should be monitored. It is therefore annotated as NonOSE_AE and should not be extracted.

Text mentioned in the description of a study procedure

Example 25h.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody including neutralizing antibody positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of antibodies to CYRAMZA with the incidence of antibodies to other products may be misleading.

In Example 25h, *antibody formation, antibody positivity, neutralizing antibody, antibodies to CYRAMZA* are mentioned in the context of a study procedure. They are therefore annotated NonOSE_AE and should not be extracted.

Terms describing an AE associated with another drug or placebo group

Example 25.i

The most commonly reported serious adverse reactions in the bortezomib treatment arm were diarrhea (3%), dehydration, herpes zoster, pyrexia, nausea, vomiting, dyspnea, and thrombocytopenia (2% each). In the dexamethasone treatment group, the most commonly reported serious adverse reactions were pneumonia (4%), hyperglycemia (3%), pyrexia, and psychotic disorder (2% each).

In Example 25i, *pneumonia*, *hyperglycemia*, *pyrexia*, and *psychotic disorder* are associated with a dexamethasone treatment group. They are therefore annotated as NonOSE_AE with respect to the drug of interest (bortezomib) and should not be extracted.
Note: *diarrhea, dehydration, herpes zoster, pyrexia, nausea, vomiting, dyspnea,* and *thrombocytopenia* are OSE_Labeled_AEs.

Example 25j.

Among patients receiving placebo, 0.6% discontinued due to dyspepsia and 0.6% withdrew due to abdominal pain.

In Example 25j, *dyspepsia* and *abdominal pain* are associated with a placebo group. They are therefore annotated as NonOSE_AE with respect to the drug of interest and should not be extracted.

Text mentioned in a description of an AE's association with another medical condition or disease state

Example 25k.

…research reveals that people with obstructive sleep apnea (OSA) have a higher risk of developing gout…

In Example 25k, *gout* is mentioned in association with another medical condition. It is therefore annotated NonOSE_AE and should not be extracted.
Note: *obstructive sleep apnea(OSA)* is Not_AE_Candidate

Text referencing another section of the drug label

Example 25l.

(see WARNINGS and PRECAUTIONS), including thyroid nodules

In Example 25l, *thyroid nodules* is mentioned in reference to another section of the drug label. It is therefore annotated NonOSE_AE: and should not be extracted,

Text describing drug therapy, such as *immunosuppressant therapy*, *hypoglycemic drugs*, *hypertensive therapy*, is annotated as NonOSE_AE.

26. AE Related to Class Effect Not Associated with Drug of Interest

If an AE is related to a class effect but the label specifically states that the AE has not been reported or associated with the drug of interest or that the AE was only reported for another drug in the class, it is annotated as NonOSE_AE and should not be extracted.

Example 26a:

Although **not reported with SEROQUEL**, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents.

In Example 26a, the text specifically states that the AE, *disruption of the body's ability to reduce core body temperature*, has not been reported with the drug of interest. Therefore, the AE is annotated as NonOSE_AE and should not be extracted.

27. AE Related to Overdose or Withdrawal

An AE related to a drug overdose or withdrawal from a drug is annotated as NonOSE_AE and should not be extracted. Note the distinction between symptoms associated with withdrawal and *withdrawal syndrome* or *discontinuation syndrome*, which are annotated as OSE_Labeled_AE. (See Section 7.)

Example 27a.

Overdoses have been reported in clinical trials and post-marketing use of VICTOZA. Effects have included severe nausea and severe vomiting.

In Example 27a, *nausea* and *vomiting* refer to AEs associated with drug overdose. They are annotated as NonOSE_AE in the training data and should not be extracted.
Note: *Overdoses* is used in the context of instructions; thus, it is a NonOSE_AE.

Example 27b.

Symptoms consistent with opioid withdrawal, including hyperhidrosis, diarrhea, abdominal pain, anxiety, and yawning have occurred in patients treated with RELISTOR (See adverse Reactions (6.1),

In Example 27b, *hyperhidrosis, diarrhea, abdominal pain, anxiety*, and *yawning* refer to AEs associated with opioid withdrawal. Consequently, they are annotated as NonOSE_AE and should not be extracted.
Note: *opioid withdrawal* is an OSE_Labeled_AEs.

28. Positive Dechallenge

Positive dechallenge refers to the partial or complete disappearance of an adverse event after withdrawal of the drug.[8] An AE that improves or disappears upon withdrawal of the drug of interest without medical intervention is annotated as NonOSE_AE.

Example 28.

[8] See Center for Drug Evaluation and Research Guidance for Industry: Guideline for Postmarketing Reporting of Adverse Drug Experiences
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM299138.pdf

At one-month follow-up visits following discontinuation of SIGNIFOR, mean FPG and HbA1c levels decreased

In Example 28, FPG (fasting plasma glucose) and HbA1c decreased or resolved following discontinuation of the drug of interest. *FPG levels decreased* and *HbA1c levels decreased* are thus annotated as NonOSE_AE and should not be extracted from this context.

29. Negated AE Text

AEs whose presence or occurrence is negated are annotated as NonOSE_AE in the training data and should not be extracted.

Example 29a.

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients.

In Example 29a, *akathisia* and *restlessness* are negated by *excluding* and therefore annotated as NonOSE_AE in the training data.
Note: *schizophrenia* is Not_AE_Candidate and *extrapyramidal symptoms (EPS)* is an OSE_Labeled_AE.

Example 29b.

No suicide attempts or completed suicides were reported in these studies.

In Example 29a, *suicide attempts* and *completed suicides* are negated by *No.* Consequently, they are annotated as NonOSE_AE in the training data.