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Adverse Reaction Information in the Prescribing Information

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Learning Objectives

- Define “adverse reactions” (AR) and identify key regulatory requirements and guidance recommendations for including drug AR information in the Prescribing Information (PI)
- Discuss content/format approaches for presenting AR data in the ADVERSE REACTIONS section
- Recognize some challenges and considerations for presenting AR-related information in labeling (e.g., AR for nonindicated uses and dosages; safety claims; AR in the Highlights of PI)

Purpose of AR Information in PI

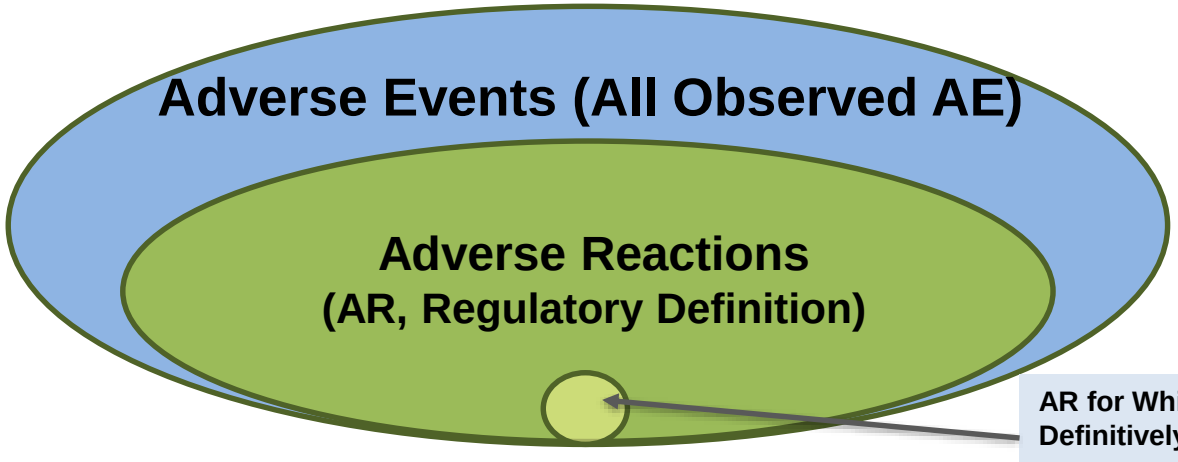
- Labeling must:
  - Contain a summary of the **essential scientific information needed for the safe and effective use** of the drug (21 CFR 201.56(a)(1))
  - Be **informative** and accurate and neither promotional in tone nor false or misleading in any particular (21 CFR 201.56(a)(2))

- *In general, the ADVERSE REACTIONS section includes only information useful to health care practitioners making **treatment decisions and monitoring and advising patients**.*[1]

➢ Informs prescribing; patient management

[1]Adverse Reactions Section Guidance

Adverse Reactions (AR) vs. Adverse Events (AE)



AR Regulatory Definition (21 CFR 201.57(c)(7)):

- **"An undesirable effect, reasonably associated with use of a drug…**
  - that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence"
- "Does not include all adverse events observed…
  - only those adverse events **for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event**"
- Causal relationship need not have been definitively established (see also §201.57(c)(6)(i))

Determining AR from All AE

Determining "some basis to believe there is a causal relationship" or "reasonably associated with use of a drug."[1]

- Based on judgment. Some factors:[2]

  (1) frequency of reporting

  (2) whether AE rate for drug exceeds placebo rate

  (3) extent of dose-response

  (4) extent to which AE is consistent with pharmacology of the drug

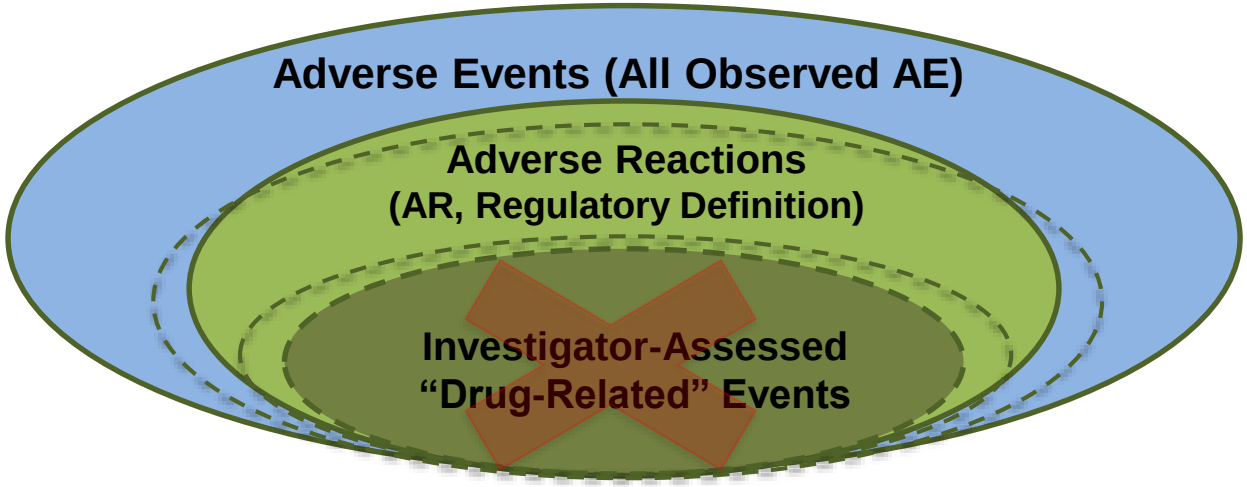
  (5) timing of AE relative to time of drug exposure

  (6) existence of challenge and dechallenge experience

  (7) whether the AE is known to be caused by related drugs

[1]21 CFR 201.57(c)(7)(ii)(A); [2]Adverse Reactions Section Guidance

Determining AR from All AE



ADVERSE REACTIONS section labeling guidance:

- AR rate "***ordinarily derived from all reported AE*** *of that type in the database used*"
- Reliance on investigator-reported causality assessment discouraged
  - *"Excluding events from the rate calculation based on the judgment of individual investigators introduces bias and inconsistency in rate determinations."*

See Adverse Reactions Section Guidance

Grouping AR Terms

AEs reported under different terms but representing the same phenomenon should ordinarily be grouped together as a single AR to avoid diluting or obscuring the true effect.[1]

Table 1: Adverse Reactions in ≥ 1% of Patients with Disease-A Treated With DRUG-X (Studies 1 and 2)

Adverse Reaction	DRUG-X N = 1306 n (%)	Placebo N = 300 n (%)
Upper respiratory infections[a]	170 (13.0)	29 (9.7)
Headache[b]	46 (3.5)	6 (2.0)
Fatigue[c]	33 (2.5)	3 (1.0)
Injection site reactions[d]	19 (1.5)	3 (1.0)
Tinea infections[e]	14 (1.1)	1 (0.3)

[a] Includes: respiratory tract infection (viral, bacterial or unspecified), sinusitis (including acute), rhinitis, nasopharyngitis, pharyngitis (including viral), tonsillitis
[b] Includes: headache, tension headache, sinus headache, cervicogenic headache
[c] Includes: fatigue, asthenia
[d] Includes: injection site bruising, erythema, extravasation, hematoma, hemorrhage, infection, inflammation, irritation, pain, pruritus, reaction, swelling, warmth
[e] Includes: tinea pedis, tinea cruris, body tinea, tinea versicolor, tinea manuum, tinea infection

[1]See Adverse Reactions Section Guidance

Distribution of AR Information in PI

- **ADVERSE REACTIONS** (Section 6)
- WARNINGS AND PRECAUTIONS (Section 5)
- BOXED WARNING
- Other locations, e.g.,[1]
  - CONTRAINDICATIONS (Section 4)
  - Limitations of Use heading in INDICATIONS AND USAGE (Section 1)
  - DRUG INTERACTIONS (Section 7)
  - USE IN SPECIFIC POPULATIONS (Section 8)
  - PATIENT COUNSELING INFORMATION (Section 17)

[1]List includes only the more frequent sections in which AR information appears; not all-inclusive

ADVERSE REACTIONS Section – Required Information and Organization

Required AR Information & Organization

Section 6 ADVERSE REACTIONS

AR listings and preceding information: [1]

- **AR** that occur with
  - the drug
  - drugs in same pharmacologically active and chemically related class, if applicable
- **Information necessary to interpret the AR**

Class-related ARs/hazards often identified under Section 5 WARNINGS AND PRECAUTIONS

Categorize AR listings by:[2]

- **Clinical trials experience**
- **Postmarketing experience**
  - Listing must be separate from the listing of AR identified in clinical trials[3]

Based on type of data, rather than timing/source

[1]See 21 CFR 201.57(c)(7)(i); [2] § 201.57(c)(7)(ii); [3] § 201.57(c)(7)(ii)(B)

Required Presentation of Drug/Comparator AR

Section 6 ADVERSE REACTIONS

Clinical Trials Experience:[1]

- Present AR rates of occurrence for:
  - **Drug**
  - **Comparator** (e.g., placebo)

  Unless cannot be determined or presentation of comparator rates would be misleading

- If potential for misinterpretation, qualify with a disclaimer statement or footnote, e.g.,

  *The data above are not an adequate basis for comparison of adverse reaction rates between DRUG-X and Drug-Y.

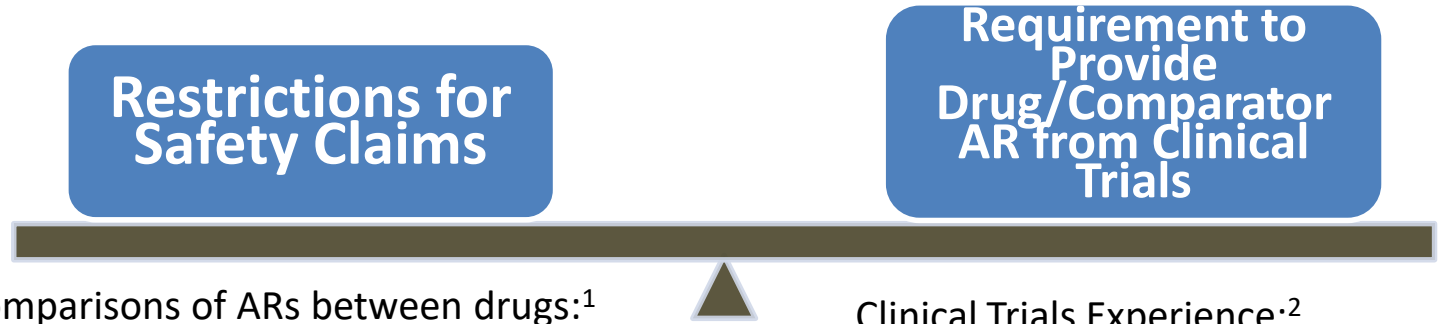
"…(e.g., if an excessive dose of an active comparator was used)"[2]

[1]See 21 CFR 201.57(c)(7)(ii)(A); [2]Adverse Reactions Section Guidance

Presenting AR for Drug and Comparator
Safety Claim vs. Data Display

(requires substantiation of claim)

(serves informational purpose)



For comparisons of ARs between drugs:[1]

- *(Drug products)* **Any claim comparing** the drug with other drugs in terms of frequency, severity, or character of ARs **must be based on adequate and well-controlled studies** (as defined in 21 CFR 314.126(b))[3]
- *(Biological products)* **Any such claim must be based on substantial evidence**

Clinical Trials Experience:[2]

- The rate of occurrence of an **adverse reaction for the drug and comparators (e.g., placebo) must be presented, unless** such data cannot be determined or presentation of comparator rates would be misleading

[1]See 21 CFR 201.57(c)(7)(iii); [2] § 201.57(c)(7)(ii)(A); [3] unless this requirement is waived under § 201.58 or § 314.126(c)

Information Preceding AR Presentation

- AR listing(s) must be preceded by the information necessary to interpret the ARs, e.g., for clinical trials[1]
  - Total number exposed
  - Extent and nature of exposure
- Also include:
  - Demographics
  - Disease severity/characteristics
- Identify important exclusions from safety database

[1]See 21 CFR 201.57(c)(7)(i)

Identify Important Exclusions From Safety Database

6.1 Clinical Trials Experience

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The DRUG-X safety database included 2,285 subjects with COPD in two 12-week efficacy studies and one 52-week long-term safety study. A total of 730 subjects received treatment with DRUG-X 175 mcg once daily. The safety data described below are based on the two 12-week trials and the one 52-week trial.

12-Week Trials

DRUG-X was studied in two 12-week replicate placebo-controlled trials in patients with moderate to very severe COPD (Trials 1 and 2). In these trials, 395 patients were treated with DRUG-X at the recommended dose of 175 mcg once daily.

The population had a mean age of 64 years (range from 41 to 88 years), with 50% males, 90% Caucasian, and had COPD with a mean post-bronchodilator forced expiratory volume in one second (FEV1) percent predicted of 55%. Of subjects enrolled in the two 12-week trials, 37% were taking concurrent LABA or ICS/LABA therapy.

Patients with unstable cardiac disease, narrow-angle glaucoma, symptomatic prostatic hypertrophy, and/or bladder outlet obstruction were excluded from these trials.

Disclaimer – AR Rates Not Comparable Across Trials

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates observed in clinical practice.

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for DRUG-X and at Least 2% Greater than Placebo (up to 6 Months of Treatment) in Studies 1, 2, and 3

Adverse Reaction	DRUG-X 120 mg Monthly N=705, %	Placebo Monthly N=1451, %
Injection site reactions	18	13

Table 1: Adverse Reactions Occurring in Adults with Migraine with an Incidence of at least 2% for Either Dosing Regimen of DRUG-Y and at Least 2% Greater than Placebo (up to 3 Months of Treatment) in Studies 1 and 2

Adverse Reaction	DRUG-Y 225 mg Monthly N=290, %	DRUG-Y 675 mg Quarterly N=667, %	Placebo Monthly N=668, %
Injection site reactions	43	45	38

E.g., from 2 different labeling, AR rates across trials should not be compared

AR Listings – Selecting AR Rate Cut-Offs and Considerations for Data Display

AR Listings— Selecting AR Rate Cut-Offs

Section 6 ADVERSE REACTIONS

- **Must describe the overall AR profile of the drug based on the entire safety database[1]**
- **Must list the AR identified in clinical trials that occurred at or above a specified rate appropriate to the safety database[2]**

- Would be expected to vary between drugs and between indications of a drug
- Factors, e.g.,[3]
  - **Size of safety database**
  - **Designs of the trials in database**
  - **Disease/condition**
- Cut-off should be noted in the listing/table header, accompanying text, or footnote.[3]
- Denominator should be provided (N = number of patients) for each column in a table/listing[4]

[1]21 CFR 201.57(c)(7); [2] § 201.57(c)(7)(ii)(A); [3]Adverse Reactions Section Guidance; [4]Except for ARs identified from postmarketing spontaneous reports

AR Listings— Considerations for Data Display

Section 6 ADVERSE REACTIONS

Consider AR Rate of Drug Relative to Comparator[1]

Include AR in listing when AR rate: **Drug > Placebo**	**If Drug ≤ Placebo, omit from AR listing…** **Unless a suspected AR:** • There is some compelling factor (e.g., timing) that suggests the event is caused by drug • Such AR (where rate of drug ≤ placebo) should be discussed in commentary (i.e., presented as text)

[1]See Adverse Reactions Section Guidance

AR Listings— Considerations for Data Display

Section 6 ADVERSE REACTIONS

Include AR in listing when AR rate:	If Drug ≤ Placebo, omit from AR listing…
Drug > Placebo	**Unless a suspected AR**

- Above approach does not account for chance findings in either direction
- **If active comparator, the above may not apply; choose appropriate rate**
  - E.g., May be different considerations if DRUG-X is indicated as monotherapy vs. in combination with Drug-Y and the comparator is Drug-Y
- Statistical significance testing should be omitted if not based on a prespecified hypothesis in an adequately designed and powered study.[1,2]

[1]See Adverse Reactions Section Guidance; [2] 21 CFR 201.57(c)(7)(iii)

Exclude AE With Rate of Drug ≤ Placebo

Table 1: Adverse Reactions in 5% or More of DRUG-X-Treated Patients With Disease-A in Studies 1 and 2

	DRUG-X N=1029, %	Placebo N=1028, %
Rash	23	16
Pyrexia	19	11
Headache	18	14
Nasopharyngitis	15	10
Back pain	12	13
Hypertension	8	6
Nausea	7	2
Arthralgia	5	5

- **Remove from AR listing/table**
- **If suspected AR, discuss separately in commentary outside of AR table**

Categorizing and Ordering AR Within an AR Listing

Table 2: Adverse Reactions in >10% of DRUG-X-Treated Group and ≥5% Greater Than in Control-Treated Group in Patients With Disease-A

Adverse Reaction	DRUG-X N=45		Control N=39	
	All Grades, %	Grade ≥3, %	All Grades, %	Grade ≥3, %
Neutropenia	49	42	44	36
Thrombocytopenia	49	40	33	26
Anemia	47	24	28	18
Peripheral neuropathy	40	0	8	0
Diarrhea	38	4.4	28	5
Pyrexia				
Decreased appetite				
Pneumonia				
Vomiting				
Infusion-related reaction				
Hypokalemia				
Weight decreased				
Lymphopenia	13	13	8	8
Hypoalbuminemia	13	2.2	8	0
Upper respiratory tract infection	13	0	8	0
Dizziness	13	0	8	0
Hypocalcemia	11	2.2	5	0

Categorize/order AR within a listing:

By body system, severity of AR, or in order of decreasing frequency (or by a combination of these), as appropriate (CFR 201.57(c)(7)(ii))

Laboratory AR

Table 4: Laboratory Abnormalities Reported in ≥ 10% (All Grade) or ≥ 5% (Grade 3–4) of Patients with Disease-A in Study 1		
	DRUG-X 8 mg daily (N=86)	
Laboratory Abnormality	**All Grades (%)**	**Grade 3–4 (%)**
Hematology		
Hemoglobin decreased	35	3
Platelets decreased	19	1
Leukocytes decreased	17	0
Neutrophils decreased	10	2
Chemistry		
Phosphate increased	76	1
Creatinine increased	52	5
Sodium decreased	40	16
Alanine aminotransferase increased	41	1
Alkaline phosphatase increased	41	1
Albumin decreased	37	0
Aspartate aminotransferase increased	30	0
Magnesium decreased	30	1
Phosphate decreased	24	9
Calcium increased	22	3
Potassium increased	16	0

Using Best Available Data[1]

Table 1 Adverse Reactions Occurring in ≥ 2% of DRUG-X-Treated Patients in at Least One Study (Studies 1 and 2)				
	Study 1		Study 2	
Adverse Reaction	Placebo (N = 3576) n (%)	DRUG-X (N = 3581) n (%)	Comparator (N = 2014) n (%)	DRUG-X (N = 2040) n (%)
Arthralgia	434 (12.1)	468 (13.1)	194 (9.6)	166 (8.1)
Headache	208 (5.8)	235 (6.6)	110 (5.5)	106 (5.2)
Muscle spasms	140 (3.9)	163 (4.6)	81 (4.0)	70 (3.4)
Edema peripheral	67 (1.9)	86 (2.4)	38 (1.9)	34 (1.7)
Asthenia	79 (2.2)	84 (2.3)	53 (2.6)	50 (2.5)
Neck pain	54 (1.5)	80 (2.2)	42 (2.1)	34 (1.7)
Insomnia	68 (1.9)	72 (2.0)	36 (1.8)	34 (1.7)
Paresthesia	62 (1.7)	72 (2.0)	34 (1.7)	29 (1.4)

The listing of common ARs should be derived from placebo-controlled and/or dose-response studies if these data are available and the databases are sufficiently large to be informative[1]

[1]See Adverse Reactions Section Guidance

Subgroup AR Information and AR for Multiple Indications

Presenting AR When There Are Multiple Indications

6.1 Clinical Trials Experience

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Migraine

The safety of DRUG-X was evaluated in 25…ose of DRUG-X, representing 1487 patient-years of exposure. Of these, 1920 patients were exp… and 526 patients were exposed for 12 months.

In placebo-controlled clinical studies (Studie…**ose of DRUG-X 120 mg once monthly**, and 1451 patients received placebo, during 3 months …*udies (14.1)]*. Of the DRUG-X-treated patients, approximately **85% were female**, 77% were…y.

The most common adverse reaction was inj…se reactions that occurred within **up to 6 months of treatment** in the migraine studies.

Table 1: Adverse Reactions Occurring in…t 2% for DRUG-X and at least 2% Greater than Placebo (up to 6 Months of Treatment) in S…

Adverse Reaction	DRUG-X 120 mg Monthly N=705, %	Placebo Monthly N=1451, %
Injection site reactions	18	13

For additional indications, if appropriate, may state that AR were consistent with the AR information presented for another indication

Episodic Cluster Headache

DRUG-X was **studied for up to 2 months** in a placebo-controlled trial in patients with episodic cluster headache (Study 4) *[see Clinical Studies (14.2)]*. A total of 106 patients were studied (**49 on DRUG-X** and 57 on placebo). Of the DRUG-X-treated patients, approximately **84% were male**, 88% were white, and the mean age was 47 years at study entry…

Overall, the safety profile observed in patients with episodic cluster headache treated with DRUG-X 300 mg monthly was consistent with the safety profile in migraine patients.

Presenting AR When There Are Multiple Indications

Multiple Indications

- A single AR table may be adequate
- Use > 1 AR table if there are substantial, clinically important differences between indications
  - Consider, if appropriate, focusing additional tables on ARs with rate differences
- Text should summarize any important differences/similarities in AR profiles among indications
- Same concept applies when there are different:
  - Demographic subgroups
  - Dosage forms
  - Dosing regimens
  - Study durations
  - Types of studies (e.g., intensely monitored small studies vs. a large outcome study)

AR in Subgroups (e.g., Renal Impairment)

6 ADVERSE REACTIONS
6.1 Clinical Trials Experi
…

Observed AR differences (if data available and important):[1,2]
- **Demographic groups (e.g., age, race, gender)**
- **Other subgroups (e.g., renal/hepatic impairment, disease severity levels)**

Adverse Reactions in Patients with Renal Impairment

In Studies 1 and 2, there were 368 patients (31%) with baseline renal impairment (defined as eGFR less than 90 mL/min/1.73m^2). In DRUG-X-treated patients with renal impairment, diarrhea, including severe diarrhea, was reported at a numerically higher frequency than in DRUG-X-treated patients with normal renal function (Table 2).

Table 2: Diarrhea (Including Severe Diarrhea) in DRUG-X-Treated Patients With Renal Impairment (Study 1 and 2)

	DRUG-X % (n/N)	Placebo % (n/N)
Patients with renal impairment	20% (39/194)	0.6% (1/174)
Patients with normal renal function	13% (53/407)	3.5% (15/426)

[1]See 21 CFR 201.57(c)(7)(ii)(A); [2]Adverse Reactions Section Guidance

Subgroups – Gender-Specific AR

Rates for gender-specific AR should be determined using appropriate denominator, and that denominator should be identified in a footnote[1]

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…
A total of 1064 subjects and 1069 subjects with moderate to se… …vere **treated with DRUG-X** and placebo, respectively, for 12 weeks in 3 controlled clinica… …only adverse drug reaction that was reported in at least 1% of subjects was nausea, DRUG-X (… …rsus placebo (2%).

The following additional adverse reactions **occurred in female DRUG-X-treated subjects: vulvovaginal mycotic infection (0.8%) and vulvovaginal candidiasis (0.7%).**

14 CLINICAL STUDIES

Efficacy was assessed in a **total of 2002 subjects** … …r. Overall, **57% were female**, 78% were Caucasian, 15% were Black or A… …% were adults (18 to 45 years of age)…

Consider including subgroup denominator:
0.8% (5/606)
0.7% (4/606)

[1]See Adverse Reactions Section Guidance

ADVERSE REACTIONS Section – Other Requirements and Topics

AR With Significant Clinical Implications

Section 6 ADVERSE REACTIONS

Clinical Trials Experience: [1]

- **For AR with significant clinical implications, the listings must be supplemented with additional detail** (if data are available and important):
  - Nature, frequency, and severity of the AR
  - Relationship of the AR to drug dose and demographic characteristics

Discuss in commentary following the AR listing/table

Discuss in commentary and consider a table showing dose-response (AR) relationship

[1]See 21 CFR 201.57(c)(7)(ii)(A)

Relationship of AR to Dose

Section 6 ADVERSE REACTIONS

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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Dose-Dependent Adverse Reactions

In the 12-week placebo-controlled clinical trials that compared doses of 37.5 mg, 75 mg, and 150 mg daily of DRUG-X to placebo, **the following adverse reactions were dose-related:** headache, nausea, decreased appetite, anxiety, diarrhea, and dry mouth.

	Placebo N = 226 (%)	DRUG-X 37.5 mg N = 58 (%)	DRUG-X 75 mg N = 120 (%)	DRUG-X 150 mg N = 218 (%)
Headache	8	7	9	13
Nausea	5	7	5	9
Decreased appetite	1	2	7	8
Anxiety	1	2	3	7
Dry mouth	2	2	3	4
Diarrhea	2	2	4	5

Separate Listing of Less Common AR

Table 2: Adverse Reactions Reported in greater than or equal to 1% of Patients with Disease-A Treated with DRUG-X 15 mg in Placebo-controlled Studies

Adverse Reaction	Placebo	DRUG-X 15 mg
	n=1042, %	n=1035, %
Upper respiratory tract infection (URTI)*	9.5	13.5
Nausea	2.2	3.5
Cough	1.0	2.2
Pyrexia	0	1.2

*URTI includes: acute sinusitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, tonsillitis, viral upper respiratory tract infection

Other adverse reactions reported in less than 1% of patients in the DRUG-X 15 mg group and at a higher rate than in the placebo group through Week 12 included pneumonia, herpes zoster, herpes simplex (includes oral herpes), and oral candidiasis.

If adverse reactions that occurred below the specified rate are included, they must be included in a separate listing (CFR 201.57(c)(7)(ii)(A))

Long-Term Extension Study (Uncontrolled) Data

- **Include data if shows new AR or more severe/frequent AR**
- Omit overstatements/unsubstantiated claims about similar long-term safety compared to controlled period if based solely on uncontrolled long-term extension study data

6.1 Clini

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Generalized

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placebo [*see*
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Table 8

Gastrointestinal Disorders		
Abdominal pain		
General Disorders and Adr Conditions		
Peripheral edema		
Pyrexia		
Infections and Infestations		
Herpes simplex virus infectio		
Injury, Poisoning, and Proce Complications		
Contusion		2(3)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain	9 (15)	5 (8)

e.g., *The most common adverse reactions (≥10%)* ***that occurred in*** *DRUG-X-treated patients in the* ***long-term extension to Study 1 that did not occur in the 3-month placebo-controlled trials were*** *headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).*

The most common adverse reactions (≥10%) that occurred in DRUG-X-treated patients in the long-term extension to Study 1 that did not occur in the 3-month placebo-controlled trials were headache (26%), nasopharyngitis (24%), diarrhea (15%), arthralgia (12%), upper respiratory tract infection (11%), and nausea (10%).

Adverse Reactions Heading in the Highlights of Prescribing Information

Highlights vs. Section 6 – AR Rate Cut-Offs

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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Table 4: Adverse Reactions (≥ 10%) in Patients Receiving DRUG-X in Studies 1 and 2

Highlights (Adverse Reactions Heading):

----------ADVERSE REACTIONS ----------

The most common adverse reactions (≥ 20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, naus… …esthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, … exia, arthralgia, and vision disorders. (6.1)

A list of *the most frequently occurring* AR… along with the criteria used to determine inclusion (e.g., incidence rate) (CFR 201.57(a)(11))

AR in Highlights – Consider Whether to Include Laboratory AR

6.1 Clinical Trials Experience

...

The most common adverse reactions (reported in ≥20%) were diarrhea, nausea, anemia, and vomiting.

Tables 3 and 4 summarize the common adverse reactions and laboratory abnormalities, respectively, in Study 1 during randomized treatment.

Table 3: Adverse Reactions Reported in ≥5% Patients With Disease-X Receiving DRUG-X 400 mg With a Difference Between Arms of >5%

Table 4: Selected Laboratory Abnormalities That Have Worsened from Baseline (≥20%) in Patients With Disease-X Receiving DRUG-X With a Difference Between Arms of >10%

Highlights:

----------ADVERSE REACTIONS ----------

The most common adverse reactions (≥20%) are diarrhea, nausea, anemia, and vomiting (6.1).

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.[1]

[1]See Adverse Reactions Section Guidance

AR (Laboratory and Nonlaboratory) in Highlights

Decide whether to list laboratory ARs separately (e.g., if using different cut-offs in Highlights)

AR listing (Table 3) cut-off in Section 6 is ≥ 10%*

----------ADVERSE REACTIONS----------

- **Most common adverse reactions (incidence ≥ 30%)** are capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia and weight increase.
- **Most common laboratory abnormalities (incidence ≥ 50%)** are decreases in albumin, platelets, hemoglobin, calcium, and sodium, and increases in glucose, ALT and AST. (6.1)

Laboratory AR listing (Table 4) cut-off in Section 6 is ≥ 10%*

*In the example illustrated

ARs (Laboratory and Nonlaboratory) in Highlights

Example of single, merged (nonlaboratory and laboratory) AR listing:

Most common adverse reactions, including laboratory abnormalities (all grades, incidence ≥ 20%), were…

----------**ADVERSE REACTIONS**----------

Most common adverse reactions including laboratory abnormalities (all grades, incidence ≥ 20%) were glucose increased, creatinine increased, diarrhea, rash, lymphocyte count decreased, GGT increased, nausea, ALT increased, fatigue, hemoglobin decreased, lipase increased, decreased appetite, stomatitis, vomiting, weight decreased, calcium decreased, aPTT prolonged, and alopecia (6.1).

AR for Different Dosage Forms in Highlights

If AR profiles differ significantly for different dosage forms or indications/populations, present the most common AR separately (use bulleted format[1])

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥2%) are:

- **DRUG-X Injection:** administration site reactions, hepatic enzyme elevation, nausea, hypokalemia, insomnia, headache. (6.1)
- **DRUG-X Tablets:** diarrhea, nausea, vomiting, hepatic enzyme elevation. (6.1)

*See 21 CFR 201.57(d)(4)

AR Information in Section 6 vs. 14

Where Should AR-Related Information Go???

Sections 6 and 14 – Regulations and Guidance

6 ADVERSE REACTIONS

- AR data (drug AR/risk)
  - O… file of drug based on e…
  - Ordinarily, …ibed …DVERSE REA…
- C… eference Section 14 fo…

…dy dis… sion[2]

A neg… absen… demons… power"[4]

14 CLINICAL STUDIES

- "A… y detailed discus… …
  "Details of studies … …basis … …tive safety claims would ordinarily be discu… …LINICA… …tion"[4]
- s-reference S… …or AR …
  …s … …iates to a ri… …se of the drug must …ections of lab… …the risk is identified …
- … … can be in C… …TUDIES section …cal stu… …ospectively eva… …portant safety …point"… …ually be include… …NICAL STUDIES …ection"[5]
  "The sectio… …o include safe… …olled studies specifically … evaluate a safe…
  - "…in some … …y be appropriate to … …nt important informatio… about safety in the C…NICAL STUDIES section (e.g., if the safety data are best und… …hen presented with a detailed study descripti… …ext of effectiveness results)."[5]
  - … … …the CLINICAL STUDIES section, they … …d in the ADVERSE REACTIONS section and other sections, as appropriate (21 CFR 201.57(c)(15)(ii))."[5]

[1]See 21 CFR 201.57(c)(7); [2] § 201.57(c)(15); [3] § 201.57(c)(15)(ii); [4]Adverse Reactions Section Guidance; [5]guidance *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products– Content and Format* (Jan 2006)

Choosing Best Location of AR-Related Information—
Section 6 vs 14

For prospectively evaluated/pre-specified safety endpoint(s)

➢ **Determine best location based on overall clinical message (depends on study findings)**

Where is a prescriber likely to look for the safety information? **Consider, e.g.,**

6 ADVERSE REACTIONS

- **AR data (drug AR/risk)** (e.g., drug demonstrates lower AR rate than active comparator, but still an AR of the drug)
  - Include appropriate statistical testing results (e.g., p-value, confidence intervals) with data presentation, as appropriate
- **Cross reference Section 14 for detailed study description**
- Safety data with unclear clinical impact

14 CLINICAL STUDIES

- **Detailed study description**
- **Cross-reference Section 6 for AR data**
- **Study results that demonstrate clinical benefit or absence of AR**

Prospectively Evaluated/Pre-specified Safety Endpoints

Bleeding-Related ARs

6.1 Clinical Trials Experience

…

The mean duration of exposure to DRUG-X was 154 days and to enoxaparin/warfarin was 152 days in the Study 1. Adverse reactions related to bleeding occurred in 417 (15.6%) DRUG-X-treated patients and 676 (25.1%) enoxaparin/warfarin-treated patients.

Primary objective of Study 1 was to determine whether DRUG-X was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE (venous thromboembolism) or VTE-related death

In Study 1, DRUG-X was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from Study 1 are summarized in Table 5.

Table 5: Bleeding During the Treatment Period in Patients with Condition-A (Study 1)

	DRUG-X N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Prospectively Evaluated/Pre-specified Safety Endpoints

Neuropsychiatric AR

6.1 Clinical Trials Experience

…

Neuropsychiatric Adverse Reactions

For Study 1, the analysis of subjects with neuropsychiatric adverse reactions by Week 48 is presented in Table 2. The proportion of subjects who reported one or more neuropsychiatric adverse reactions was 24% and 57% in the DRUG-X and Drug-Y groups, respectively.

A statistically significantly lower proportion of DRUG-X-treated subjects compared to Drug-Y-treated subjects reported neuropsychiatric adverse reactions by Week 48 in the three pre-specified categories of dizziness, sleep disorders and disturbances, and altered sensorium.

Table 2: Neuropsychiatric Adverse Reactions in Patients With Disease-A (Study 1, Week 48)

	DRUG-X N=364	DRUG-Y N=364	Treatment Difference (DRUG-X — Drug-Y) Estimate (95% CI)
Sleep disorders and disturbances‡	12%	26%	-13.5 (-19.1, -7.9)
Dizziness	9%	37%	-28.3 (-34.0, -22.5)
Altered sensorium§	4%	8%	-3.8 (-7.6, -0.3)

* All causality and all grade events were included in the analysis.

† The 95% CIs were calculated using Miettinen and Nurminen's method. Categories pre-specified for statistical testing were dizziness (p <0.001), sleep disorders and disturbances (p <0.001), and altered sensorium (p=0.033)

Prospectively Evaluated Safety

CV Benefit as an Indication

1 INDICATIONS AND USAGE

DRUG-X is indicated:

- as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus,
- **to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease** *[see Clinical Studies (14.3)]*.

Limitations of Use:

The use of DRUG-X is not recommended in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis because it would not be effective in these settings.

Prospectively Evaluated Safety

Cardiovascular Outcomes Trial – CV Benefit as an Indication

14.3 Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes Mellitu… e

Study 1 (NCT01234567) was a …tional, multi-center, placebo-controll…, doub… 2 diabetes mellitus and atherosclerotic c…diovascular disease…Patients eligible to en…

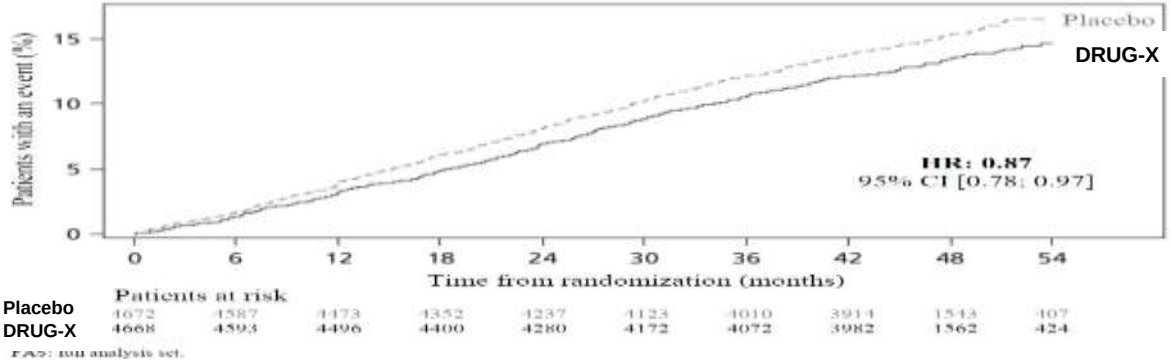
…

For the primary analysis, a Cox proportional hazards model was used to test for non… in of 1.3 for the hazard ratio of MACE and to test for superiority on MACE if non-inferio… controlled across multiple tests.

Safety (CV) benefit indication – CV outcomes trial presented in CLINICAL STUDIES section

DRUG-X significantly reduced the occurrence of MACE. The estimated hazard ratio (95% CI) for time to first MACE was 0.87 (0.78, 0.97)…

Figure 5 Kaplan-Meier: Time to First Occurrence of a MACE in Study 1 (Patients with T2DM and Atherosclerotic CVD)



Postmarketing Observational Study Data

- If presented in *Postmarketing Experience* subsection, consider headings:

> **6.1 Clinical Trials Experience**
> **6.2 Postmarketing Experience**
> Adverse Reactions from Observational Studies
> Adverse Reactions from Postmarketing Spontaneous Reports

- AR categorization – **Based on type of data**, rather than timing/source of data
- Spontaneous reports[2] (under *Postmarketing Experience*) incorporates voluntary, unsolicited ARs (outside of clinical study context) reported by/in:
  - Patients, caregivers
  - Health care providers
  - Application holders
  - FAERS
  - Published literature

Presenting AR Information for Nonindicated Uses or Dosages

Importance of Conveying Clinically Significant AR/Risk Information

- Ordinarily, information in PI must be for approved indications/dosages
  - *Indications or uses must not be implied or suggested in other sections of the labeling if not included in (INDICATIONS AND USAGE) section*[1]
  - *Dosing regimens must not be implied or suggested in other sections of the labeling if not included in (DOSAGE AND ADMINISTRATION) section*[2]
- Some exceptions, e.g.,
  - **When there are important ARs/risks for a commonly prescribed unapproved use**[3]
  - **When the AR/safety profile of an approved use relied on AR data from other studied but unapproved uses**
- *When presenting AR data for unapproved uses, include disclaimer if needed (statement that the drug is not approved for those uses/dosages)*

[1]See 21 CFR 201.57(c)(2)(iv) and (v); [2] § 201.57(c)(3)(ii); [3] § 201.57(c)(6)(i); see also § 201.57(c)(15)(i); and § 201.56(a)(3)

Presenting ARs for Nonindicated Uses or Dosages

Risk Information in Boxed Warning Covering Nonindicated Use

WARNING: RISK OF SERIOUS DEHYDRATION IN PEDIATRIC PATIENTS

- **DRUG-X is contraindicated in patients less than 6 years of age. In nonclinical studies in young juvenile rats, administration of drug-x caused deaths presumed to be due to dehydration *[see Contraindications, Use in Specific Populations (8.4)]*.**
- **Avoid use of DRUG-X in patients 6 years to less than 12 years of age *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.**
- **The safety and effectiveness of DRUG-X have not been established in patients less than 18 years of age *[see Use in Specific Populations (8.4)]*.**

DRUG-X is indicated for treatment of irritable bowel syndrome with constipation (IBS-C) in adults.

ARs for Nonindicated Dosages Within Pooled Safety Data

6.1 Clinical Trials Experience

…

The safety of DRUG-X was evaluated in 208 adult and pediatric patients 5 years of age and older in 6 clinical trials for the treatment of disease-X; 186 patients received a single dose of 10 mg/kg/day and 28 patients received 20 mg/kg/day. **The 10 mg/kg/day dosing regimen is not approved** *[see Dosage and Administration (2)].* **Pooled data** for adverse reactions reported in 2% or more of the patients in these clinical trials are presented in Table 1.

Table 1: Adverse Reactions Occurring in >2% of Patients Who Received a Total of 10 mg/kg or 20 mg/kg DRUG-X for Disease-X Treatment (Pooled across 6 studies)

Adverse Reactions	DRUG-X (10 mg/kg/day or 20 mg/kg/day) N=208, %
Abdominal pain	58
Hyperhidrosis	23
Nausea	9
Vertigo	8
Headache	8
Urticaria	7
Vomiting	6
Decreased appetite	5
Dyspnea	4
Pruritus	4
Musculoskeletal chest pain	4
Asthenia	3
Cough	3
Chest pain	2
Pyrexia	2
Diarrhea	2

Include a disclaimer statement for the nonindicated dosage if necessary to present its AR

ARs for Nonindicated Uses Within Pooled Safety Data

1 INDICATIONS AND USAGE

Drug-X is indicated for the treatment of adults with Cancer type C.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

...

The safety of DRUG-X was assessed **in a single-arm clinical trial that included 280 adults with Cancer types A, B, and C (60 adults had Cancer type C).**

Disclaimer not needed if drug indication is clear (e.g., if the pooled presentation of AR is not likely misunderstood as approved population

Summary

- Labeling regulations identify, generally, the AR information that must be contained in the ADVERSE REACTIONS section of the PI and how to categorize it
- Clinical judgment is needed to determine what data to include and how to present it
  - E.g., choosing data cut-offs; whether to present ARs for nonindicated uses/dosages
- Consider the overall clinical message when deciding upon location and presentation of AR information in labeling
  - E.g., ADVERSE REACTIONS vs. CLINICAL STUDIES section; use of qualifiers/disclaimers, if appropriate

Challenge Question 1

For adverse reactions (AR) with significant clinical implications, AR listing(s) must be supplemented with information on which of the following:

a) Nature, frequency, and severity of the AR

b) Relationship of the AR to drug dose

c) Relationship of the AR to demographic characteristics

d) All of the above, if data are available and important

Selected Regulatory References

- Statute: Food, Drug, & Cosmetic Act (FD&C Act)
- Regulations: 21 CFR 201.57(c)(7), (6), (1), (15); (a)(11), (10), (4)
- Guidance for Industry:
  - *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products– Content and Format* (Jan 2006)
  - *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products– Content and Format* (Oct 2011)
  - *Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (Jan 2006)
  - *Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (Feb 2013)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Backup Slides

Where Should AR-Related Information Go???

Sections 6 and 14 – Regulations and Guidance

6 ADVERSE REACTIONS

- **AR data (drug AR/risk)**
  - **Overall AR profile of drug based on entire safety database**[1]
  - Ordinarily, safety data are described in the ADVERSE REACTIONS section[5]
- **Cross reference Section 14 for detailed study discussion**[2]
- "**A negative finding can be reported** if the absence of the reaction is convincingly demonstrated in a trial of adequate design and power"[4]

Regulations/guidance allows some flexibility

14 CLINICAL STUDIES

- **"Any detailed discussion of the study"**[2]
  - "**Details of studies** that are the basis for comparative safety claims would ordinarily be discussed in the CLINICAL STUDIES section"[4]
- **Cross-reference Section 6 for AR data**
  - **"Any discussion… that relates to a risk from the use of the drug must also refer to the other sections of labeling where the risk is identified or discussed"**[3]
- Sometimes, AR/safety data can be in CLINICAL STUDIES section
  - "**Clinical studies** that prospectively evaluate an important safety endpoint"… "should usually be included in the CLINICAL STUDIES section"[5]
  - "The section should also include safety data from controlled studies specifically designed to evaluate a safety endpoint"[5]
  - "…**in some cases it may be appropriate to present important information about safety in the CLINICAL STUDIES section (e.g., if the safety data are best understood when presented with a detailed study description or in the context of effectiveness results).**"[5]
  - "**If safety data are presented in the CLINICAL STUDIES section, they must be cross-referenced in the ADVERSE REACTIONS section and other sections, as appropriate** (21 CFR 201.57(c)(15)(ii))."[5]

[1]See 21 CFR 201.57(c)(7); [2] § 201.57(c)(15); [3] § 201.57(c)(15)(ii); [4]guidance *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products– Content and Format* (Jan 2006); [5]guidance Clinical Studies Section of Labeling for Human Prescription Drug and Biological Products– Content and Format (Jan 2006)