Annotation Guidelines
TAC 2017 Adverse Drug Reaction Extraction from Drug Labels

The following guidelines are presented to participants to help understand why certain annotation choices were made, based on issues brought up during the annotation process. The overview of the task and annotations should be read first, as it provides a complete high-level overview of the annotations. For the most part, the examples below represent the hard, corner cases for adverse drug reaction annotation based on questions and disagreements among the annotators. It is not intended to be a complete documentation of every reason to annotate, or not annotate, a given mention, relation, or reaction.

Furthermore, due to the specific needs of FDA, there are some atypical choices made in terms of what and how certain annotations are created. This document is not intended to provide a complete justification for these reasons, simply the specific annotation decisions.

Definitions

FDA guidelines define adverse events, adverse reactions and severe adverse reactions as shown here: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf

**Adverse Event**: “refers to any untoward medical event associated with the use of a drug in humans, whether or not considered drug-related.”

**Adverse Reaction**: “an undesirable effect, reasonably associated with the use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. Adverse reactions may include signs and symptoms, changes in laboratory parameters, and changes in other measures of critical body function, such as vital signs and ECG.”

**Serious Adverse Reaction**: “refers to any reaction occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect.”

Fine-Grained Linguistic Annotation (Tasks 1 and 2)

**Annotate** Adverse Events, Adverse Reactions, and Serious Adverse Reactions (defined above) as **AdverseReaction** (AR) mentions. The semantic types of the mentions to be annotated are in the UMLS semantic group Disorders.

**Annotate** all occurrences of an **AdverseReaction** in the text, even if AR is a broad class of disorders. Annotate all adverse reactions in the following sentence, including eye disorders:

(1) Most commonly observed adverse reactions (> 5% of patients) are: muscular weakness, dysphagia, dry mouth, injection site discomfort, fatigue, headache, neck pain, musculoskeletal pain, dysphonia, injection site pain, and eye disorders.

**Annotate** **AR** instances only once in the following order asserted > hypothetical > negated. For example, if only “TNF blockers” in Example (2) below were mentioned, we would have annotated “ANA” [Antinuclear Antibodies] as hypothetical due to class effect (see below), but the sentence also indicates that the **AR** was reported for the label drug CIMZIA, so annotate this **AR** as asserted.
In clinical trials of TNF blockers, including CIMZIA, in patients with RA, some patients have developed ANA.

Annotate all ARs in “chains of events”, i.e. Clinical Outcomes of AR (long-term sequelae). Do not establish causal relations in the chains: annotate each AR separately, for example, annotate “Rhabdomyolysis” and “acute prerenal failure” separately in:

(3) Rhabdomyolysis resulting in acute prerenal failure and long-term dialysis has been associated with Livalo.

Note: If a more specific AR could be inferred from the sequence of events, add an inferred annotation. For example, in “Sepsis followed by shock”, annotate sepsis alone, shock alone, and sepsis + shock.

Mentions in the UMLS semantic group Disorders play semantic roles other than AdverseReactions. Annotate only AdverseReactions and do not annotate mentions in the following semantic roles: Contraindications, Indications, Conditions associated with indications, and Risk factors or predisposing conditions for experiencing AR. Additionally, do not annotate withdrawal symptoms: these are not ARs caused by the drug.

Do not annotate immunoreactivity and antibodies within normal limits or any other normal physiologic processes. Annotate abnormal immunogenicity, e.g., annotate “ANA” in Example (2).

Do not annotate monitoring for AR or tests to diagnose an AR, for example, do not annotate hypertension, hypokalemia, and fluid retention in “Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month.” Similarly, do not annotate anything in the following:

(4) BYDUREON is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of BYDUREON and inform them of symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for detection of MTC in patients treated with BYDUREON [see Contraindications (4.1) and Warnings and Precautions (5.1)].

Do not annotate therapeutic recommendations. For example, do not annotate pancreatitis in “TANZEUM has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.”

Do not annotate general background information. For example, do not annotate “overgrowth of C. difficile” in “Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of C. difficile”

Do not annotate general lab test results. For example, do not annotate “hematology laboratory test” in “The Grade 3 and 4 hematology laboratory test values by treatment group in the randomized CLL clinical study are described in Table 2.”

Do not annotate ARs of a non-label drug of a different class that was used concomitantly with the label drug. For example, do not annotate TEN in the following:

(5) In a study of TREANDA (90 mg/m 2) in combination with rituximab, one case of toxic epidermal necrolysis (TEN) occurred. TEN has been reported for rituximab (see rituximab package insert).
Do not annotate section headings: while many headers could be easily mapped to MedDRA PTs, these are often general and do not adequately describe the specific AR that the label is attempting to convey. For example, only the following should be annotated in Examples (6)-(8):

(6) Nervous System Disorders – Headache
(7) Gastrointestinal Disorders – Nausea, Diarrhea
(8) Reproductive System and Breast Disorders – Gynecomastia, Breast Enlargement

Do not annotate general subheadings in the lists, e.g. Example (2), and tables, e.g. Example (3) below. Do not annotate Skin and subcutaneous tissue disorders; annotate the specific skin disorders (highlighted). Do not annotate Infections and infestations and Respiratory disorders even if occurrence data are provided and more specific disorders are not listed or the counts for more specific disorders don’t add up to the general subheading total.

(9) | Skin and subcutaneous tissue disorders | 57 |
| Rash | 27 |
| Pruritis | 17 |
| Alopecia | 13 |
| Infections and infestations | 13 |
| Respiratory disorders | 12 |
| Dysphonia | 6 |

Note: Annotate bulleted lists if they are clearly introduced as lists of adverse reactions, e.g., “The following adverse reactions are described in greater detail in other sections:” If a list item consists of a heading and an enumeration of ARs, do not annotate the heading. For example, do not annotate “Bullous and Exfoliative Skin Disorders” in the first bullet of Example (10) below. Exception: if only the header mentions the AR and it is clear that it was omitted from the enumeration/incidence description, annotate the header, e.g., annotate “ILD” and “keratitis” as shown in Example (10).

(10)

- Bullous and Exfoliative Skin Disorders: Severe bullous, blistering, and exfoliating lesions occurred in 0.15% of patients. Discontinue for life-threatening cutaneous reactions. Withhold GILOTRIF for severe and prolonged cutaneous reactions. (2.3, 5.2)
- Interstitial lung disease (ILD): Occurs in 1.5% of patients. Withhold GILOTRIF for acute onset or worsening of pulmonary symptoms. Discontinue GILOTRIF if ILD is diagnosed. (2.3, 5.3)
- Hepatic toxicity: Fatal hepatic impairment occurs in 0.18% of patients. Monitor with periodic liver testing. Withhold or discontinue GILOTRIF for severe or worsening liver tests. (2.3, 5.4)
- Keratitis: Occurs in 0.8% of patients. Withhold GILOTRIF for keratitis evaluation. Withhold or discontinue GILOTRIF for confirmed ulcerative keratitis. (2.3, 5.5)

The descriptions of AdverseReaction might require the following details to be annotated in the form of mentions (purple) and relations (orange).

→ Negation and Negated

AdverseReactions can be negated in the text. Annotate the negation triggers for negated events and the Negated relation: in “There were no infusion-related reactions reported”.
Annotate ARs in the placebo arms as negated events. Annotate the AdverseReaction, the “placebo” as Factor and connect with the Negated relation. For instance:

(11) Mycotic infections occurred in 0.5% of patients treated with placebo.

- Animal/DrugClass/Factor and Hypothetical

FDA guidelines indicate that “there are circumstances in which an adverse reaction that has not been observed with a drug can nonetheless be anticipated to occur.” The events are anticipated (referred to here as hypothetical) if they were observed in animal trials or in other drugs of the same drug class. Annotate the evidence for the hypothesis (Animal, DrugClass or other Factor) and the Hypothetical relation. For instance, the DrugClass “IL-1 inhibitors” should be connected to both AdverseReactions via a Hypothetical relation in the following:

(12) Use of IL-1 inhibitors increases reactivation of tuberculosis or opportunistic infections

Annotate hedging as Hypothetical, labeling modality markers (e.g., should, might, may, could) as Factor. For example, the Factor “may” should be connected to “paradoxical bronchospasm” via a Hypothetical relation:

(13) TUDORZA PRESSAIR may cause paradoxical bronchospasm

- Severity and Effect/Negated

Annotate the Severity of the AdverseReaction and connect via an Effect relation (unless the severity indicates a Negated relation, e.g., “normal levels”). For instance, in the following “Grade 1-3” is a Severity, connected via an Effect relation to “palmar-plantar erythrodysesthesia syndrome”:

(14) Grade 3 palmar-plantar erythrodysesthesia syndrome

If an AR contains ranges, for example, “Grade 1-3” as opposed to the single grade shown in Example (14), Annotate the ends of the range as disconnected spans (not shown above due to difficulty conveying in a text document). But given “Grade 1-3”, then three Severity annotations would be created: (i) “Grade 1-3”, (ii) “Grade 1”, and (iii) “Grade” and “3” as a disconnected span (possible in Brat). All three would then be connected to the AdverseReaction using an Effect relation. Annotate only clearly stated grades; do not annotate unknown grades, e.g., “grade greater than 3” should not be annotated. If Severity does not pertain to all patients annotate the AR twice – once with Severity and once without, for example, in the following “keratitis” should be annotated twice, and only once connected (via Effect) with the Severity “Grade 3”:

(15) keratitis was reported in 5 patients, with Grade 3 in 1.

Note: Annotate “fatal” as AdverseReaction, not Severity.

Note: Limit all relation annotations to one sentence.
Patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with VIBATIV for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed versus vancomycin. Use of VIBATIV in patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) should be considered only when the anticipated benefit to the patient outweighs the potential risk. (5.1)

- **Nephrotoxicity**: New onset or worsening renal impairment has occurred. Monitor renal function in all patients. (5.3)
- Women of childbearing potential should have a serum pregnancy test prior to administration of VIBATIV. (5.4, 8.1)
- Avoid use of VIBATIV during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. (8.1)
- **Adverse developmental outcomes** observed in 3 animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes in humans. (8.1)

**Note** the following annotations (or lack thereof):

- **renal impairment**: this text in the first sentence would not be annotated because it is a pre-existing condition.
- **CrCl ≤50 mL/min**: would not be annotated because it is a pre-existing condition.
- **hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia**: this would not be annotated because these are indications.
- **mortality**: this would be annotated because this is an AR.
- **nephrotoxicity**: this would not be annotated because it is a header.
- **new onset renal impairment**: This disconnected span is an AR.
- **worsening renal impairment**: This is an AR.
- **monitor renal function**: this would not be annotated because it is a monitoring recommendation.
- **pregnancy test**: this would not be annotated because it is a therapeutic recommendation/diagnostic work-up.
- **pregnancy**: this would not be annotated because it is a contraindication/therapeutic recommendation (avoid use during pregnancy).
- **adverse developmental outcomes** (first instance): this would be annotated because it is an AR and would also be connected to animal (type Animal) using a Hypothetical relation.
- **adverse developmental outcomes** (second instance): this would be annotated because it is an AR and would also be connected to potential (type Factor) using a Hypothetical relation.
Drug Label Reference Standard (Tasks 3 and 4)

For each drug label, the reference standard consists of a set of distinct AdverseReactions mapped to MedDRA preferred term (PT). Note that it is additionally possible for an AR to (i) have no mapping to MedDRA, (ii) map to a higher level term, or (iii) map to multiple PTs. When the MedDRA lower level term (LLT) better matches an AR, the LLT will be provided in addition to its corresponding PT.

The following process will be used to map each AdverseReaction to the relevant PT(s):

1) Use the UTS API to automatically obtain candidate CUIs for each AdverseReaction that is asserted in the label (an asserted AdverseReaction has no Negated relation, nor a Hypothetical relation with an Animal or DrugClass). Only retain those CUIs for which the AdverseReaction string exactly matches the UMLS term.

2) If one AR term maps to several CUIs, manually pick one most appropriate CUI.

3) Manually search the UTS browser for AdverseReactions that did not have an exact CUI match. If no semantically equivalent term can be found, mark the AR as CUI-less and try to find a PT directly, using https://tools.meddra.org/wbb/

4) Use the LHC CUI-to-MedDRA PT converter to obtain preferred terms for each CUI

5) Manually verify that the AdverseReaction term and PT match. If the term and PT match exactly or semantically (for example “cardiac failure” in text = “heart failure” in PT) you are done.

6) If the PT doesn’t match the AR semantically, do a manual search using https://tools.meddra.org/wbb/.

7) If one CUI maps to several PTs, pick the PT that is closest to the AR term in the text.

8) In no CUI-to-PT match was found, manually search https://tools.meddra.org/wbb/ If a term semantically equivalent to the AR cannot be found, mark the AR as PT-less

9) Review all PT-less terms in a meeting with all annotators.